Respiratory Care: Facing the Challenges

WORKSHOPS

RS Penyakit Infeksi
Prof. Dr. Sulianti Saroso, Sunter, Jakarta
June 16th, 2023

The Ritz-Carlton Hotel, Mega Kuningan, Jakarta
June 15 - 16, 2023

SYMPOSIUM

The Ritz Carlton,
Mega Kuningan Hotel, Jakarta
June 17 - 18, 2023

24th International Meeting on Respiratory Care Indonesia (Respina) 2023

Proceeding eBook

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Symposium June 17 - 18, 2023

Respiratory Care Indonesia (Respina) 2023

PROCEEDING
24th International Meeting on Respiratory Care
"Respiratory Care: Facing the Challenges"

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"Respiratory Care: Facing the Challenges"

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Preface

Dear Colleagues,

I am very delighted to present to you the 24th International Meeting of Respiratory Care Indonesia (Respina) will be held onsite at The Ritz-Carlton Hotel Mega Kuningan on 15th to 18th June 2023.

Our beloved the science committee have organized an outstanding line up of remarkable speakers for the Meeting from national and international which I believe will provide something of interest to all healthcare professionals and researchers to improve their comprehensive care of respiratory diseases.

This year, Respina will present a full programme of named workshops, Major Symposia, Lessons Learned, RespiQuizz for medical students, Case Report Forum, Studium Generale, Free Paper, Poster presentation and health promotion seminar for the community.

As the COVID-19 pandemic has been eased by the government and the world, the Respina meeting this year is going to be special because it will be our first face-to-face meeting following two virtual conferences which was held during the pandemic. Being back onsite will brought the Respina's spirit of togetherness and to provide the better one-to-one interactions with all speakers, colleagues, and committees.

I am so thankful for all good efforts and team works of the Respina committees from 14 medical societies as the member of Respina and I am looking forward to welcoming you in person without boundaries at all. Welcome to Respina!.

Sincerely yours,

Dian Yulianti, MD

Chairperson

About Respina 2023

Respiratory Care Indonesia (Respina) is an annual international meeting in Indonesia on respiratory care. Respina is a result of collaboration of five pillars, which are Department of Pulmonology and Respiratory Medicine Faculty of Medicine University of Indonesia, American College of Chest Physician-Indonesia Chapter, Asian Pacific Society of Respirology, Indonesia Society of Bronchoscopy and Indonesian Society of Respirology, in answering the global problem of respiratory care. The mission of the meeting is to bring the up-to-date and latest information of respiratory care and as media of collaboration to each respiratory care practitioners in cooperative spirit.

Starting on 2006, Respina is proudly joined by societies that shared the same interest particularly in respiratory care, and they are as follows:

- Indonesian Society of Respirology
- Indonesian Association of Thoracic and Cardiovascular Surgeons
- Indonesian Radiological Society
- Indonesian Neurological Association
- Indonesian Heart Association
- The Indonesian Society of Anesthesiology and Intensive Therapy
- The Indonesian of Physical Medicine and Rehabilitation Association
- Indonesian Pediatric Society
- The Indonesian Otorhinolaryngological Head and Neck Surgery Society

Four other professional organizations joined Respina in 2011, they are:

- Indonesian Association of Clinical Pathologists
- The Indonesian Physician of community medicine and Public Health Association
- Indonesian Sports Medicine Association
- Indonesian Society for Clinical Microbiology

One professional organization joined Respina 2021,

- Indonesian Association of Obstetrics and Gynecology

Respina 2023 is the 24th meeting we have been conducting and during the years, Respina has become one of the major respiratory events in Indonesia and gained greater and still growing interest from physicians across the regions, particularly from our colleagues in Southeast Asia.

Invited Speakers

Amanda J. Piper, (AUS)

Bülent TUTLUOĞLU (TUR)

Chiaki Toida, (JPN)

David Chi-Leung Lam(HKG)

Edward Thomas Hamilton Fysh (AUS)

Francis Lee Chun Yue (SIN)

Jennifer Ann Mendoza-Wi, (PHI)

Puah Ser Hon (SGP)

Steve Tze Yi Yang (SGP)

Venugopal S. Reddy, (USA)

And Most Valuable National Speakers

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Content

SYMPOSIUM DAY 1

SATURDAY, JUNE 17th 2023

24th INTERNATIONAL MEETING ON RESPIRATORY CARE INDONESIA (Respina) 2023

EARLY WARNING SYSTEMS IN ACUTE DYSPNEA

Puah Ser Hon

ABSTRACT

Breathlessness is an unpleasant sensation or the presence of uncomfortable respiratory sensations which represents a mismatch between central respiratory motor activity and information through the afferent nerves from the receptors of the lungs. Various tools have been developed to diagnose and prognosticate illnesses presenting with acute dyspnea. However, there has not been any particular tool that has been discerning enough to warn of an impending deterioration. NEWS2 is a robust scoring system taking into account patients with chronic respiratory illnesses and was promising to predict deterioration by incorporating respiratory rate into the set of physiological parameters. There have been other predictive modals that incorporate respiratory rate to look at specific illnesses and also success of certain treatment modalities like high flow nasal cannula. The importance of dyspnea can't not be emphasized more and should be taken seriously as a marker of an underlying dangerous process.

MANAGEMENT OF ACUTE AIRWAY OBSTRUCTION IN PEDIATRIC PATIENT

Madeleine Ramdhani Jasin

ABSTRACT

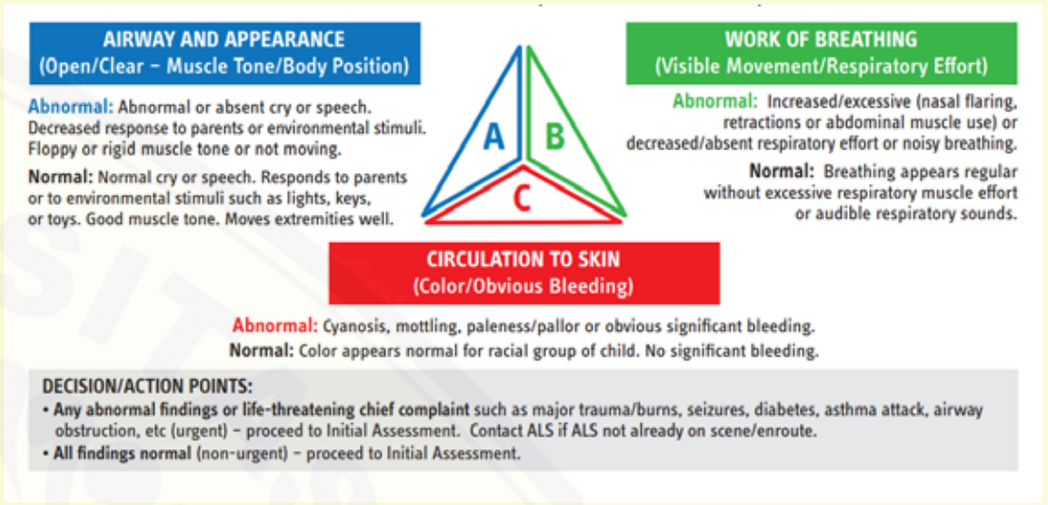
Respiratory airway diseases are among the leading cause of admission in hospital and clinic for children. Respiratory distress, accounting for 10% of pediatric visit to emergency department, is more common in children than in adults because of their unique features in anatomic and physiology. In children, even a partial airway obstruction can lead to severe symptoms.1

Airway anatomy can be divided as upper and lower airway, at the level of larynx. Airway obstruction can affect at any level, and maybe differentiated by the noisy breathing sounds occurring in the affected patients. In addition to the level of obstruction, this pathology may also happen acutely or chronically, depending on the onset of symptoms. Acute airway obstruction generally develops suddenly, within short time frame, usually in few days up to one week. It is important to recognize the causes of acute airway obstruction, as those can be life threatening. Appropriate recognition of the etiology is promptly necessary, as they are often treatable.1,2

When encountering acute airway obstruction in emergency settings, there are few steps in approaching this condition in order to perform a successful medical management. In emergency situation, rapid assessment of airway – breathing – circulation (ABC) or pediatric assessment triangle should be the first and foremost, followed with necessary medical action, such as giving oxygen therapy and resuscitation. Second step is to evaluate in what level, airway obstruction occurs. This can be done by performing meticulous physical examination. Identifying abnormal breathing sounds or noisy breathing is helpful to recognize the at which level airway obstruction occurs. Abnormal breathing sounds to identify are stertor, inspiratory stridor, biphasic stridor, and wheeze. The third step is to distinguish whether the etiology is acute or congenital. Acute airway obstruction is usually due to acquired causes, rather than congenital etiology alone. Acquired etiologies can be divided into infective and non-infective causes. The next step is to perform necessary additional examination, such as X-ray, and airway endoscopy. Subsequently, prompt management to the etiologies is warranted.

Step 1: Pediatric assessment triangle

Initial rapid assessment at emergency settings, recognized as pediatric assessment triangle, is by rapidly assessing three areas to look for visual and auditory tools, namely the appearance, (work of) breathing, and circulation. This is a continuous sequence of evaluating and identifying clinical condition, then intervening appropriately. However, do not continue assessment if a life-threatening emergency is observed and start proper management immediately. Assessment areas of pediatric assessment triangle can be seen in Picture 1. After completing pediatric assessment triangle, physician can define whether the patient is sick or not sick, and which area is involved.[3,4]



Any signs of abnormality in work of breathing mainly, accompanied with abnormalities in airway & appearance, also circulation lead to suspicion of problems in respiratory system, either airway or parenchymal. However, if the problems are mainly in the airway, abnormal breathing sounds are prominent in the patient.

Rapid assessment can be done to evaluate airway patency and respiratory status. Thus, severity of airway obstruction can be assessed quickly, as seen in Table 1.

Table 1. Differentiating severity of airway obstruction[6]

Mild obstruction	Moderate obstruction	Severe to complete obstruction
Able to speak or cry, maybe hoarse	Tachypnea	Hypoxia (late sign)
Intermittent stridor or occasional stertor	Stridor	Bradypnea or marked tachypnea
Minimal or no work of breathing	Prolonged inspiratory time	Sniffing or tripod position
Good air entry	Moderate work of breathing, nasal flaring, grunting, paradoxical chest movement	Agitated, or drowsy
	Decreased air entry	Severe work of breathing
		Markedly reduced, or no air movement
		Silent gagging or coughing
		Total obstruction will rapidly progress to unconsciousness and cardiorespiratory arrest

Step 2: Identifying level of obstruction

Adventitial breath sounds or noisy breathing can be clues for determining level of airway obstruction. Breath sounds are generated by air moving through the trachea and bronchi, and the abnormal breath sounds that can help identifying the obstruction are:[2,5,6]

- **Stertor** is described as hoarse coarse noises generated by turbulent airflow above the larynx, in the **supraglottic space.** The supraglottic comprises the vallecula, epiglottis, arytenoid cartilages, and aryepiglottic folds. Stertor is often louder during sleep because of reduced tone of the pharyngeal muscles.
- Stridor is defined as a harsh monophonic noise coming **below the larynx,** as a result of narrowing. This sound can be heard with or without a stethoscope. When the extra-thoracic airway is affected, stridor always has an inspiratory component, yet can be biphasic (inspiratory and expiratory) if the narrowing is severe. A purely inspiratory stridor indicates narrowing of the extra-thoracic airway. When the intra-thoracic trachea is affected, the stridor will usually be biphasic, with relatively loud expiratory phase. In summary, inspiratory stridor will be heard if the obstruction is at supraglottic level, expiratory phase if at glottic level, and biphasic of at subglottic or trachea.
- **Wheeze** is a whistling musical noise due to turbulent airflow passing through **narrowed medium sized airways, such as bronchus.** Wheeze always occurs in expiratory phase.

Step 3: Distinguish the etiology

In regards of acute airway obstruction, etiology is more likely to be acquired, than can be further divided to infective and non-infective causes, as seen in **Table 2.**[3]

Table 2. Etiology of acute airway obstruction

	Etiology	
	Infective	**Non-infective**
Upper airway	Tonsilitis F	oreign body aspiration
	Peritonsillar abscess	Laryngeal edema
	Epiglottitis	Burn injury
	Croup/ laryngotracheitis	Anaphylaxis reaction
	Retropharyngeal abscess	
	Parapharyngeal abscess	
Lower airway	Bronchiolitis	Foreign body aspiration
		Anaphylaxis reaction
		Asthma exacerbation

Common feature of infective etiologies is fever, with other more specific features according to each disease, as seen in **Table 3.**

Table 3. Clinical manifestations of etiology of acute airway obstruction

Infective etiologies		Non-infective etiologies	
Diagnosis	**Manifestations**	**Diagnosis**	**Manifestations**
Tonsilitis	Febrile Sore throat Cough Mouth breathing	Foreign body aspirations	Sudden onset Coughing, choking, vomiting episode Stridor, or wheeze, according to level of dislodged foreign body
Peritonsillar abscess	Febrile Severe sore throat Stertor Trismus Swollen posterior palate and tonsil, medial displacement of tonsil and deviation of the uvula	Laryngeal edema	Stridor History of intubation
Epiglottitis	High fever, systemically unwell Stertor Hyperextension of the neck Dysphagia Drooling Absent of cough	Burn injury / inhalation trauma	Stertor, stridor History of burn Soot in nasal area
Croup	Rapid onset harsh barking cough Hoarse Stridor Febrile	Anaphylaxis reaction	Stridor, wheeze Facial edema History of allergen exposure
Retropharyngeal abscess, parapharyngeal abscess	Sore throat Fever Neck pain and stiffness or torticollis Dysphagia and drooling Fullness and redness of posterior pharyngeal wall	Asthma exacerbation	Dyspnea Wheeze History taking shows exposure to allergen in a previously asthmatic child
Bronchiolitis	Cough Dyspnea Wheeze Febrile		

Step 4: Performing necessary additional examination

Children with moderate to severe upper airway obstruction are at high risk of deteriorating and complete obstruction if they are upset, sedated, or repositioned. Thus, investigations should be deferred until airway

is secure. If emergency situation is able to overcome, some examinations can be done according to the working diagnosis, namely X-ray, and flexible airway endoscopy.[6,]

Table 4. Additional examination[3,6-8]

Working diagnosis	Additional examination
Infective etiologies	
Epiglottitis L	ateral neck x-ray showing thumb sign
Croup	AP neck x-ray showing steeple sign
Peritonsillar abscess, retropharyngeal abscess, parapharyngeal abscess	Neck x-ray, CT-scan
Bronchiolitis	Chest x-ray showing hyperinflation
Non-infective etiologies	
Foreign body aspiration	Chest x-ray
Laryngeal edema	RPL
Burn injury/ inhalation trauma B	ronchoscopy

AP: antero-posterior, RPL: rhino-pharyngo-laryngoscopy

Step 5: Prompt management according to each etiology

As mentioned above, the initial step in airway obstruction management is ABC, abbreviation from airway, breathing, circulation. Oxygen supplementation therapy should be initiated if saturation is lower than 94% and an oxygen saturation monitor should be placed. Thereafter, management according to each etiology should take place.

Table 5. Management of acute airway obstruction according to etiology[5-9]

Diagnosis	Management
Infective etiologies	
Tonsillitis	Ambulatory care; for Streptococcal tonsillitis: antibiotic given, such as amoxicillin, erythromycin, azithromycin, or clarithromycin
Epiglottitis	Hospital care; cefotaxime, added with clindamycin if age < 12 years old
Croup	Inhaled epinephrin, intravenous steroid, oxygen supplementation if necessary
Peritonsillar abscess, retropharyngeal abscess, parapharyngeal abscess	Abscess drainage, parenteral antibiotic such as intravenous ampicillin-sulbactam or clindamycin
Bronchiolitis	Hydration and supportive therapy, other therapies are controversial, such as hypertonic saline or steroid or salbutamol nebulization
Non-infective etiologies	
Foreign body aspiration	Bronchoscopy for foreign body extraction as soon as possible
Laryngeal edema	Intravenous dexamethasone, or methylprednisolone
Burn injury/ inhalation trauma	Oxygenation support, therapeutic bronchoscopy, inhaled bronchodilator, mucolytic agents
Anaphylaxis reaction	ABC, intramuscular epinephrine, adjunctive agents such as antihistamines
Asthma exacerbation	Inhaled salbutamol, inhaled steroid, intravenous/oral steroid

Prognosis of airway obstruction depends on the severity and the prompt treatment applied, as untreated airway obstruction causes respiratory distress that can lead to cardiorespiratory arrest. This consider transfer to intensive care setting when the patient is at risk for deteriorating and requires more advanced airway management. Furthermore, after patient's condition is improving, and the cause for acute airway obstruction is identified, treatment has been undertaken, consider discharge.

In conclusion, acute airway obstruction is a life-threatening condition, acknowledged by abnormal noisy breathing, in addition to other symptoms such as cough and dyspnea. There are five steps to recognize and treat acute airway obstruction, to improve a better patients' condition. Prognosis and complication depend on the severity and prompt treatment in managing each patient.

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ACUTE AIRWAY OBSTRUCTION MANAGEMENT IN ADULT PATIENT

Bulent Tutluoglu

ABSTRACT

Airway obstruction may be divided into upper airway obstruction and lower airway obstruction. Most prominent causes for upper airway obstruction are: Loss of pharyngeal muscle tone ,vomit ,blood , foreign body aspiration , epiglottis swelling ,soft tissue oedema, laryngospasm,trauma and tumours. Most frequent causes for lower airway obstruction are: Obstruction due to secretions or foreign body , pulmonary oedema , bronchospasm and tumours.The primary objective of airway management is to secure unobstructed gas exchange and protect the lungs. Airway management techniques are generally classified as non-invasive or invasive. The technique of choice will depend on each individual situation and is determined by the interaction of patient and clinical factors.While securing the airway opening it is very important to start concomitant medical therapy depending on the aetiology of airway obstruction.

Keywords: *airway obstruction, aspiration, airway obstruction management*

WHY ADHERENCE TO GOLD IS THE KEY NOVEL STRATEGY TO ADDRESS THE COPD BURDENS?

dr. Kasum Supriadi, Sp.P

ABSTRACT

Failure to achieve therapeutic goals begins with noncompliance in understanding and applying GOLD in daily practice. Misdiagnosed or undiagnosed COPD occurs in approximately 50% of patients. The error will have many effects: misclassification of disease severity, treatment and management errors, increased risk factors for drug side effects and disease exacerbation, increased health related costs. Compliance in following GOLD recommendations shows consistency in reducing the incidence of exacerbations, pneumonia and costs. Therefore, it is important to increase understanding and ensure that GOLD recommendations are followed in daily practice, starting from primary care, from diagnosis to disease management. GOLD recognizes Tiotropium as an essential therapy for COPD with proven efficacy and long-term safety profile. Not all combinations of therapy are better vs Tiotropium alone in reducing the risk of exacerbations. Only Tiotropium/Olodaterol is a better combination therapy vs Tiotropium, vs LABA/ICS and vs other LAMA/LABA both in terms of efficacy and cost-therapy. Only Tiotropium/Olodaterol is a combination therapy that is delivered via the SMI Respimat, making it easy for COPD patients to inhale.

GOLD Strategy 2022 recommends an individualized approach for COPD treatment, including selecting inhaler device. Maximizing inhaled bronchodilators in COPD are central to achieve treatment goals of stable COPD. Initial treatment with monotherapy should be sufficient if we consider that the predominant symptom is dyspnea for majority COPD patients. LAMAs have greater effects to reduce exacerbations and decrease hospitalizations, compared with LABAs.

Many COPD patients struggle to inhale and have suboptimal peak inspiratory flow (PIF). Selecting the most appropriate inhalation device from the wide range available is essential for the successful management of patients with chronic obstructive pulmonary disease. Although choice is good for healthcare professionals, knowing which inhaler to prescribe is a complex consideration. Among the key factors to consider are quality of disease control, inhaler technique, inhaler resistance and inspiratory flow, inhaler design and mechanisms of drug delivery, insurance and reimbursement restrictions, environmental impact.

Respimat has several advantages that benefits COPD patients. Unique design mechanism for drug delivery of Respimat actively generate soft mist particle that optimize lung deposition. Low device resistance allows Respimat to be used for wide variety of COPD patients, uninfluenced by patient's ability to inhale. COPD patients just need to inhale slowly without much effort. New reusable Respimat can be used up to six cartridges and bring less environmental impact.

THE IMPORTANCE OF ANTI-INFLAMMATORY RELIEVER CONCEPT FOR BETTER ASTHMA CARE

Jennifer Ann Mendoza-Wi, MD, FPCP, FPCCP, FCCP, FAPSR
Professor, Lyceum University College of Medicine, Philippines

ABSTRACT

Anti-inflammatory Reliever (AIR) therapy with ICS-formoterol, either alone or with regular maintenance use according to the MART (Maintenance and Reliever Therapy) regimen, has resulted in a paradigm shift in asthma management, and the evidence is now sufficient to warrant its use as the preferred reliever regimen in adult and adolescent asthma. This was one of the most important change in asthma management recommended by The Global Initiative for Asthma (GINA) strategy 2019 update. In addition, short-acting beta2-agonists (SABA) should not be used alone as sole therapy without inhaled corticosteroids (ICS). Several studies including open-label studies which investigated the way that patients would use as-needed ICS-formoterol in real life, and included patients with baseline SABA use as infrequent as twice a month, have been published thereby extending the evidence of efficacy to the mildest patients with very infrequent symptoms. There was a reduction in severe exacerbation risk compared with as-needed SABA or with maintenance ICS plus as-needed SABA in mild asthma. This evidence enabled GINA to strengthen its recommendations regarding the preferred use of ICS-formoterol rather than SABA reliever therapy in the 2020 update. The key objectives of asthma management is to reduce the risk of asthma-related exacerbations and death including in patients with so-called mild asthma. For those in whom symptom control is the priority, both regimens, MART and higher maintenance dose ICS-LABA plus as-needed SABA have similar benefit in terms of this outcome measure.

The presentation will highlight the importance of an inhaled anti-inflammatory (ICS) in asthma management which includes the mild asthmatic.

UPDATE ON PEDIATRIC ASTHMA: HOW TO CLOSE THE GAP IN THE ASTHMA MANAGEMENT

Nastiti Kaswandani

ABSTRACT

Introduction
Asthma is still the most common chronic respiratory disease in children and continues to be a significant health problem worldwide. Global Burden of Disease Study reported that Asthma affected an estimated 262 million people in 2019 and caused 455.000 deaths. Asthma has been included in the WHO Global Action Plan for the Prevention and Control of NCDs and the United Nations 2030 Agenda for Sustainable Development.[1]

The prevalence of asthma consistantly increases in both developed and LMICs (low-middle income countries), also both in urban and rural areas in the last few decades. The ways of life such as modern life-style, air polutions and huge exposure to chemical substances are the influencing factors of this conditions.[2]

When Covid-19 became the greatest health pandemic in the world, many diseases showed changes in various aspects and volume. The multinational cohort called PeARL STudy included 1,054 children with asthma and 505 non-asthmatic children aged between 4 and 18 years from 15 countries. They found that during Covid pandemic, children with asthma experienced fewer upper respiratory tract infections, episodes of pyrexia, emergency visits, hospital admissions, asthma attacks, and hospitalizations due to asthma. Sixty-six percent of asthmatic children had improved asthma control while in 33% the improvement exceeded the minimal clinically important difference. The lung spirometry were improved during the pandemi.[3]

The explaination or the reason is probably because of reduced exposure to asthma triggers and increased treatment adherence during pandemic. It also suggest that environmental control is apparent to improve childhood asthma out-comes. After the global situation is back to normal, the alter of pediatric asthma control should be anticipated.

Burden and Challenges of Pediatric Asthma
The disparities and barriers to asthma diagnosis, therapy, and prevention may impact children's lives. The Global Burden of Disease estimated that more than 4 hundred thousand deaths occurred from asthma in 2019 worldwide, and although asthma prevalence is higher in high-income countries, most asthma-related mortality occurs in LMICs. Asthma is often under-diagnosed and under-treated especially in LMICs where asthma patients still face many barriers to accees the appropriate allergy and asthma care.[4]

A recent study from Sub Sahara reported the challenges of diagnosis asthma in children in Nigeria, South Africa and Uganda. The causes of under-diagnosis of asthma include lack of community knowledge and perception of asthma, poor accessibility to health care, strained health systems, lack of diagnostic tests including spirometry, low levels of knowledge among health-care workers and lack of or non-implementation of asthma guidelines.[5]

In developed countries, the problems reported in many publications were the quality of life (QoL) of children

with asthma, mainly in severe/difficult to treat asthma. The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens (TENOR), a 3-year observational study, evaluated QoL of children with severe/ difficult-to-treat asthma. QOL was examined using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and found the lower QOL in children with severe/difficult-to-treat asthma.[6]

Unmet Need of Pediatric Asthma Management

There are still unmet needs in prevention, diagnosis, treatment, and progression of asthma in childhood. In developed countries, the unmet needs that are mainly concerned or discussed by experts or published articles are more about the lack of phenotypes-based guideline and potential non-steroid treatment options. In the other side, the unmet needs of asthma management in LMICs are still the sub-optimal implementations of asthma care based on established guidelines. A 2017 survey of 112 countries participating in the Global Asthma Network found that only 26 countries (23%) had a national asthma plan for children, with a lower proportion in LMICs. Papadopoulos et al reported that unmet needs include a lack of clinical efficacy and safety evidence, and limited availability of non steroid based alternative therapies in patients <6 years-old. It also stated about the need of a uniform definition of pediatric asthma, clearly distinguishable from adult asthma which provide specific treatment recommendations for the management of pediatric asthma.[7]

JAMA has published the survey of 1228 health care professionals in childhood asthma from 88 countries with a balanced distribution across different various care settings (305 [22.7%] primary care, 401 [29.9%] secondary, and 522 [38.9%] tertiary care) and 91 researchers. Monitoring of symptoms and control, adherence, comorbidities, lung function, medication adverse effects, and allergy were considered to be very high or high priority by more than 75% of the respondents. These survey suggested that pediatric asthma monitoring was performed generally homogeneously worldwide, in most cases following evidence-based standards. Unfortunately, in this study only less than 20% respondents were recruited from LMICs so that it might not reprensent the actual conditions in LMICs.[8]

The real conditions of pediatric asthma care in LMIC in Asia Pasific regions were might be more accurately described by a letter from Jusuf et al.9 The problems in pediatric asthma care in LMICs have already started with the reluctancy of asthma diagnosis by the parents. The issue of diagnosis acceptance also drove the parents to bring the child to the alternative or traditional medicine and resulted in delayed treatment. Contrary with the developed countries, asthma control was difficult to achieve because of poor compliance due to several factors such as steroid-phobia, the ignorance of hired caregivers and poor air environment (environmental tobacco smoke / ETS). Access to prompt treatment especially the spacer for pMDI is also still become an issue.[9]

Children with uncontrolled asthma become a significant health burden on the patients themselves, the parents and also the community. Uncontrolled asthma defined as poor symptom control and/or frequent exacerbations that require OCS treatment or hospitalisation. Uncontrolled asthma can reduce child's QoL when they have limitations due to physical health problems, fitness, social functioning and emotional wellbeing. Children are are more likely to have anxiety and depression compared to patients with well asthma control. Children with uncontrolled asthma may have later bedtimes, insomnia, frequent night-time awakenings and poor sleep quality. Absence from work/school, and decreased productivity are also associated with uncontrolled asthma, not only the children are affected, but also their parents or caregivers. Patients with uncontrolled asthma also have higher risk of side-effects from corticosteroids because frequent acute exacerbation also means frequent systemic steroid prescriptions. Children with uncontrolled or difficult to treat asthma are not necessarily have a severe asthma phenotype.[2,10]

The first evaluation of uncontrolled asthma condition is whether the child really has asthma. Particularly in younger children, asthma has many differential diagnosis so that other potential diagnosis should be excluded. The common cause of uncontrolled asthma is the lack of consistant behaviour to avoid the trigger factors. Asthma patient must avoid house dust mites, moulds, pets, pollens, air pollution, weather/ temperature changes, viral infections and smoking, including e-cigarettes. Adherence of asthma patients is not only about avoidance but the adherence of taking the controller medication also plays an important role to control asthma. The other crucial factor that may contribute to uncontrolled asthma is improper inhalation technique. Many publications reported that poor inhalation technique in children is common, so that every physician taking care of asthma child should check whether the child can use the inhalation device properly. The limited options or access for spacer or holding chamber in LMICs drove the innovation of simple spacer made from paper cup or plastic bottle.

After doing the evaluation of proper diagnosis, adherence of avoidance and medication, correct use of inhalation device, the physician should evaluate the comorbidities before stepping-up the controller. The most important and common comorbidity in uncontrolled asthma is allergic rhinitis. From 619 children with asthma who completed at least 4 of 6 visits, rhinitis was present in 93.5%, and phenotypes identified at baseline were confirmed during the observation/management year. Perennial allergic rhinitis with seasonal exacerbations (PARSE) was most common (34.2%).[11] Other comorbidities which are frequently mentioned in the guidelines are chronic sinusitis, gastroesophageal reflux disease (GERD), obesity, obstructive sleep apnea syndrome (OSAS) and also psychological problem such as anxiety and depression. Clinicians should seek and overcome the comorbidities before stepping-up or adding the drugs.[2,10]

The challenges of asthma diagnosis is more likely happens in younger age group, but for management of asthma the adolescent group has more challenges compared to other age group. Adolescence is a unique transitional period when a child is entering adulthood. The challenges of adolescence due to accelerated changes in physical dimension, emotional, and psychological condition. The additional contributing factors of this specific age group such as behavior risks e.g. smoking/vaping, and psychologic manners e.g. denial, anxiety or depression. Being afraid of embarrassment or seeming different from their peers, adolescents may hide their symptoms and not take their medication. In later adolescence, common misconception among this age group is mistaking improvement of symptoms with "outgrowing asthma.[12]

How to Close the Gap in Pediatric Asthma

To overcome the gap of asthma management in children, the effort should be done in multi-level of scope, from national policy maker to individual professionals who taking care of asthma patient, also from pediatric pulmonology subspecialist to primary care doctor. The management of asthma should be improved in both pharmacological therapy or medication and non-pharmacological management. For children who have uncontrolled asthma, the intervention should be done by starting to identify the cause of uncontrolled asthma and continue to make a suitable management plan as presented in Figure 1.[13]

Despite of the new asthma drugs eg biologics as potential non-steroid controllers, the efforts should be prioritized on best-practice considering many limitations in clinical seting. The potential solutions contains of non-pharmacologycal approach and pharmacological ones.13,14

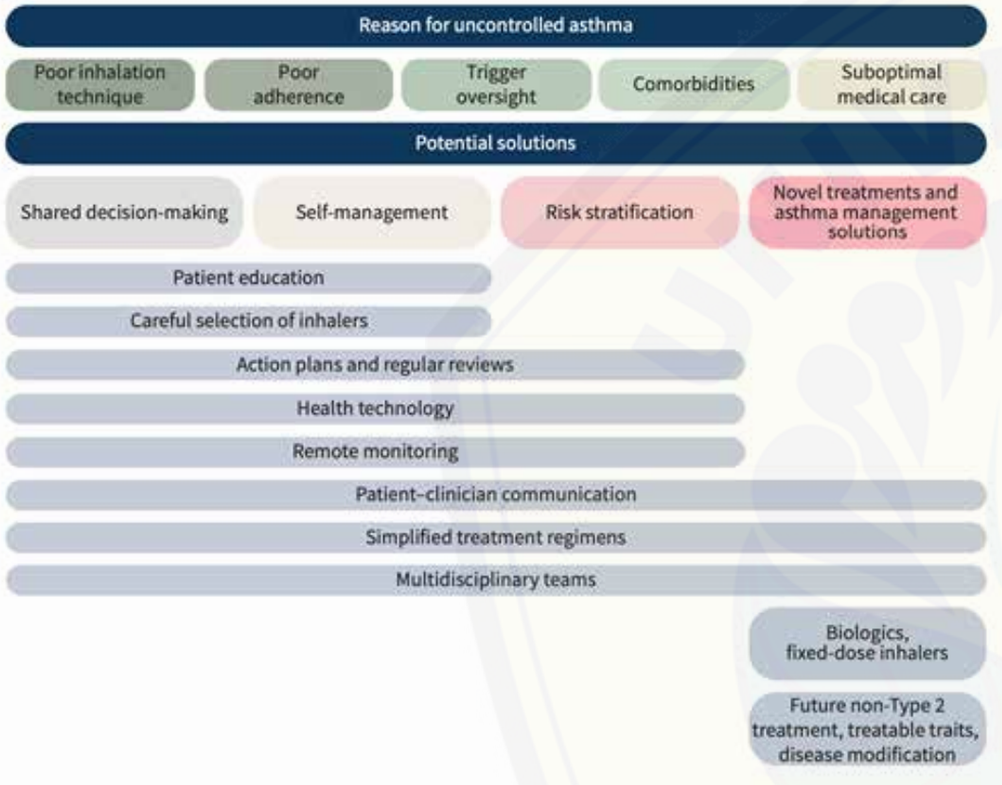

Figure 1. Interventions for uncontrolled asthma.[13]

Pharmacology therapy

The basic management steps for asthma preventive controller should be with ICS. When a moderate dose of ICS fails to achieve good control of asthma, addition of a long-acting Beta2 agonist (LABA), preferably as a combination ICS/LABA inhaler, improves clinical asthma outcomes. It reduces the number of exacerbations, achieves asthma control in more patients, more rapidly and at a lower dose of ICS than ICS given alone. Fixed combination inhalers may increase adherence and ensure that the LABA is always accompanied by ICS.

The National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group of the National Heart, Lung, and Blood Institute recently published its 2020 Focused Updates to the Asthma Management Guidelines. The most highly pediatric-relevant recommendations of medications involve three treatment options: (1) intermittent ICS dosing with as-needed short- acting b2-agonist (SABA) for quick-relief therapy, (2) single maintenance and reliever therapy (SMART), and (3) add-on LAMA therapy.[15]

The use of single maintenance and reliever therapy (SMART) with a single inhaler containing a corticosteroid (budesonide) and a LABA (formoterol) not only for maintenance, but also for additional 'rescue' use as reliever provides reduction in exacerbations and improvements in asthma control. It is recommended as the preferred therapy for children 4 years who are not well controlled on a low- or medium-dose daily ICS alone. Formoterol is the LABA of choice because it has a rapid onset of action and can be used more than twice daily. For patients, SMART is a “double win,” reducing exacerbation rates and overall corticosteroid use.[16]

A meta-analysis of 15 RCTs has evaluated SMART as a combination therapy with budesonide and formoterol in a dry-powder inhaler in patients aged 12 years or older (n = 22 524) This study reported that patients with persistent asthma, the use of single maintenance and reliever therapy compared with inhaled corticosteroids as the controller therapy (with or without a long-acting -agonist) and short-acting β-agonists as the relief therapy was associated with a lower risk of asthma exacerbations.[17]

For pediatric clinicians, the most exciting updates are those affirming several treatment options for using ICS with long-acting b2-agonists (LABAs) and LAMAs. These recommendations apply only to patients >12 years; LAMA therapy is approved for children 6 to 11 years of age but was not considered in the systematic reviews used to develop the recommendations. Daily ICS- LAMA is an alternative therapy after SMART (preferred choice) and after daily ICS-LABA (secondary choice) for moderate persistent disease. For severe persistent asthma, the preferred therapy for individuals not controlled on ICS-LABA is triple therapy with daily medium- to high- dose ICS-LABA plus add-on LAMA and as-needed SABA. The updates did not address biological therapies because at the time only one biologic (omalizumab) was available.

Tiotropium bromide is the only long-acting muscarinic antagonist (LAMA) approved for treatment of patients aged ≥6 years old who have symptoms of uncontrolled asthma. Results from several clinical trials have found that once-daily inhaled tiotropium bromide as an add-on medication is safe and efficacious in 6 to 17-year-olds with symptomatic asthma. The pharmacological effects of the LAMA tiotropium bromide, provide an overview about current asthma studies at different pediatric ages, however, long- term safety should be evaluated in future studies including longer periods of treatment.[18] Other modalities such as SLIT was only recently recommended for adults with allergic rhinitis and sensitized by house dust mite with certain clinical condition.[14]

Considering the limitations of longterm safety evidence and access availability of new drugs, SMART strategy is one of best-practice to lower asthma treatment gap in children.

Non-pharmacology therapy

Educating the patients and/or parents about asthma is very crucial to achieve asthma control. More than that, strategies to improve asthma education should include community and school. The patient/ parents-doctor relationship is an essential intervention point to ensure a clear understanding of severity and medication. Patients has to be able to know how to avoid triggers, to recognise asthma worsening, and

to understand the importance of taking their medications properly. Non-pharmacological efforts such as avoidance and smoking cessation should be consistantly done.

Nowadays, asthma education can be also accessible via pamphlets, websites and smartphone applications. For children, innovative and interacive ways have been utilised, such as activity books, music, videos and smartphone apps that include games and quizzes. Smartphone or mHealth apps present an opportunity to engage with patients on an everyday basis using a familiar format. Considering that 73% of adolescents in the United States have access to smartphones, mobile health (mHealth) applications—smart phone apps—could be a useful intervention for self-management. One mHealth application, the Adolescent Adherence Patient Tool (ADAPT), is equipped with features such as a symptom monitor, medication alarm, educational videos, peer chat, pharmacist chat, and adherence monitor.2,10,14

Summary

Pediatric asthma still become the important health problems in both developed and LMICs. Children with uncontrolled asthma have a significant reduced QoL. Management of uncontrolled asthma is started by evaluating the possible causes such as incorrect diagnosis, adherence problems, improper inhalation technique and untreated comorbidities. To close the gap in therapy, the best-practice in pharmacological therapy mostly written in guidelines is the use of single maintenance and reliever therapy containing budesonide and formoterol in single inhaler (SMART strategy). The smartphone used by majority of patients can provide innovative application which can help educating asthma and self-management asthma plan.

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CURRENT UPDATES ON MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRACT

Lower respiratory tract infections, particularly pneumonia, are a leading cause of global mortality, with community-acquired pneumonia (CAP) imposing a significant burden on vulnerable populations. Accurate diagnosis and effective management strategies are crucial for combating this public health issue. The diagnosis of CAP involves clinical symptoms, radiology examination, and laboratory tests. Streptococcus pneumoniae, Chlamydophila pneumoniae, and Mycoplasma pneumoniae are commonly implicated pathogens. Treatment strategies depend on comorbidities and risk factors for methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa. Empiric treatment recommendations vary for outpatient and hospitalized settings, with combinations of antibiotics often prescribed for broad-spectrum coverage. The current guidelines highlight the significance of precise diagnosis and suitable treatment according to individual patient characteristics and risk factors.

Keywords: *pneumonia, community-acquired pneumonia, update, guideline*

Introduction

According to the World Health Organization, lower respiratory tract infections are the leading infectious cause of death globally, accounting for 3.5 million fatalities each year. Pneumonia defined as acute inflammation affecting lungs parenchyma, which is caused by pathogen (bacteria, virus, fungi, parasite). When the immune system fails to eliminate a pathogen from the lower airways and alveoli, pneumonia may occur.[1]

According to clinical and epidemiological entity, pneumonia is currently divided into four categories: community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia, and ventilator-associated pneumonia. CAP remains a significant burden in Southeast Asia, particularly in vulnerable populations such as children, elderly, and patients with comorbidities. For instance, in 2017, pneumonia was the second-leading cause of death for children under 5 years old in Indonesia, accounting for 15% of all childhood mortality.[2,3] In general population, case fatality rate (CFR) has been reported up to 7.6% in hospitalized patients.[4] Thus, effective management strategy should be sought to combat the emerging problems regarding CAP based on available high-quality evidence.

Management of CAP

Diagnosis of CAP primarily consists of clinical symptoms and signs with laboratory and radiology examination. Clinical symptoms and signs that may indicate the presence of CAP include cough, changes in sputum characteristics, fever (≥38oC), and dyspnea. Diagnosis of CAP is confirmed with the presence of infiltrate, consolidation, or air bronchogram in chest X-ray, usually in asymmetric lobar distribution. The most common causative agents of CAP are *Streptococcus pneumonia*, atypical bacteria *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae,* with less common bacteria including Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila, and *Moraxella catarrhalis*.[5]

In addition to radiology examination, Gram stain and culture from sputum and culture from blood samples may be required, specifically in hospitalized patients. There are several conditions in which sputum Gram stain and culture as well as blood culture are recommended before treatment, including severe CAP (**Table 1**), empirically treated for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa,* previously infected with MRSA or *P. aeruginosa*, and patients with history of hospitalization with parenteral antibiotics for the last 90 days. The rationale behind pre-treatment Gram stain and culture in some patients were to identify possible resistance prior to antibiotic administration.6 Thus, treatment may be tailored to the patient needs. The duration of antibiotic treatment should be determined based on a reliable assessment of clinical stability, which includes the resolution of abnormal vital signs (such as heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature), the ability to eat, and normal mental state. It is recommended to continue antibiotic therapy until the patient reaches stability, and the treatment duration should not be less than a total of 5 days.[6]

Table 1. Criteria of Severe CAP based on 2007 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS).[7]

Either **one** major criterion or **three or more** minor criteria	
Minor criteria	Major criteria
• Respiratory rate ≥30 breaths/min • Pa_{O2}/Fi_{O2} ratio ≤250 • Multilobar infiltrates • Confusion/disorientation • Uremia (BUN level ≥20 mg/dL) • Leukopenia (WBC count <4,000 cells/μL) • Thrombocytopenia (platelet count <100,000/μL) • Hypothermia (core temperature <36°C) • Hypotension requiring aggressive fluid resuscitation	• Septic shock with need for vasopressors • Respiratory failure requiring mechanical ventilation

Both the American Thoracic Society (ATS) and the British Thoracic Society (BTS) suggest considering both clinical expertise and a validated clinical prediction rule when deciding on the appropriate treatment setting (inpatient or outpatient) for adults with community-acquired pneumonia (CAP). However, they have different preferences for the specific clinical prediction rule to use. The ATS recommends using the Pneumonia Severity Index (PSI) as the preferred choice6, whereas the BTS[8] prefers the CURB-65 tool. The PSI considers various factors such as age, underlying health conditions, vital signs, and laboratory results to evaluate the severity of pneumonia and help determine whether inpatient or outpatient treatment is more suitable. On the other hand, the evidence supporting the effectiveness of the CURB-65 tool as a decision aid in determining the initial treatment location is relatively limited in comparison to the PSI. The level of confidence in its accuracy and reliability is not as robust.[6]

1. Outpatient Settings

In outpatient settings, current recommendation for treatment was primarily depends on presence of comorbidities (including chronic heart, liver, lung, or renal disease; alcoholism; diabetes mellitus; malignancy; or asplenia) or risk factors for MRSA or *P. aeruginosa*. Several risk factors for MRSA include elderly (≥65 years), prior use of beta-lactam antibiotics in the last three months, and immunodeficiency. Risk factors for *P. aeruginosa* infection include patients with bronchiectasis, history of corticosteroid medication >10 mg/day, prior broad-spectrum antibiotic >7 days in the last month, and malnutrition.[4]

In patients without comorbidities or risk factors for MRSA and P. aeruginosa (**Table 2**), standard regimen for empiric treatment includes amoxycillin 1 g three times daily or doxycycline 100 mg twice daily. Macrolide was no longer considered as standard regimen, as it is now should only be considered in cases where local pneumococcal resistance is <25%.6

Table 2. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia).[6]

	Standard Regimen Options	**Dosage**
No comorbidities or risk factors for MRSA or Pseudomonas aeruginosa	Amoxicillin	1 g three times daily
	Doxycycline	100 mg twice daily
	Macrolide (if local pneumococcal resistance is <25%)	- Azithromycin 500 mg on first day then 250 mg daily; **or** - Clarithromycin 500 mg twice daily; **or** - Clarithromycin extended release 1 g daily.
With comorbidities	Amoxicillin/clavulanate or cephalosporin **AND** macrolide or doxycycline	- Amoxicillin/clavulanate 500 mg/125 mg three times daily, **or** 875 mg/125 mg twice daily, **or** 2,000 mg/125 mg twice daily, **or** a cephalosporin (cefpodoxime 200 mg twice daily **or** cefuroxime 500 mg twice daily); **AND** - Azithromycin 500 mg on first day then 250 mg daily, **or** clarithromycin (500 mg twice daily **or** extended release 1,000 mg once daily), **or** doxycycline 100 mg twice daily.
	Respiratory fluoroquinolone (monotherapy)	- Levofloxacin 750 mg daily; **or** - Moxifloxacin 400 mg daily; **or** - Gemifloxacin 320 mg daily.

In patients with comorbidities **(Table 2)**, current recommendations suggested combination therapy using amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline. Monotherapy using fluoroquinolone (e.g., levofloxacin 70 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) can also be used in comorbidities in the outpatient settings. Combination therapy is indicated in comorbidities to achieve adequate coverage, particularly for pathogens that produce beta-lactamase, pathogens with antibiotic resistance, or atypical pathogens commonly found in hospital settings.6 However, the choice of antibiotic regimen should also consider epidemiological studies, as each country may have a different pathogen distribution. For instance, there were concerns regarding high resistance rates of pathogen to penicillin in Asia-Pacific region. Combination of antibiotic regimen, such as amoxicillin/clavulanate, has therefore emerged as the mainstay of therapy even in patients without comorbidities.[9]

Individuals who are suspected to have community-acquired pneumonia (CAP) should be given advice to prioritize rest, stay well-hydrated, and refrain from smoking. Advise patients to seek advice if symptoms do not improve, or worsen, after 3 days of antibiotic therapy.[8]

2. Inpatient Settings

In the inpatient setting, it is recommended that all patients undergoing general management therapy receive appropriate oxygen therapy. This includes monitoring their oxygen saturations and the concentration of inspired oxygen. The goal is to maintain a sufficient level of arterial oxygen tension (Pao2) at a minimum of 8 kPa and an oxygen saturation (SpO_2) between 94% and 98%.[8] It is safe to administer high levels of oxygen to patients who are not at risk of experiencing hypercapnic respiratory failure. Additionally, patients should be evaluated for signs of dehydration and may require intravenous fluids. To prevent venous thromboembolism, it is advisable to consider administering low molecular weight heparins as prophylaxis for all patients who are unable to move around fully.[8]

For hospitalized adults with nonsevere community-acquired pneumonia and no risk factors for MRSA or P. aeruginosa, the recommended empiric treatment options are as follows[6] (**Table 3**):

a) combination therapy with a beta-lactam antibiotic along with a macrolide antibiotic, or

b) monotherapy with a respiratory fluoroquinolone antibiotic (levofloxacin 750 mg daily or moxifloxacin 400 mg daily)

If both macrolides and fluoroquinolones are contraindicated, the alternative option is combination therapy with a beta-lactam antibiotic (ampicillin-sulbactam, cefotaxime, ceftaroline, or ceftriaxone, as mentioned above) and doxycycline 100 mg twice daily.[6] Anaerobic coverage is not recommended for suspected aspiration pneumonia unless there are indications of lung abscess or empyema.10 The use of corticosteroids in adults experiencing nonsevere and severe CAP is also not advised. Nevertheless, it is worth considering the administration of corticosteroids in individuals diagnosed with CAP and refractory septic shock.[6]

The American Thoracic Society (ATS) no longer recommends using the previous classification of healthcare-associated pneumonia (HCAP) to guide the selection of extended antibiotic coverage in adults with CAP. Instead, empiric coverage for MRSA or *P. aeruginosa* in adults with CAP should only be considered if locally validated risk factors for either pathogen are present.[6] For MRSA, empiric treatment options include vancomycin (15 mg/kg every 12 hours) or linezolid (600 mg every 12 hours). For *P. aeruginosa*, empiric treatment options include piperacillin-tazobactam (4.5 g every 6 hours), cefepime (2 g every 8 hours), ceftazidime (2 g every 8 hours), aztreonam (2 g every 8 hours), meropenem (1 g every 8 hours), or imipenem (500 mg every 6 hours).[11] It is advised to continue empiric coverage while collecting culture data if clinicians are providing empiric coverage for MRSA or *P. aeruginosa* in adults with CAP based on published

risk factors but lack local etiological data. This is done to check for the presence of these infections and to support continuing treatment for them after the first few days of empiric medication.[7]

Conclusion

The management of CAP requires a tailored approach, considering epidemiological variations in pathogen distribution. Current guidelines emphasize the importance of accurate diagnosis and appropriate treatment based on patient characteristics and risk factors. The use of corticosteroids and the previous classification of healthcare-associated pneumonia (HCAP) have undergone changes. Empiric coverage for MRSA or P. aeruginosa is advised only in the presence of locally validated risk factors. By implementing these evidence-based recommendations, healthcare providers can enhance the management of CAP and reduce its associated morbidity and mortality.

Table 3. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance.[7]

	Nonsevere inpatient pneumonia		**Severe inpatient pneumonia**	
	Treatment options	Dosage	Treatment options	Dosage
Standard Regimen	β-lactam **AND** macrolide	- Ampicillin + sulbactam 1.5–3 g every 6 hours, **or** cefotaxime 1–2 g every 8 hours, **or** ceftriaxone 1–2 g daily, **or** ceftaroline 600 mg every 12 hours; **AND** - Azithromycin 500 mg daily **or** clarithromycin 500 mg twice daily	β-lactam **AND** macrolide	Antibiotics used and the dosage for each antibiotic are identical to that used for nonsevere inpatient pneumonia.
	Respiratory fluoroquinolone	- Levofloxacin 750 mg daily; **or** - Moxifloxacin 400 mg daily.	β-lactam **AND** fluoroquinolone	
Prior MRSA Respiratory Isolation	Add MRSA coverage*	- Vancomycin (15 mg/kg every 12 h, adjust based on levels); **or** - Linezolid (600 mg every 12 h).	MRSA coverage*	Antibiotics used and the dosage for each antibiotic are identical to that used for nonsevere inpatient pneumonia.
Prior *P. aeruginosa* Respiratory Isolation	Add *P. aeruginosa* coverage**	- Piperacillin-tazobactam (4.5 g every 6 h); **or** - Cefepime (2 g every 8 h); **or** - Ceftazidime (2 g every 8 h); **or** - Imipenem (500 mg every 6 h); **or** - Meropenem (1 g every 8 h); **or** - Aztreonam (2 g every 8 h).	Add *P. aeruginosa* coverage**	Antibiotics used and the dosage for each antibiotic are identical to that used for nonsevere inpatient pneumonia.
Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Add MRSA coverage only if culture results or rapid nasal PCR are positive	- Vancomycin (15 mg/kg every 12 h, adjust based on levels); **or** - Linezolid (600 mg every 12 h).	Add MRSA coverage*	Antibiotics used and the dosage for each antibiotic are identical to that used for nonsevere inpatient pneumonia.
Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*	Add *P. aeruginosa* coverage only if culture results are positive	- Piperacillin-tazobactam (4.5 g every 6 h); **or** - Cefepime (2 g every 8 h); **or** - Ceftazidime (2 g every 8 h); **or** - Imipenem (500 mg every 6 h); **or** - Meropenem (1 g every 8 h); **or** - Aztreonam (2 g every 8 h).	Add *P. aeruginosa* coverage**	Antibiotics used and the dosage for each antibiotic are identical to that used for nonsevere inpatient pneumonia.

*Cultures and nasal PCR should be obtained to facilitate de-escalation of therapy or confirm the necessity of continued treatment

**Cultures should be obtained to facilitate de-escalation of therapy or confirm the necessity of continued treatment. The recommended treatment options mentioned do not include coverage for extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. The consideration for ESBL coverage should be based on patient-specific factors or local microbiological data.

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WHAT'S NEW IN RESPIRATORY VACCINATION

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ABSTRACT

One-third of the annual deaths occurring in the world are thought to be due to infectious diseases. Acute respiratory infections (ARIs) remain one of the most common infectious disease in children, especially those under 5 years old, accounting for millions of episodes of severe acute lower respiratory infections that result in hospital admissions of healthy infants and young children worldwide. According to the World Health Organization (WHO), pneumonia kills more children worldwide than any other disease, even more than acquired immune deficiency syndrome (AIDS), malaria and measles combined. Infectious respiratory diseases such as influenza, COVID-19, and RSV spread from person to person. Etiologic agents associated with acute lower respiratory infections include viruses, bacteria, mycoplasma and fungi. The most common bacterial agent is Streptococcus pneumoniae, *Haemophilus influenzae* and *Staphylococcus aureus.* The other common bacteria is pertussis and the new COVID-19. Viruses cause most cases of bronchitis and bronchiolitis. Respiratory viruses including influenza viruses, respiratory syncytial virus (RSV), human rhino-viruses (HRV), human metapneumovirus (HMPV), parainfluenza viruses, adenovirus (ADV) and human bocavirus (BoV) are responsible for approximately 35–87% of ARIs in children. For some of the responsible pathogens, vaccines are available. There has recently been an increase in the number of available vaccines against respiratory pathogens recommended for children and adolescents. The available Vaccines are *Influenza, Pneumococcal, Pertussis, Haemophilus influenzae, Measles, Varicella , Tuberculosis, COVID-19* vaccines and *the Respiratory Syncytial Virus (RSV).* Vaccination coverage rates must be improved to achieve the full benefits of these vaccines.

Key words: *Acute Lower Respiratory Infections, Bacterial agents, Respiratory Virus, Respiratory vaccination*

TRANSLATIONAL RESEARCH IN CANCER: WHAT IS THE CHALLENGE IN THE FUTURE LUNG CANCER MANAGEMENT ?

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide. Precision medicine in lung cancer management refers to management based on the identifcation of biomarkers. These biomarkers can be biomarkers for screening, for diagnosis or to guide selection of therapies.

Lung screening using low-dose CT Thorax has been shown to reduce mortality by detecting lung cancer in early stage, achieving stage-shift towards early detection, but most evidence was derived from heavy smokers. The efficacy and outcome benefit of lung screening in non-smokers await results from screening trials in this region where non-smoker is a prominent group among subjects with lung cancer. Implementation of lung screening and early detection of lung cancer are still issues in most regions, especially in the Asian Pacific region. The detection and surveillance of incidental lung nodules that may eventually turn into lung cancer remains another issue on lung screening program and respiratory service.

Tumor biopsy as the gold standard for histological diagnosis of lung cancer is often limited by tumor accessibility. Liquid biopsy aiming analysis of circulating biomarkers could act as supplementary source of information to guide diagnosis and management of lung cancer. There are, however, technological and cost challenges to be solved before liquid biopsy could expand its clinical application.

Recent understanding of the molecular pathogenesis support the use of targeted therapies, such as *EGFR*- or *ALK*-tyrosine kinase inhibitors in lung cancer. Newer therapies targeting *KRAS, ROS1, BRAF, RET* and *MET* mutations are beccoming available for use. Immunotherapy alone as a first treatment significantly improved survival for patients with high expression level of PD-L1 on lung cancer cells. Immunotherapy and chemotherapy combined therapy pushed the clinical benefits of immunotherapy further up in lung cancers. Patients who had driver mutations in lung tumors, however, usually show suboptimal therapeutic response to immunotherapy alone. Acquired resistance to targeted therapies remains the major obstacle to long-term maintenance treatment for lung adenocarcinoma patients.

Overall, the management of lung cancer patients are supported in many different steps with biomaker driven management. Further research is, however, still much needed to bridge the knowledge gap and to improve quality-survival in lung cancer patients.

TOWARDS TUBERCULOSIS ELIMINATION POST-PANDEMIC ERA- A GLOBAL ISSUE IN TB ELIMINATION

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ABSTRACT

Tuberculosis remains a highly prevalent disease worldwide and, until April of 2020, had accounted for the highest number of deaths per day worldwide. All over the world there was reallocation of health care workers to fight Covid-19 pandemic; the closure of many tuberculosis outpatient clinics and laboratories; the shortage of laboratory reagents for the diagnosis of tuberculosis and even the shortage of anti-tuberculosis drugs. In a study including 37 tuberculosis centers worldwide, the Global Tuberculosis Network compared the first quarters of 2019 with those of 2020 and concluded that there were reductions in newly diagnosed cases of active tuberculosis and of latent tuberculosis, as well as in the number of outpatient visits with active and latent tuberculosis. It is now important to identify the harms, redefine strategies and get back on the road towards tuberculosis elimination.

According to the 2021 Global TB Report by the World Health Organization (WHO), ten million people developed TB and nearly 1.5 million people died because of TB infection in 2020, and for the first time in a decade, there is an increase in TB-caused deaths. In the last decades, the WHO has deployed a series of global strategies that have since been the backbone of the global fight against TB. In 1995, the Directed Observed Treatment Strategy was introduced, which significantly strengthened the capacity of national programs to diagnose and treat TB cases. Later, the Stop TB Strategy, announced in 2006, was the first of such plans at setting a TB elimination horizon, defined as a reduction of incidence levels under one case per million and year by 2050. A redefinition of the eradication goal took place in 2014 when the previous objective was moved forward to 2035 within the End TB Strategy.

In a recent article *"Tuberculosis: The Unseen Pandemic", Peter Sands, Executive Director of The Global Fund, says that "TB will likely kill more people in low- and middle- income countries in 2023 than COVID-19. Yet it attracts a tiny fraction of the political attention and financial resources we've deployed against the new virus. The Global Fund provides 77% of all financial support to countries fighting TB, or about $800 million per year. This compares to the over 30 billion provided to the same countries to fight COVID-19 via the Access to Covid-19 Tools Accelerator (ACT-A). Despite TB being curable, progress against it is at a snail's pace. Over the last decade, deaths from TB fell 2% per year. Deaths from TB actually increased during the COVID-19 pandemic, as experts, equipment and money were diverted."*

This was in connection with the recent celebration of World TB Day 2023 with the theme- ***"Yes! We Can End TB!"*** We look towards a "global push" to eradicate the disease by 2030 primarily through diagnosis, treatment and the development of a vaccine.

There have been changes in our usual practice to minimize the impact that the Covid-19 pandemic has on tuberculosis. Some of the tools that have been used for years in the fight against tuberculosis, namely masks, physical distancing and molecular diagnosis, are now helpful in the battle against Covid-19. New strategies set up to fight Covid-19 can also be adapted and targeted to fighting tuberculosis: the repurposing of newly created geospatial tracking systems to locate tuberculosis contacts, the use of virtual systems to ensure treatment compliance and the redirection of financial support from Covid-19 patients to tuberculosis patients, prioritizing those living in poverty. Some of the significant good examples on how to maintain the standard of care in the fight against tuberculosis are: 1) education on tuberculosis both for the population and health professionals through virtual conferences, seminars, workshops and 2) community awareness.

Can we eliminate TB? We are faced with a paradigm shift: from TB control to TB elimination.

TB control is classically seen as the strategy aimed at diagnosing and rapidly rendering infectious cases non-infectious, in order to break the chain of transmission. The TB elimination strategy broadens the concept of TB control to identify and treat the pool of latently infected individuals from which future TB cases will be generated. TB elimination, defined as less than one TB case per million population, is seen as a scenario where TB is not eradicated but rather kept at such a low level that it no longer constitutes a public health problem. TB eradication (e.g. the complete disappearance of the disease) is not considered possible considering the dynamic model of its transmission (large "reservoir" of infected individuals, of whom only a low proportion develops the disease) and the absence of a vaccine able to protect all individuals vaccinated.

"Ending TB is not just a public health problem, but a development challenge and opportunity. The goal of the ***WHO Global Tuberculosis Program,*** is a ***world free of TB, with zero deaths, disease and suffering due to the disease.***

The WHO and the European Respiratory Society developed a framework and identified eight core activities to achieve TB elimination in countries at low incidence of TB. These priority action areas are:

1) Ensure political commitment, funding and stewardship for planning and essential services of high quality
2) Address the most vulnerable and hard to reach groups
3) Address special needs of migrants and cross-border issues
4) Undertake screening for active TB and LTBI in TB contacts and selected high risk groups, and provide appropriate treatment
5) Optimize the prevention and care of drug-resistant TB
6) Ensure continued surveillance, program monitoring and evaluation and case-based data management
7) Invest in research and new tools
8) Support global TB prevention, care and control.

The presentation will include a few country experiences and that being implemented in the Philippines.

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FLUID THERAPY MANAGEMENT IN ARDS

Puah Ser Hon

ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) suffers from an inflammatory cascade that promotes exudation into the alveolar spaces, causing ventilation perfusion mismatch and eventually shunting. Fluid therapy has always been a conundrum in intensive care management, in sepsis, requiring fluid boluses while conservative fluids showing better outcomes. Like all aspects of Intensive Care Unit (ICU) care, most studies on treatment have produced variable results. The ROSE (Resuscitation phase, Optimization phase and Stabilization and Evacuation phases) Concept may provide some insights on the different phases of ARDS management. The future of ICU management will likely be gearing towards personalized care. It is important to know when fluids will benefit patients and the modalities that are sensitive and specific to help make these decisions.

ANTIVIRAL AGENT FOR SARS-COV-2 IN HIGH-RISK PATIENTS

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ABSTRACT

The emergence of SARS-CoV-2 has led to a global pandemic, with high-risk patients being particularly susceptible to severe illness. Antiviral agents can effectively stop viral reproduction and halt the disease progression towards a more severe stage. Reduced rate of hospitalization and mortality has been observed in trials involving these medications, which is of great value for this particular population. This paper reviews the characteristics of patients in high risk of severe COVID-19 and the latest updates on antiviral agents available for this particular population compiled from several guidelines and reviews. Older adults, people with underlying medical conditions, poor living conditions, and others further described in the paper are the population with a higher risk of severe illness from COVID-19. Certain drugs, like Nirmatrelvir-Ritonavir (Paxlovid), have been in extensive clinical trials and are strongly recommended. Other drugs like Molnupiravir have been found to be inferior to Paxlovid. Newly developed monoclonal antibodies have also been greatly studied. In conclusion, this paper underlines the clinical importance of early identification of high-risk COVID-19 cases, the emphasis on timely administration of appropriate and adequate antiviral agents, and the ever increasing need of further research on the safety and efficacy of antiviral drugs.

Keywords: *antiviral, COVID-19, SARS-CoV-2, high-risk*

Introduction

It has been 4 years since the World Health Organization (WHO) announced the global pandemic of coronavirus disease 2019 (COVID-19).[1] The fight against the virus has come in waves of different variants, with differences in rates of transmission and mortality. The latest widespread variant of concern, Omicron (B.1.1.529), has led researchers to identify certain clinical characteristics of patients with increased risk of severe illness that may lead to intensive care and mortality. One of the most crucial aspects of COVID-19 prevention is the identification of these high-risk populations.

The rapid development of vaccines has been a significant advance in the battle against COVID-19. However, patients at high risk for adverse reactions or with possible low levels of antibody production might not be able to rely on vaccines. Instead, such patients need a variety of therapeutic interventions suitable to the severity of their illness.2 Antiviral agents play a crucial role in COVID-19 management by reducing the viral load in infected individuals. These drugs can effectively stop SARS-CoV-2 reproduction and stop the disease from progressing to a more severe stage.[3] The timing of antiviral medication administration has been extremely important. The general impact that COVID-19 can have on the healthcare system is lessened by the ability to manage SARS-CoV-2 infection without the requirement for hospital admission thanks to oral antiviral medications.[2,3]

High-risk patients in COVID-19 cases

Several guidelines have dictated different definitions of high-risk patients for COVID-19. Generally, high-risk patients can be defined as those at higher likelihood of getting infected and transmitting the infection such as healthcare workers, and those for whom the infection, if acquired, has a higher likelihood of causing severe disease or death.4 As the pandemic progresses through different phases, we have been introduced to several different definitions of COVID-19 disease severity. The latest living guideline of COVID-19 clinical management simplified the stages to non-severe, severe, and critical disease.[5] There are groups of people that are more likely to progress to severe/critical clinical manifestation when they contracted COVID-19, which is mainly described as the high-risk population.

CDC explained that older adults are at a higher risk to be hospitalized, in need of intensive therapy, need a ventilator to help them breathe, or die. Deaths from COVID-19 affect adults over 65 in more of 81% of cases. Deaths among those over 65 are 97 times more common than those between the ages of 18 and 29. As a person's number of underlying medical issues rises, so does their risk of developing a serious illness from COVID-19. Because of their residence or place of employment, or because they lack access to healthcare, some people are also more likely to contract COVID-19 and become seriously ill or pass away. This includes a significant number of people with disabilities and members of racial and ethnic minorities.[6]

Age

Age continues to be the strongest risk factor for serious COVID-19 outcomes, with the likelihood of serious outcomes rising sharply with age. The risk of death is 25 times higher in people aged 50 to 64, 60 times higher in people aged 65 to 74, 140 times higher in people aged 75 to 84, and 340 times higher in people aged 85 and over, according to data from the National Vital Statistics System (NVSS) at NCHS (Table 1)7. Notably, all deaths that occurred in the United States throughout the pandemic, from February 2020 to July 1, 2022, are included in these numbers, even those of those who were not immunized.

Table 1. Age group rate ratios compared to ages 18-29 years old.[7]

Rate compared to 18-29 years old	0-4 yrs	5-17 yrs	18-29 yrs	30-39 yrs	40-49 yrs	50-64 yrs
Hospitalization	0.7x	0.2x	Reference group	1.5x	1.8x	3.1x
Death	0.3x	0.1x	Reference group	3.5x	10x	25x

People with specific underlying medical disorders and those who are 50 years of age or beyond are at a greater risk of experiencing severe outcomes, with the risk increasing significantly at ages >65 years.4,5 Long-term care facility residents, who make up less than 1% of the US population but are responsible for more than 35% of all COVID-19 deaths, are likewise at higher risk.[7]

Race and Ethnicity

Racial, cultural, and socioeconomic differences in COVID-19 diseases, hospitalizations, and fatalities have been brought to light by the COVID-19 pandemic. Several obstacles, such as a lack of insurance, transportation, child care, or the capacity to take time out of work, are more likely to be present for some racial and ethnic minority groups when trying to get health care.[7]

Studies have found racial and ethnic variations in the usage of at-home COVID-19 tests, vaccine coverage, and access to outpatient treatments.[6] Estimates of COVID-19 mortality in the U.S. reveal that people from racial and ethnic minority groups are dying from COVID-19 disproportionately and deaths are occurring earlier in these groups. People in racial and ethnic minority groups may be more likely to have several medical diseases and are frequently younger when they first develop chronic medical conditions.[6,7] Once infected, members of racial and ethnic minority groups have higher hospitalization rates, ICU admission rates, and COVID-19 mortality rates at younger ages.[7]

Underlying Medical Conditions

Patients who have several specific underlying medical conditions are also at a higher risk of progressing into severe clinical manifestation. The list of underlying medical conditions that increase a person's chance of developing a serious illness from COVID-19 is based on evidence. The three categories are higher risk, suggestive higher risk, and mixed evidence conditions.[7]

Table 2. Summary of underlying conditions and their risks.[7]

Higher Risk (conclusive)	• Asthma
	• Cancer
	  ○ Hematologic malignancies
	• Cerebrovascular disease
	• Chronic kidney disease
	  ○ People receiving dialysis
	• Chronic lung diseases limited to:
	  ○ Bronchiectasis
	  ○ COPD (Chronic obstructive pulmonary disease)
	  ○ Pulmonary embolism
	  ○ Pulmonary hypertension
	  ○ Interstitial lung disease
	• Chronic liver diseases limited to:
	  ○ Cirrhosis
	  ○ Alcoholic liver disease
	  ○ Non-alcoholic fatty liver disease
	  ○ Autoimmune hepatitis
	• Cystic Fibrosis
	• Diabetes mellitus type 1 and type 2
	• Heart conditions (such as heart failure, coronary artery disease)
	• HIV (Human immunodeficiency virus)
	• Obesity (BMI > 30 kg/m^2)
	• Primary immunodeficiencies
	• Patient receiving transplantation
	• Tuberculosis

Suggestive Higher Risk	• Children with underlying conditions • Overweight (BMI >= 25 kg/m^2 but <30 kg/m^2) • Sickle cell disease
Mixed Evidence (inconclusive)	• Alpha 1 antitrypsin deficiency • Bronchopulmonary dysplasia • Hepatitis B, Hepatitis C • Hypertension • Thalasemia

Living Conditions

People who live in armed group-controlled regions, refugees, asylum seekers, and those who are homeless and stateless face more severe effects (restricted access to secure employment prospects, secure housing, sanitary facilities, and health treatment).[8] People with disabilities are also more likely than people without disabilities to live in communal (also known as "congregate") settings, have chronic health concerns, and encounter greater obstacles when trying to get medical care. According to studies, some individuals with particular disabilities are more prone to develop COVID-19 and have negative effects.[6]

Antiviral agents

The fundamental problem with antiviral treatments is that they must be started as soon as the illness is contracted in order to effectively stop viral replication; delayed treatment may not be as successful as the clinical studies indicated.[9] All drugs listed below have been either approved or listed for Emergency Usage Approval (EUA) by the U.S. Food and Drug Administration (FDA).

a. Nirmatrelvir-Ritonavir

In January 13th, 2023, WHO living guidelines for therapeutics strongly recommended treatment with Nirmatrelvir-Ritonavir (Paxlovid) on non-severe patients with highest risk of hospitalization.[5] A meta-analysis concluded that Paxlovid effectively reduced hospitalization rate of confirmed COVID-19 cases by 68%.10 The recommended dose for Nirmatrelvir-Ritonavir is 300 mg (two 150 mg tablets) of Nirmatrelvir and 100 mg of Ritonavir every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation. In renal insufficiency (GFR 30–59 mL/min), the dose is reduced to 150 mg of Nirmatrelvir and 100 mg of Ritonavir every 12 hours daily for 5 days. Administration should be as early as possible in the time course of the disease. For non-severe patients with low risk of hospitalization, Paxlovid is not recommended.[5]

b. Remdesivir

Remdesivir, previously a drug developed for Hepatitis C, is conditionally recommended for patients with non-severe COVID-19 and high-risk of hospitalization by the WHO living guideline. Treatment with Remdesivir benefits patients with decreased rate of hospitalization (73 fewer hospitalizations per

1000 cases) along with little to no serious adverse effects of drug usage.[5] Latest meta-analysis stated that Remdesivir offers a high probability of mortality reduction in patients requiring oxygen therapy but not yet ventilated.[11] One of the justification that it is comparably inferior against Nirmatrelvir-Ritonavir is because Remdesivir has to be administered intravenously. The recommended dose is one dose daily for 3 consecutive days, given as 200 mg intravenously on day 1, followed by 100 mg intravenously on days 2 and 3. Remdesivir is not recommended on other severity of diseases. It offers minimal benefits on severe to critical cases and the harm outweighs the benefits in low-risk non-severe cases.[5]

c. Molnupiravir

Molnupiravir has been conditionally recommended for non-severe, high-risk of hospitalization COVID-19 since March 2022. It is considerably inferior to Paxlovid from its unavailability of long-term drug safety data.[5] This is thought to come from Molnupiravir's unique mechanism of action; it works by mutating the virus to kill itself.12 Molnupiravir reduced 60 cases of hospitalizations per 1000 patients. It is recommended to administer Molnupiravir in one 800 mg tablet twice daily for 5 days. No significant benefit was observed with Molnupiravir in severe COVID-19.[5]

d. Lopinavir-Ritonavir

The recommendation in the current living guideline and in BMJ strongly against the use of lopinavir-ritonavir in COVID-19 patients with any disease severity and any duration of symptoms. The GDG panel found that there are no improved outcomes that are significant to patients such as need for mechanical ventilation, reduced mortality, time for clinical improvement and others. Subgroup analysis was done and the result indicated no effect modification based on age (comparing those aged <70 years versus those older) or severity of illness (comparing severe/non-severe vs critical or non-severe vs severe/critical). More to that, in patients with untreated or undiagnosed HIV, uses of lopinavir-ritonavir alone may promote resistance to important antiretrovirals.[5]

e. Favipiravir

Favipiravir is a repurposed drug originally designed for use against resistant influenza in Japan back in 2013.[13] Several countries have included the use of Favipiravir in their guidelines against COVID-19, including Indonesia since May 2020.[14] The justification of this inclusion was the widespread availability of the drug, well-known safety profile, and the emergency of the situation in related countries. Numerous clinical trials have been done to compare the efficacy against other drugs, and a systematic review revealed Favipiravir has no close to no benefits on reducing fatality rate or the use of mechanical ventilation.[15] Most guidelines recommend against the use of Favipiravir in any disease severity of COVID-19 as it has virtually no benefit.[16,17]

Monoclonal antibodies

An antibody is a protein that binds to an antigen, a different protein, to join the immune system and kill tumor cells. Similar to convalescent plasma guarding against severe acute respiratory syndrome, monoclonal antibodies are synthetic proteins that aid in neutralizing pathogenic pathogens. Hence, monoclonal antibodies are a part of therapeutic strategies that prevent viral invasion by binding to the viral spike protein and angiotensin-converting enzyme 2 (ACE2) receptors. For instance, monoclonal antibodies are administered intravenously in the case of COVID-19 and function similarly to the immune system.[18]

Clinical studies have demonstrated the efficacy of monoclonal antibodies (mAbs) against the SARS-CoV-2 spike protein in the management of SARS-CoV-2 infection. However, laboratory research has shown that anti-SARS-CoV-2 mAb efficacy against various subvariants and variations might vary significantly. These medications are therefore not anticipated to be efficient COVID-19 therapies or preventives in regions where the circulating variants and subvariants are mAb-resistant.[19]

a. Casirivimab and imdevimab

Casirivimab and imdevimab are two human antibodies. Their mechanism of action is by binding to the SARS-CoV-2 spike protein and demonstrated antiviral activity in animal trials. Studies about the pharmacokinetic of these antibodies in patients with non-severe COVID-19 show that antiviral concentration against pre-Omicron variants are maintained and achieved for at least 28 days after intravenous administration at a total dose of 1200 mg (600 mg each) or above. These concentrations are also maintained and achieved using a subcutaneous route at a total dose of 1200 mg for prophylaxis in uninfected individuals. Regardless of those studies, new reports have demonstrated that in vitro neutralization is dramatically reduced or lost for casirivimab-imdevimab.5

In the previous living guideline, a conditional recommendation was provided regarding the use of the neutralizing antibodies casirivimab-imdevimab for patients with severe and critical illness with seronegative status and for non-severe COVID-19 patients at highest risk of hospitalization. Following the currently circulating SARS-CoV-2 variants and subvariants now dominating the world (such as omicron), and availability of in vitro data demonstrating that casirivimab-imdevimab has a very diminished neutralization activity to variants of SARS-CoV-2 and their sub variants, the GDG made a strong recommendation not to use casirivimab-imdevimab for all COVID-19 patients in the 13th guideline. A consensus was made regarding the reduction of in vitro neutralization suggests absence of clinical effectiveness of monoclonal antibodies such as casirivimab-imdevimab and sotrovimab.5

b. Sotrovimab

Sotrovimab (VIR-7831) is a single human monoclonal antibody. Its mechanism of action is binding to a conserved epitope of the SARS-CoV-2 spike protein thus preventing the virus from entering human cells. On the basis of clinical trial evidence, in the 8th version of the living guideline, GDG previously made a conditional recommendation for use of sotrovimab in non-severe patients at highest risk of hospitalization. At the time, the panel acknowledged that the emergence of new SARS-CoV-2 variants might reduce the clinical effectiveness of sotrovimab. The change in recommendation in the previous guideline was triggered by new evidence demonstrating that it has very diminished in vitro neutralization activity against currently circulating SARS-CoV-2 sub variants. In the latest version of the guideline, the incremental evidence supports the change in recommendation to strongly against the use of sotrovimab (and casirivimab-imdevimab) to the current SARS-CoV-2 ecology.5

Conclusions

This review emphasizes the significance of early identification and treatment of high-risk populations related to COVID-19. These groups, including older individuals, certain races and ethnicities, and those with

underlying medical conditions, are more susceptible to severe disease and complications. It is crucial to prioritize them in therapeutic interventions.

Promising therapeutic agents discussed in this review include antiviral agents like Paxlovid, remdesivir, molnupiravir, and lopinavir-ritonavir, as well as monoclonal antibodies such as casirivimab, imdevimab, and sotrovimab. While Paxlovid has been strongly recommended due to its robust antiviral activity and promising clinical data, it is important to acknowledge the role of other drugs in addressing different aspects of the disease. Ongoing research is necessary to fill knowledge gaps regarding the long-term safety and efficacy of these drugs, particularly among high-risk cases. By continually adapting and evolving treatment strategies based on new data and the evolving pandemic landscape, the aim is to protect the health and well-being of high-risk populations. We aim to inspire continued research and discussion in the ongoing pursuit of effective therapeutic agents against COVID-19.

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RESPIRATORY MANAGEMENT OF NEUROMUSCULAR PATIENTS

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ABSTRACT

Recently, the American College of Chest Physicians published an evidence-based guideline for best practices in the respiratory management in NMD (1). These guidelines made a number of recommendations including 1) the need for regular pulmonary function testing to assist with management decisions; 2) the use of polysomnography in symptomatic patients with normal oximetry; 3) the use of NIV for those with respiratory failure; 4) the importance of individualising NIV therapy; 5) the role of invasive ventilation for those failing NIV; 6) anti-cholingeric medications as first line therapy for those developing sialorrhea, and 7) the use of lung volume recruitment techniques to aid in airway clearance with the addition of mechanical cough assist if simple techniques prove ineffective.

The timing and extent of intervention will vary depending on the individual's primary underlying disease process, the pattern of respiratory muscle involvement and comorbid conditions. Respiratory care involves assessment and management of inspiratory muscle weakness by providing ventilatory support, when and if indicated. However, attention to issues arising from expiratory and upper airway muscle dysfunction are also necessary to provide comprehensive care for these individuals. Severe sialorrhea (excessive saliva) is a distressing but common problem for many with a neuromuscular condition. In addition to the social consequences of this condition, it also places the patient at increased risk of aspiration. Pharmacotherapy is commonly used, although the evidence base is limited.

In considering respiratory management for people with neuromuscular disorders, the need for shared decision-making about various interventions is necessary. Decisions around care options will need to incorporate patient preferences, burdens on the family, treatment goals and quality of life. Furthermore, as highlighted by the authors of these recent guidelines (1), the extent to which these clinical practice recommendations can be implemented will depend greatly on local resources and healthcare structure. More work is needed in lower resourced countries to identify how these recommendations can be implemented (2) and what modifications can occur without compromising care.

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PEDIATRIC RESPIRATORY EMERGENCIES

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ABSTRACT

Pediatric respiratory emergencies can result from severe respiratory distress or imminent respiratory failure. A high index of suspicion is necessary for prompt diagnosis and treatment. This review discusses the emergency recognition and management of common acute-onset conditions that can rapidly progress to airway compromise, obstruction, and respiratory failure.

Introduction

Respiratory emergencies are the most common causes of cardiopulmonary arrest in pediatric patients. To obtain the best possible outcomes in critically ill pediatric patients with respiratory emergencies, prompt recognition, standard assessment, and expert management based on clinical evidence are necessary. However, large variations in body size and respiratory maturity have contributed to a lack of clinical evidence supporting the daily practice of pediatric respiratory care. Most of what we do for critically ill children is based on personal experiences or how they work as adults. Therefore, pediatric critical care practitioners should understand the specific anatomical and physiological characteristics of children that are distinct from those of adults to fill the knowledge gap between children and adults, and provide respiratory care suitable for pediatric patients with respiratory emergencies based on clinical evidence in adults.

There are several potential causes of respiratory emergencies in children, including infections, inflammatory and allergic processes, foreign body obstruction, and trauma. This review discusses the emergency recognition and management of common conditions presenting with an acute onset, considering the differences between children and adults.

Anatomical and physiological characteristics of children in respiratory system [1)]

Children exhibit age-related variations in body size and physiological variables, depending on their development and growth. As for the respiratory system of children, physiological function develops to the equivalent level of that of adults in almost 2 years after birth, and the anatomical size increases to the equivalent level as that of adults from a school child to the adolescent period.

Young children have proportionally larger heads, prominent occiputs, and relatively lax cervical support, which increases the likelihood of airway obstruction in the supine position. A relatively large tongue compared to a small oropharynx further contributes to this problem. Moreover, the respiratory system in children younger than 2 years of age has the following characteristics: easy airway obstruction, low functional residual capacity per body weight, high respiratory system compliance and resistance, and an immature respiratory control system. Younger children with respiratory emergencies should be carefully assessed and treated because they have a higher frequency of respiratory emergencies and can easily developed more serious conditions than the other age groups.

General Assessment Skills and Management

Not all pediatric patients with respiratory emergencies appear acutely ill and should be treated as if they have a potentially life-threatening event. Although there are many specific causes of respiratory emergencies in children, certain basic principles of assessment and management can be applied universally. When treating suspected respiratory emergencies, it is important to evaluate and manage them systematically. The systematic approach algorithm recommended by Pediatric Advanced Life Support [2] is shown in Figure 1.

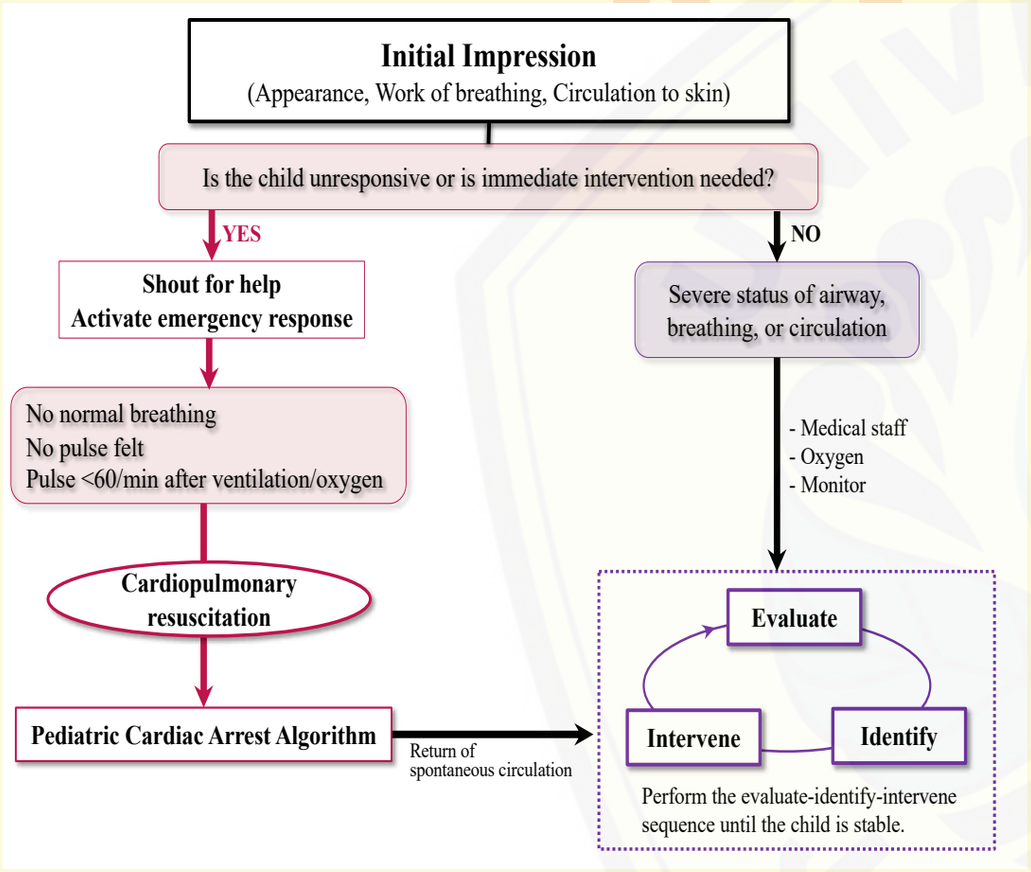

Figure 1. Pediatric systematic approach algorithm by Pediatric Advanced Life Support [2]

The initial impression of appearance, work of breathing, and circulation to skin helps to answer the following question: "is the child unresponsive with no breathing or only gasping?" The left-hand side of the algorithm leads to a Pediatric Cardiac Arrest algorithm. The right-hand side of the algorithm represents the effective treatment of pediatric patients. It is important to prevent cardiopulmonary arrest by using an evaluation-identifying-intervention Sequence.

Part 1-Sequence: Evaluate

The evaluation portion of the sequence comprises three assessment tools: primary, secondary,

and diagnostic tests. The primary assessment consisted of the ABCDE approach, which evaluates Airway, Breathing, Circulation, Dysfunction of central nervous system, and Exposure & environment. We should always begin with basic life support airway/breathing management because airway urgencies can quickly progress to airway emergencies. The secondary assessment consisted of a focused history and physical examination. Diagnostic tests, including arterial blood gas, radiography, and laboratory blood tests, can help to identify the cause of pediatric emergencies.

Part 2-Sequence: Identify

Identifying the causes of pediatric emergencies is essential for improving patient outcomes. Specific problems relating to respiratory emergencies should be reviewed thoroughly. Identification of the cause of the dysfunction may be determined from the history and physical examination and can dictate specific treatment.

Part 2-sequence: Intervene

The degree of respiratory dysfunction drives the treatment priorities. Interventions for treating patients with respiratory emergencies include both general and specific interventions.

Once this evaluation-identifying-intervention Sequence is complete, the sequence should be carried out repeatedly until pediatric patients are stable.

Signs/symptoms and management of children with respiratory emergencies

Many pediatric respiratory emergencies can progress rapidly and become life threatening. Pediatric practitioners must maintain a high index of suspicion and make a rapid and precise diagnosis, often based solely on the patient's signs and symptoms, brief history, and/or limited examination. In respiratory emergencies, appropriate treatment must be implemented immediately.

Tachypnea is one of the earliest objective signs of respiratory emergency in children. Unfortunately, this important clinical clue may be missed by physicians who are unfamiliar with pediatric respiratory patterns or age-related vital signs. Therefore, it may be effective to prepare a list that shows the normal range of vital signs according to pediatric age for accurate and prompt evaluation. Moreover, under normal conditions, breathing in newborns and infants should be effortless, even at higher respiratory frequencies. Accessory respiratory muscles and nasal flaring contributes to the evaluation of respiratory emergencies in children.

Stridor is also a common sign of upper airway obstruction and warrants prompt investigation. Stridor suggests upper respiratory tract problems, such as croup, anaphylaxis, and inhaled foreign bodies. Further progression of lower airway obstruction can lead to biphasic respiratory murmur, such as stridor and wheezing. Wheezing suggests lower respiratory tract problems, such as allergy, asthma, inhaled foreign bodies and/or aspiration pneumonia, bronchiolitis, and pneumonia.

Fine crackles indicate inflammation in smaller airways, whereas coarse crackles indicate branchial involvement. If there are voluminous secretions, inspiratory crackles are usually

audible; however, expiratory crackles can also be audible. Bronchiolitis causes bilateral, fine- ended inspiratory crackles, whereas pneumonia causes uni- or bilateral coarse crackles.

Cyanosis is a late sign consistent with impending respiratory failure. Therefore, although the presence of cyanosis requires immediate attention and intervention, its absence should not be considered a sign of stability in children presenting with other symptoms of respiratory failure.

Regardless of stability, we must evaluate the detailed history of fever, cough, exposure to allergens, concomitant illnesses, or trauma, as well as the onset and duration of the presenting signs and symptoms. Unstable pediatric patients must be treated rapidly with emergency airway stabilization and should receive the highest priority. Spontaneously breathing children should be offered supplemental 100% oxygen in a nonthreatening manner, keeping them as calm as possible while preparing for definitive treatment. Non or weak spontaneously breathing children must be ventilated with a combination of the bag-valve-mask technique and proper head positioning (slight neck extension, chin lift, and jaw-thrust maneuvers). Suction, pulse oximetry, and ECG monitor are strongly recommended during evaluation and treatment.[2,3)]

Figure 1 shows specific management according to the type of pediatric respiratory emergencies. [3)] According to the disease-specific condition using the tape of respiratory emergencies, each management shown in figure 1 should be carried out as the first choice.

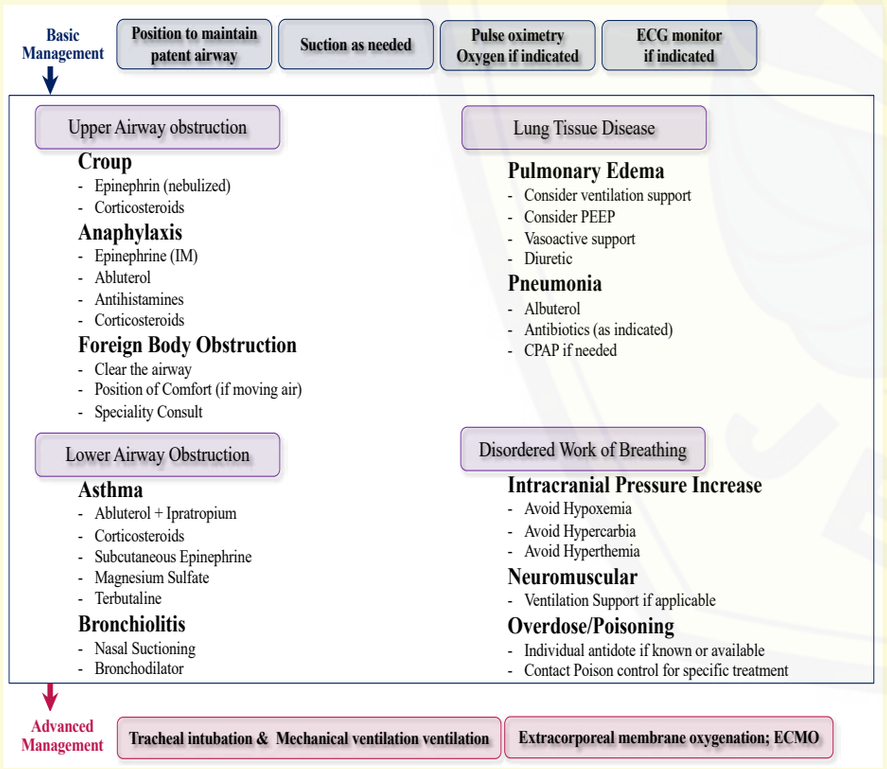

Figure 2. Management of pediatric respiratory emergencies by type [3)]

When pediatric patients have a poor response after disease-specific management, assessment should be largely clinical as the signs of impending respiratory failure to severe respiratory distress should be identifiable without the need for blood gas analysis and should prompt an intervention, either noninvasive or invasive ventilation. The intubation must be determined on a case-by-case basis, considering the cause of respiratory distress, predicted airway diffculty, equipment and available medical staff, and risk of aspiration. Monitoring, including end-tidal carbon dioxide, should be conducted in advance. Thought must be given to the most appropriate medical staff to lead the intubation, and expert help should be called where necessary.

Preoxygenation of the lungs is invaluable, if achieved. It may be most appropriate to continue the mode of delivery of oxygen currently in place in settled children, as disturbing them with a tight-fitting face mask may cause distress and increased breathing work and oxygen demand. Considering the potential inability to preoxygenate, increased oxygen consumption, and closing capacity in small children, the tolerated duration of apnea before desaturation is low. Oxygenation must remain the priority, and most would advocate continued gentle mask ventilation whilst waiting for adequate neuromuscular block regardless of fasting status.[5)] In adult practice, the introduction of transnasal humidified rapid-insu ation ventilatory exchange (THRIVE) using high-flow nasal cannule during apnea has allowed a significant increase in apnea times before oxygen desaturation. THRIVE is beginning to be used in pediatric practice with promising results in case reports, and so is an option to prolong apnea time in carefully selected pediatric patients, if the equipment is available.[6)]

When tracheal intubation is performed, straight laryngoscope blades are generally used in babies aged up to 6 months, and curved blades thereafter. Tracheal tube size and length were calculated using the following standard formulae: [4)]

- Sizes for cuffed tracheal tube:
  >3 kg up to 1 year: start with size 3.0 mm
  1–2 years: start with size 3.5 mm
  >2 years: (age/4) +3.5 mm
- Size for uncuffed Tracheal tube:
  <1 year: 1 kg: size 2.5 mm 2 kg: size 3.0 mm
  >3 kg: size 3.5 mm
  >1 year (age/4) +4 mm
- Depth of tracheal tube:
  (Age/2) + 12 cm
  Or internal diameter of tracheal tube size × 3

After intubation, ventilation strategy must be considered: [7,8)] there is a much smaller evidence base for specific ventilation strategies compared with adults, but the trend is towards a “lung- protective strategy” with the aim of achieving adequate gas exchange at the lowest possible pressures and volumes to avoid alveolar trauma secondary to stretching.

Prone positioning can be considered an option. It has been shown to decrease mortality in adult patients with acute respiratory distress syndrome but has yet to be shown in pediatric patients. The mechanism of action is thought to be the recruitment of previously collapsed dorsal areas of the lung and subsequent

improvement in ventilation/perfusion matching.[9] Before using this technique, the potential hemodynamic effects of the prone position, potentially catastrophic loss of a secured airway, and any predicted difficulty in securing the airway while maintaining oxygenation must be considered.

Extracorporeal membrane oxygenation (ECMO) is considered in cases where there is borderline or inadequate gas exchange with a high risk of ventilator-induced lung injury (mean airway pressure >20–25 cmH_20) and continued severe respiratory failure (PaO_2/F_1O_2 ratio <60–80 or oxygen index>40), despite less invasive treatments, such as those mentioned previously. It confers a survival advantage in neonates with respiratory failure and remains an option in pediatric respiratory failure. A recent small paired cohort study confirmed this and highlighted the need for further research on the benefits of ECMO, which remains an expensive and invasive treatment option.[10]

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ULTRASOUND IMAGING IN RESPIRATORY EMERGENCY

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ABSTRACT

Point of care ultrasound (POCUS) should be a routine part of assessment in the patient with a respiratory emergency. An immediate evaluation of the heart and lungs will answer many urgent clinical questions and set the patient on the right management pathway. Echocardiography will evaluate the heart's role in respiratory distress while the complementary lung ultrasound will help define the pathophysiological processes in the lung, the "end organ". Ultrasound also serves as a safety tool for invasive emergency procedures, such as thoracostomy, central line placement and endotracheal intubation. The FALLS protocol, using lung ultrasound, is very useful in setting the limits for fluid resuscitation in a critically ill patient.

SIMPLE APPROACH IN ACHIEVING ASTHMA CONTROL WITH PROACTIVE REGULAR DOSING (PRD)

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ABSTRACT

Asthma is heterogenous disease, usually characterize by chronic inflammation airway. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. When we looked at asthma we can picture it as iceberg where the tip of iceberg is something that we can see it clearly such as symptoms and exacerbations, while the underlying cause is chronic inflammation which resulted in bronchial hyperactivity and airway remodelling. On Managment asthma, we can also see 2 approach, PRD ICS/LABA with SABA as needed and MART-maintenance and reliever therapy. PRD is asthma management strategy with objective achieving asthma control proactively, mainly controlling symptoms and reduce exacerbations using regular dose ICS or ICS/LABA. First PRD treatment, using GOAL study as landmark we can see evidence of asthma control achievement using PRD regimen in asthma patient. PRD ICS/LABA also have data showing achievement of total control- control criteria that require patient to have no symptoms and no use of reliever for the last 4 weeks which stringent than GINA well control criteria. In addition, PRD also shows benefit in improving quality of life using AQLQ measurement and exacerbation reduction. MART also have their own benefits, using data from Rabe at el, we can see benefits of using MART regimen on reducing exacerbations in asthmatic patients. When we look at number of asthma control patient, we can see PRD approach resulting in more patient achieving controlled asthma. Last point, using latest modelling study data, we can see how PRD method on benefit/risk ratio. Use of PRD with salmeterol/fluticasone results in better benefit/risk ratio than other method on moderate- severe asthma management.

In summary, use of PRD regimen can help asthmatic patient achieve reduction in symptoms and exacerbations, improvement lung function and long term improvement in airway responsiveness.

Key words : *PRD, ICS-LABA, MART*

LUNG ASPECT IN GUT LUNG AXIS

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INTRODUCTION

Recent advances in microbiota explorations have led to an improved knowledge of the communities of commensal microorganisms within the human body. Human skin and mucosal surfaces are associated with rich and complex ecosystems (microbiota) composed of bacteria (bacteriobiota), fungi (mycobiota), viruses (virobiota), phages, archaea, protists, and helminths (Cho and Blaser, 2012). The role of the gut bacteriobiota in local health homeostasis and diseases is being increasingly investigated, but its long-distance impacts still need to be clarified (Chiu et al., 2017). Among the relevant inter-organ connections, the gut–lung axis (GLA) remains less studied than the gut–brain axis. So far, microbiota studies mainly focused on the bacterial component, neglecting However, the understanding of mycobiota involvement in human health and inter-organ connections should not be overlooked (Nguyen et al., 2015; Enaud et al., 2018). Viruses are also known to be key players in numerous respiratory diseases and to interact with the human immune system, but technical issues still limit the amount of data regarding virobiota (Mitchell and Glanville, 2018). Therefore, we will focus on bacterial and fungal components of the microbiota and their close interactions that are able to shape local or longreached host responses within the GLA. While GLA microbiota also influences chronic gut diseases such as IBD, we will not address this key role in the present review: we aimed at analyzing how lung and gut bacteriobiota and microbiota influence each other, how they interact with the human immune system, and their role in respiratory diseases.

THE CONCEPT OF GUT-LUNG AXIS

The gut and lungs are anatomically distinct, but potential anatomic communications and complex pathways involving their respective microbiota have reinforced the existence of a gut–lung axis (GLA). Compared to the better-studied gut microbiota, the lung microbiota, only considered in recent years, represents a more discreet part of the whole microbiota associated to human hosts (Raphaël Enaud, 2020).

Microbiota plays a critical role in maintaining the homeostasis of the colonized organs or tissues. However, more and more studies found that the local microbiota changes could influence the immunity at the distal tissues, especially the interaction between the intestinal tract and respiratory tract (Budden et al., 2017; Schleiermacher and Hoffmann, 2007; Trompette et al., 2014) Increasing evidence shows that the complex interactions between the intestinal microbiota and host immune system are important not only for the intestinal local but also for other organs or tissues. Dysbiosis of the intestinal microbiota is linkage to the pathogenesis and progression of chronic lung diseases, such as asthma. (Arrieta et al., 2015; Kozakova et al., 2016; Liu and Marc Rhoads, 2016).

The balance of interactions between microbiota, nutrients, and broad host cells has physiological effects in metabolic processes, barriers, and trophic functions. (Id CAW et al.,2022) Infectious conditions occur due to the production of toxins produced by bacteria that invade the mucosa of the gastrointestinal tract (Yang W et al., 2022)

INTERACTIONS BETWEEN THE GUT AND LUNGS

The epithelial surfaces of the GIT (gasto intestinal tract) and respiratory tract are exposed to a wide variety of microorganisms; ingested microorganisms can access both sites and the microbiota from the GIT can enter the lungs through aspiration. Both the gut and respiratory mucosa provide a physical barrier against microbial penetration, and colonization with the normal microbiota generates resistance to pathogens; for example, through the production of bacteriocins (Buffie, C. G et al., 2013). Furthermore, a rapidly expanding collection of commensal gut bacteria, including segmented filamentous bacteria (SFB), Bifidobacterium spp. and members of the colonic Bacteroides genus, induce the production of antimicrobial peptides, secretory immunoglobulin A (sIgA) and pro-inflammatory cytokines.

Immune homeostasis is dependent on a microbiome that provides cues, including microbial components and metabolites, for appropriate maturation and priming of the immune system. (Rooks, M. G. & Garrett, W. S.,2016) In humans, environmental factors, such as diet, antibiotic treatment, and stress can shift the gut microbiota towards decreased abundance of beneficial bacterial species accompanied by outgrowth of pathogenic ones. This perturbation in microbial composition and function, referred to as dysbiosis, disrupts tissue and immune homeostasis and is associated with diverse inflammatory diseases within and outside the gastrointestinal tract (Shreiner, A. B., et al., 2015) Although most evidence indicates the primary direction of cross-talk occurs from the gut to the lung, there remains the possibility of communication in the opposite direction. Chronic lung disorders, such as asthma, COPD, and cystic fibrosis (CF) exhibit not only a dysbiotic airway microbiota but also components of gastrointestinal perturbation such as IBS (irritable bowel syndrome). Moreover, respiratory influenza infections in mice can indirectly induce intestinal immune injury and alter the intestinal microbiota. The resulting gut dysbiosis promotes inflammation through the outgrowth of Enterobacteriaceae and the reduction of Lactobacilli and Lactococci (Wang, J. et al., 2014) Overall, there is a clear cross-talk between the gut and the lungs, which is vital for maintaining homeostasis and educating the host immune system. The mechanisms through which the gut impacts on lung health or disease and vice versa are only starting to be uncovered. (Tulic, M. K, et al., 2016)

THE ORIGIN AND COMPOSITION OF MICROBIOTA IN THE LUNGS

In comparison to the intestinal microbiota, studies on the lung microbiome are still in their infancy. The lower respiratory tract was historically considered to be 'sterile', mostly due to the failure to grow lung microbes in routine microbiological cultures from healthy individuals. This dogma was contested with advances in sequencing techniques that were able to detect microbial DNA in the lungs of individuals, even under healthy steady-state conditions. Historically, traditional culture-based studies and classic teaching indicated that the normal lungs are free from bacteria, and this notion has persisted in contemporary medicine (Dickson et al., 2016) Overall, there is a clear cross-talk between the gut and the lungs, which is vital for maintaining homeostasis and educating the host immune system. The mechanisms through which the gut impacts on lung health or disease and vice versa are only starting to be uncovered (Tulic, M. K., Piche,2016).

The composition of the microbiota differs significantly between the upper and lower respiratory tract in healthy individuals, questioning if samples of the upper airways can reflect the microbiome in the lower respiratory tract (Goddard, A. F. et al., 2012). Several factors have been shown to exert their functions along the gut–lung axis including systemic dissemination of bacterial-derived components and metabolic degradation products, with SCFAs being the most prominent immunomodulatory metabolites (Dang and BJ Marsland, 2019) functions along the gut–lung axis including systemic dissemination of bacterial-derived components and metabolic degradation products, with SCFAs being the most prominent immunomodulatory metabolites.

The prevalence of distinct bacterial species in these compartments supports the concept of niche-specific microbial colonization at distinct anatomical sites. Nonetheless, some bacterial communities are shared between the lung and the oral cavity although at different abundances, suggesting that the lung microbial community is partially seeded through microaspiration of the oral microbiome (Bassis, C. M. et al., 2015). A comparative study on microbial communities in the lower airways and the oral cavity of non-smoking and smoking individuals has contributed to the identification of a 'healthy' lower respiratory tract microbiome. The overall bacterial communities in the lung resemble those in the oral cavity with Streptococcus, Prevotella, and Veillonella being the most common genera (Morris, A. et al., 2013)

THE MICROBIOTA IN LUNG HOMEOSTASIS MAINTENANCE

For maintaining the homeostasis of intestinal system, pattern recognition receptors (PRRs) sense microbial compounds and induce the differentiation of regulatory T cells (Treg) and Th17 cells (Song et al., 2016). Similarly, PRRs in the lungs could also sense microbial compounds from lung microbiota and shift naive T cells to Th1 cells but not Th2 cells. Before birth, the unsound pattern of immune system is dominated by Th2 cells. After birth, the polarization of naïve T cells in the lungs will switch from Th2 phenotype to Th1 phenotype, which will protect against neonatal asthma and allergic disease (Lloyd and Hessel, 2010). Germ-free and specific-pathogen-free mice mount immune response development toward Th2 type and display susceptibility to house dust mite-induced allergic asthma (Remot et al., 2017). Mucosal administration of innocuous whole bacteria or component such as lipopeptide, peptidoglycan, LPS or DNA can induce Th1 immune response and protect mice against asthma and allergy (Saeedi et al., 2015). The homeostasis maintenancefor lung microbiota is shown in Figures 1 and 2

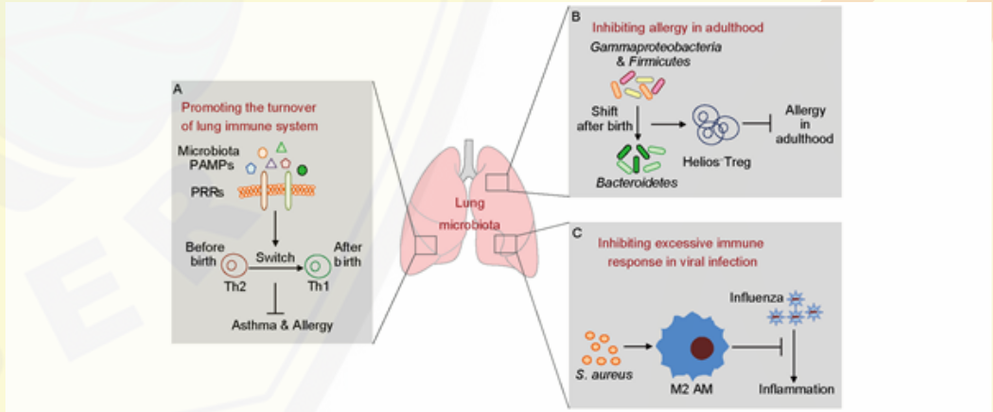

Figure 1 (Color online) The lung microbiota play roles in lung homeostasis maintenance. A, Similar as intestinal microbiota, lung microbiota might also be recognized by pattern recognition receptors (PRRs) and then promote the polarization of naïve T cells in the lungs from Th2 to Th1 after birth to protect against neonatal asthma and allergy. This issue needs to be determined. B, In neonate's lungs, the bacterial load increases, and the bacterial phyla shifts from *Gammaproteobacteria* and *Firmicutes* towards *Bacteroidetes*. The changes of the microbiota are associated with the development of Helios-negative Treg cells in the lungs that subsequently inhibit the exaggerated inflammatory response to allergens through to adulthood. C, *Staphylococcus aureus* (*S. aureus*), a common microbiota in upper respiratory tract and lung, promote the differentiation of M2 alveolar macrophages then provide protection against lethal inflammation in the lungs caused by influenza infection.

Wang, J., et al. Sci China Life Sci (2017)

A crucial role of lung microbiota in the maturation and homeostasis of lung immunity has emerged over the last few years (Dickson et al., 2018). Colonization of the respiratory tract provides essential signals for maturing local immune cells with long-term consequences. Preclinical studies confirm the causality between airway microbial colonization and the regulation and maturation of the airways' immune cells. Germ-free mice exhibit increased local Th2- associated cytokine and IgE production, promoting allergic airway inflammation (Herbst et al., 2011). Consistently, lung exposure to commensal bacteria reduces Th2-associated cytokine production after an allergen challenge and induces regulatory cells early in life. The establishment of resident memory B cells in lungs also requires encountering lung microbiota local antigens, especially regarding immunity against viruses such as influenza. Interactions between lung microbiota and immunity are also a two-way process; a major inflammation in the lungs can morbidly transform the lung microbiota composition (Herbst, T., et al. (2011). Dysregulation of allergic airway inflammation in the absence of microbial colonization.

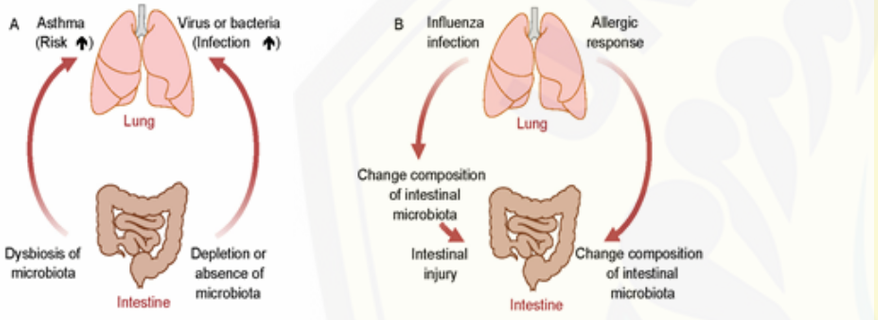

Figure 2 (Color online) The bridge function of microbiota in the gut-lung axis. A, Dysbiosis of the intestinal microbiota is linkage to the pathogenesis and progression of asthma, and depletion or absence of intestinal microbiota leads to impaired immune responses following viral or bacterial respiratory infection. B, Respiratory influenza infection changes the composition of intestinal microbiota and causes intestinal immune injury, and the allergic response in the lungs affects the composition of the intestinal microbiota.

Wang, J., et al. Sci China Life Sci (2017)

GUT–LUNG AXIS IN RESPIRATORY DISEASES

Acute Infectious Diseases Regarding influenza infection and the impact of gut and lung microbiota, our knowledge is still fragmentary; human data are not yet available. However, antibiotic treatment causes significantly reduced immune responses against influenza virus in mice (Ichinohe et al., 2011). Conversely, influenza-infected HFD-fed mice exhibit increased survival rates compared to infected controls thanks to an enhanced generation of Ly6cpatrolling monocytes. These monocytes increase the numbers of macrophages that have a limited capacity to produce CXCL1 locally, reducing neutrophil recruitment to the airways and thus tissue damage. In parallel, diet-derived SCFAs boost CD8+ T-cell effector function in HFD-fed mice (Trompette et al., 2018). Both lung and gut microbiota are essential against bacterial pneumonia. The lung microbiota is able to protect against respiratory infections with Streptococcus pneumoniae and Klebsiella pneumoniae by priming the pulmonary production of granulocyte-macrophage colony-stimulating factor (GM-CSF) via IL-17 and Nod2 stimulation (Brown et al., 2017). The gut microbiota also plays a crucial role in response to lung bacterial infections. Studies on germ-free mice showed an increased morbidity and mortality during K. pneumoniae, S. pneumoniae, or P. aeruginosa acute lung infection (Brown et al., 2017). The use of broad-spectrum antibiotic treatments, to disrupt mouse gut microbiota, results in worse outcome in lung infection mouse models. Mechanistically, alveolar macrophages from mice deprived of gut microbiota through antibiotic treatment are less responsive to stimulation and show reduced phagocytic capacity. Interestingly, priming of antibiotic-treated animals with TLR agonists restores resistance to pulmonary infections (Fagundes et al., 2012). SFBs appear to be an important gut microbiota component for lung defense against bacterial infection thanks to their capacity to induce the production of the Th17 cytokine, IL-22, and to increase neutrophil counts in the lungs during Staphylococcus aureus pneumonia (Gauguet et al., 2015). Modulating chronic infectious diseases will similarly depend on gut and lung microbiotas. For instance, Mycobacterium tuberculosis infection severity is correlated with gut microbiota. Chronic Respiratory Diseases Multiple studies have addressed the impact of gut and lung microbiota on chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma, and CF. Decreased lung microbiota diversity and Proteobacteria expansion are associated with both COPD severity and exacerbations (Wang et al., 2016). The fact that patients with genetic mannose binding lectin deficiency exhibit a more diverse pulmonary microbiota and a lower risk of exacerbation suggests not only association but also causality (Dicker et al., 2018). Besides the lung flora, the gut microbiota is involved in exacerbations, as suggested by the increased gastrointestinal permeability in patients admitted for COPD exacerbations. Whatever the permeability's origin (hypoxemia or proinflammatory status), the level of circulating gut microbiota– dependent trimethylamine-N-oxide has been associated with mortality in COPD patients (Ottiger et al., 2018). This association being explained by comorbidities and age, its impact per se is not guaranteed. Further studies are warranted to investigate the role of GLA in COPD and to assess causality. Early-life perturbations in fungal and bacterial gut colonization, such as low gut microbial diversity, e.g., after neonatal antibiotic use, are critical to induce childhood asthma development (Arrieta et al., 2018). This microbial disruption is associated with modifications of fecal SCFA levels. Causality has been assessed in murine models. Inoculation of the bacteria absent in the microbiota of asthmatic patients decreases airways inflammation (Arrieta et al., 2015). Furthermore, Bacteroides fragilis seems to play a major role in immune homeostasis, balancing the host systemic Th1/Th2 ratio and therefore conferring protection against allergen-induced airway disorders (Mazmanian et al, 2015; Arrieta et al., 2018). Nevertheless, it is still not fully deciphered, as some studies conversely found that an early colonization with Bacteroides, including B. fragilis, could be an early indicator of asthma later in life. Regarding fungi, gut fungal overgrowth (after antibiotic administration or a gut colonization protocol with Candida or Wallemia mellicola) increases the occurrence of asthma via IL-13 without any fungal expansion in the lungs (Skalski et al., 2018). The prostaglandin E2 produced in the gut by Candida can reach the lungs and promotes lung M2 macrophage polarization and allergic airway inflammation (Kim et al., 2014). In mice, a gut overrepresentation of W. mellicola associated with several intestinal microbiome disturbances appears to have long-reaching effects on the pulmonary immune response and severity of asthma, by involving the Th2 pathways, especially IL-13 and to a lesser degree IL-17, goblet cell differentiation, fibroblasts activation, and IgE production by B cells (Skalski et al., 2018). Taken together, these results indicate that the GLA, mainly through the gut microbiota, is likely to play a major role in asthma.

CONCLUSION

The gut–lung axis or GLA has emerged as a specific axis with intensive dialogues between the gut and lungs, involving each compartment in a two-way manner, with both microbial and immune interactions. The dysbiosis of lung microbiota is linked to the lung chronic disease, but it is not clear whether dysbiosis is a cause or a consequence of immune dysregulation and disease initiation or progression. In the future, we may constitute a healthy lung microbiota community to further our understanding of the complexity of lung microbiota as well as their genetic and metabolic potential and even manipulate the lung microbiota as a potential therapeutic way to treat chronic lung disease

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TARGETING THERAPY IN LUNG CANCER

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC), with which lung adenocarcinoma accounts for the majority of cases. Recent advances in the understanding of the molecular pathogenesis of lung cancer together with the advancement of molecular analysis support the clinical use of targeted therapies, such as epidermal growth factor receptor *(EGFR)* tyrosine kinase inhibitors (TKI) or anaplastic lymphoma kinase *(ALK)* TKI. Further research into the drug resistance mechanisms and new opportunities to target those with or without acquired resistant mutations are much awaited.

Patients who had oncogenic driver mutations used to show lesser therapeutic response to immunotherapy. Immunotherapy alone as a first treatment significantly improved survival for patients with a high level of the PD-L1 protein in their cancer and with fewer side effects. Immunotherapy and chemotherapy combined therapy (IO-chemo) pushed the clinical benefits of immunotherapy further up in lung cancers. Research into the the interaction between lung cancer cells and immune cells may reveal opportunities to better targeting immune reactions in lung cancer.

While lung tumor tissue biopsy remains the gold standard for both histological diagnosis and molecular profiling, tissue biopsy is often limited by tumor accessibility because of the high risk and invasive nature of pulmonary intervention procedures. Liquid biopsy aims at analysis of circulating biomarkers in peripheral blood, such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). These act as alternative or supplementary source of cancer-derived information that may be able to overcome the issue of representativeness of a small biopsy out of a sizable tumor. Research into the heterogeneity of lung tumors may imply the presence of different malignant cell types in a suspicious lesion. Tumor-related biomarkers released into bloodstream could be assayed and that could reflect the molecular properties of cancer cells, their release or non-release may be helpful to support the clinical decision making. There are indeed challenges that remain to be addressed before new circulating biomarkers could enter into routine clinical use.

THE ROLE OF HEPATOPROTECTOR IN TREATING DILI IN TB MANAGEMEN

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ABSTRACT

Tuberculosis (TB) remains a global health concern, and the adverse effects of anti-TB drugs, particularly drug-induced liver injury (DILI), pose significant challenges in the treatment of TB. DILI can lead to liver failure and treatment modification, resulting in non-adherence and reduced treatment effectiveness. This paper provides an overview of DILI in TB patients, including its diagnosis, classification, and clinical manifestations. It emphasizes the importance of comprehensive evaluation and the use of causality assessment instruments to determine drug causality. The paper discusses the fundamentals of DILI management, highlighting the challenges of discontinuing medications due to the potential consequences and the need for individualized risk assessment. Additionally, it explores the role of hepatoprotective agents, such as N-acetylcysteine, glycyrrhizin acid preparations, polyene phosphatidylcholine, bicyclol, and silymarin, in mitigating DILI. The specific mechanisms of action and evidence supporting the use of these agents are discussed. However, further prospective randomized controlled trials are needed to establish their definitive therapeutic efficacy. Overall, this paper underscores the importance of monitoring liver function tests, individualized patient management, and the potential benefits of hepatoprotective agents in managing DILI in TB patients.

Keyword: *liver injury, treatment, drug, tuberculosis, management*

Introduction

Tuberculosis (TB) remains a major health problem worldwide. In 2021, it's estimated that about 10.6 million new cases of TB reported with more than 1.4 million deaths1. Adverse drug reactions during the course of anti-TB treatment pose a challenge in tuberculosis treatment. Anti-tuberculosis drug-induced liver injury (DILI) is one of the most important adverse effects with a potential to lead to liver failure and death. DILI is the most common adverse reaction causing treatment modification and interruption, which ultimately leads to non-adherence and hinders the effectiveness of treatment. The occurrence of DILI varies significantly, ranging from 2% to 28%, depending on the specific group of individuals, the drug regimens used, and the specific thresholds for liver enzymes and bilirubin levels used to diagnose DILI[1].

Given the potential liver-damaging effects of anti-TB drug, there has been increased interest in using hepatoprotective agents as a means to mitigate DILI in TB patients. Several hepatoprotective agents, such as N-acetylcysteine, Glutathione, Glycyrrhizin acid preparation, Polyene phosphatidylcholine, Bicyclol, and Silymarin have demonstrated promising results for DILI treatment[2]. As of now, there is a lack of an official protocol in Indonesia that provides comprehensive instructions on how to manage drug-induced liver injury (DILI) in individuals with tuberculosis (TB).

Overview of Drug-Induced Liver Injury

DILI is a liver disease characterized by elevated liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST)[2]. It can manifest in a variety of clinical patterns, including asymptomatic liver enzyme elevations to severe hepatocellular injury, cholestatic injury, or combined patterns[2]. In cases of suspected

DILI, clinicians often use standardized criteria to determine the probability of drug causality[2]. DILI can be classified according to a variety of factors, including temporal pattern, clinical presentation, and histopathological characteristics[3]. Temporal patterns of DILI can be broadly classified as either predictable or peculiar, while idiosyncratic DILI is unpredictable and occurs in a small subset of susceptible individuals[3]. Hepatocellular DILI is characterized by elevated ALT and AST levels, while cholestatic DILI is characterized by obstruction of bile flow. Variable design DILI displays characteristics of hepatocellular and cholestatic injury[3]. These classifications aid in the identification of the underlying mechanisms of liver damage and guide the development of appropriate therapeutic interventions[3].

DILI can have multiple causes. Medication use is one of the primary causes, with certain drug classes such as antibiotics, nonsteroidal anti-inflammatory medications (NSAIDs), antiepileptic drugs, and antituberculosis agents being linked to DILI[3]. Overdose and polypharmacy are two additional common causes of DILI. Risk factors that can increase an individual's susceptibility include advanced age, gender differences, genetic factors, comorbidities, and alcohol consumption3. Individuals with a history of liver disease, such as hepatitis or nonalcoholic fatty liver disease (NAFLD), are more susceptible to DILI due to impaired liver function, comorbidities, and alcohol consumption[3].

DILI in patients with tuberculosis can manifest in a variety of clinical manifestations[4]. Common symptoms include fatigue, vertigo, anorexia, jaundice, and abdominal discomfort in the upper right quadrant[4]. However, these symptoms are nonspecific and may result from other conditions as well. Within weeks to months of initiating anti-TB treatment, clinical manifestations may manifest. Monitoring liver function tests is essential for detecting DILI early on[4].

The diagnosis of DILI in TB patients is contingent upon a thorough evaluation. Assessing the probability of DILI requires a comprehensive medical history, including a detailed substance history[5]. It is essential to establish the temporal relationship between drug administration and the commencement of liver injury[5]. Hepatotoxicity can be detected by monitoring liver function tests, such as transaminases, bilirubin, and alkaline phosphatase[5]. Ultrasound and computed tomography (CT) scans can be used to evaluate liver morphology and rule out other causes of liver injury[6]. When diagnosing DILI, it is crucial to rule out alternative causes of liver damage. It is necessary to rule out viral hepatitis (such as hepatitis B and C), autoimmune liver diseases, and other medications known to induce hepatotoxicity[5]. Due to its invasive character, liver biopsies are rarely administered[5]. However, they may be considered when the diagnosis is ambiguous or when other liver diseases must be ruled out. Using causality assessment instruments, such as the Roussel Uclaf Causality Assessment Method (RUCAM), the likelihood of a substance causing liver injury can be determined[7]. These tools take into account variables such as the temporal relationship, dechallenge and rechallenge data, and alternative liver injury causes[7].

Fundamentals of Drug-Induced Liver Injury Management

Avoiding exposure to the offending medication or substances is the treatment of choice for DILI. A few days to several weeks are required for the liver to recover after substance withdrawal. Recovery following cessation of the offending substance or treatment is an essential factor in determining causation[8]. It is difficult to determine which drugs or pharmacological interactions cause liver injury, however, due to the fact that numerous suspect drugs are frequently administered concurrently in clinical practice[2].

A significant obstacle in the clinical treatment of drug-induced liver injury is that numerous medications are required for the treatment of the underlying illness, and discontinuing these medications may have catastrophic consequences[8]. In addition, minor increases in liver parameters caused by medications (such as antituberculosis drugs and statins) may be transient and may revert to baseline even if treatment is protracted. These increases may indicate mild liver injury that resolves on its own, a phenomenon known as "adaptation." At this time, the processes that may undergird this "adaptation phenomenon" are unknown[2].

A comprehensive risk assessment is required due to the possibility of both drug withdrawal-induced primary disease progression and ongoing drug use-induced liver injury. To prevent the unnecessary withdrawal of medications, the International Serious Adverse Events Consortium (iSAEC) proposed in 2011 modified biochemical criteria for the diagnosis of DILI, which include any of the following: 1) an increased alanine aminotransferase level (ALT) of more than 5 times the upper limit of normal (ULN); 2) an elevated alkaline phosphatase level (ALP) of more than 2 times the ULN, particularly in patients with high GGT; and 3) 3-fold ALT elevation and 2-fold TBil elevation over ULN[9]. It is not a diagnostic criterion for DILI, but it can be used as a guide when determining how to treat a patient. Since repeated exposure to the offending agent or similar substances with known cross-reactivity may result in chronic or severe liver injury, the DILI patient should be warned and given an alert card[2].

Patients with severe hepatitis and acute liver failure (ALF) significantly benefit from DILI drug therapy. Pharmacotherapy's primary objectives include hepatocyte protection, free radical scavenging and anti-oxidation, hepatocyte membrane stabilization, detoxification, transaminase reduction, immunological control, and so on[9]. As stated, DILI clinical pattern-based medication administration is essential. The sections that follow will provide an exhaustive overview of this topic. In addition, individuals with ALF or subacute liver failure (SALF) should consider artificial liver supportive therapy and liver transplantation[2].

Risks associated with the reintroduction of anti-tuberculosis drugs must be weighed against their potential advantages[10]. When it is uncertain which medication caused symptoms or elevated transaminases, a rechallenge may be considered. Rechallenge may also be considered if an increase in transaminase concentration did not reach the standard treatment-limiting threshold[10]. Patients who have reached a treatment-limiting threshold and have been rechallenged should undergo clinical and biochemical monitoring every two to four weeks. In the event of hepatitis symptoms, rechallenged patients should be instructed to discontinue medication[10].

Once drug-induced hepatitis has been resolved, the reintroduction of antituberculosis drugs should be performed sequentially according to the recommendations of the American Thoracic Society. The optimal starting point for drug administration is Rifampicin, with or without ethambutol. After 3 to 7 days, and after confirming that serum glutamic pyruvic transaminase (SGPT) levels have not increased, isoniazid can be administered. Patients with a history of severe drug-induced hepatitis who are able to tolerate Rifampicin and Isoniazid do not require reintroduction of Pirazinamide. Alternative regimens, tailored to the specific antituberculosis medications that do not induce hepatitis in the individual patient, can be considered for these patients[10,11].

Role of Hepatoprotectors in Drug-Induced Liver Injury

Hepatoprotectors are a category of drugs that possess the potential to enhance liver functionality, stimulate the regeneration of liver cells, and improve liver detoxification processes. However, there is currently no consensus regarding the standardized classification of these drugs. Based on their distinct mechanisms of action, they can be broadly categorized as detoxification agents (such as N-acetylcysteine and glutathione), anti-inflammatory agents (like preparations containing glycyrrhizic acid), hepatocyte membrane protectors (for instance, polyene phosphatidylcholine), and antioxidant agents (such as bicyclol and silymarin)[2].

1. *N-acetylcysteine as detoxification agents*

   N-acetylcysteine (NAC) is an L-cysteine derivative that possesses pharmacological attributes, including antioxidative, anti-inflammatory, microvessel dilation, and DNA protective effects[12]. NAC has been widely acknowledged as an effective antidote for acetaminophen (APAP) overdose, administered either intravenously or orally. Furthermore, NAC has demonstrated its applicability in the treatment of liver injury induced by various other drugs, as well as DILI accompanied by acute liver failure (ALF). An investigation demonstrated that the administration of a combined regimen comprising NAC and prednisolone exhibited favorable outcomes in patients suffering from severe idiosyncratic DILI caused by fupirtine, a centrally acting non-opioid analgesic[12]. This therapeutic approach resulted in significant enhancements in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and international normalized ratio (INR) levels within a span of two weeks, as opposed to individuals who did not receive NAC treatment(3).

   A separate study aimed to investigate the potential of intravenous NAC in expediting liver recovery among adult patients hospitalized with Anti-TB DILI[13]. The findings indicated that NAC did not lead to a shorter duration until ALT levels dropped below 100 U/L in individuals with Anti-TB DILI. However, it was found to significantly reduce the length of hospitalization among the participants[2].

2. *Glycyrrhizic acid as an anti-inflammatory agents*

   Glycyrrhizin is the common name for the triterpenoid molecule glycyrrhizin acid. Glycyrrhizin acid formulations are being used extensively DILI management in clinical settings all over the globe[14]. Medicines like magnesium isoglycyrrhizinate (MgIG) and compound glycyrrhizin tablets fall under this category. Glycyrrhizin acid's antioxidant, anti-inflammatory, and hormone-like characteristics protect the liver against inflammatory damage when used in the context of treating DILI[14]. Acute DILI, which includes acute hepatocellular damage with markedly high blood ALT levels, has been treated with MgIG. Low and high doses of MgIG lowered ALT levels early in medication administration[14], as shown in a research comparing the safety and effectiveness of MgIG to tiopronin, a typical treatment in China that operates similarly to NAC. A further research looking at MgIG's usefulness in treating acute drug-induced liver impairment caused by antineoplastic drugs found that MgIG was more effective than tiopronin at restoring normal ALT and AST levels[2].

3. *Polyene phosphatidylcholine as hepatocyte membrane protectors*

   Polyene phosphatidylcholine (PPC) is a refined product derived from phospholipids, with diacylphospholipidcholine (DLPC) being the primary active component[15]. It has the ability to supply endogenous phospholipids, which aids in the restoration of damaged liver cell. This restoration process enhances membrane functionality, increases cell membrane fluidity and stability, and provides protection against liver diseases induced by various factors[15]. A study conducted in China revealed that the recurrence rate of ALT in DILI patients managed by PPC was comparable to that of MgIG[16]. PPC has been frequently employed as a control or combination agent in numerous clinical studies on DILI, consistently demonstrating effective therapeutic outcomes. Although its usage is predominantly limited to China at present, PPC holds significant potential for clinical applications[2].

   Another study focusing on patients with anti-TB DILI demonstrated that PPC significantly elevated serum levels of heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), thereby reducing oxidative stress responses[2]. For patients with certain liver illnesses, PPC was an efficient and economical liver protective medication because it improved the protective effects of glutathione and magnesium isoglycyrrhizinate on the liver1[5,16]. Additionally, a number of studies have demonstrated that the safety profile of PPC does not reveal any significant variations in safety biomarkers[16].

4. *Bicylol and silymarin as antioxidant agents*

   The clinical guidelines of Russian physicians recommend bicyclol for the treatment of DILI. It suppresses the expression and function of inflammatory factors such as NF-B, IL-1, IL-18, TNF-, and TGF-1, reactive oxygen species (ROS) and nitric oxide (NO), which contribute to the depletion of antioxidants such as glutathione (GSH). Numerous clinical studies have demonstrated bicyclol's protective effect on the liver in cases of liver injury caused by a variety of chemical contaminants, alcohol, and other agents. A study showed that bicyclol demonstrated a substantially greater decrease in ALT levels than the PPC for patients with statin-induced liver injury. Furthermore, the incidence of adverse reactions did not differ significantly between the two groups[2].

   Bicyclol showed greater effectiveness than silybin and diammonium glycyrrhizinate in a research comparing the pharmacoeconomics of three therapy regimens for the treatment of anti-tuberculosis (TB) DILI. Bicyclol has a beneficial therapeutic impact on anti-TB DILI, according to a meta-analysis of seven RCTs. However, all seven researches included were of poor quality, showed considerable variation across trials, and showed signs of possible publication bias[2].

   Another antioxidant, silymarin, may aid in the prevention of DILI by inhibiting lipid peroxidation and enhancing the membrane's resistance to damage from multiple sources. Silymarin substantially decreased the mortality rate of patients with toadstool toxicity (from 14.1% to 5.5%) based on clinical evidence from 2,000 patients with hepatic impairment caused by toadstools over a 20-year period[17]. In a study comparing the efficacy and tolerability of Silymarin and Ursodeoxycholic acid (UDCA) anticonvulsive medications that produced hypertransaminasemia, ALT changes were notably better after 1 month compared to those in the UDCA group, with no discernible adverse effects. However, numerous studies have questioned its efficacy as a treatment. A randomized trial comparing silymarin and a placebo among individuals experiencing liver injury caused by anti-TB drugs showed there was no significant difference in the severity of liver injury, the time required to restore normal liver function, hospital stay duration, or the number of adverse events. The authors conclude, based on their findings, that silymarin is a safe herbal option but ineffective to reducing the adverse effects of anti-tuberculosis drugs on the liver[2].

Supplementation with vitamins, such as vitamin B12, has been shown to have beneficial effects in the therapy of patients with DILI. A study demonstrated that vitamin B12 showed a noteworthy hepatoprotective effect, suggesting its potential as an alternative therapeutic agent to NAC in cases of acute acetaminophen overdose[18]. Another study found that pretreatment with vitamins C, B12, E, or a combination of these vitamins had a positive impact in preventing in vivo hepatic oxidative stress induced by acetaminophen (APAP) overdose. These findings highlight the potential role of vitamin supplementation in ameliorating the hepatic effects of DILI and warrant further investigation[19].

Conclusion and Future Recommendations

There are no established standards or criteria for the pharmaceutical treatment of DILI. Within a few days to a few weeks of stopping the offending medicine, most cases of DILI resolve completely or almost completely. It's still unclear where to begin when administering protective medications. Therefore, all clinical practice recommendations stress the need of continuously monitoring liver biochemical markers.

Patients with DILI often exhibit unique clinical presentations, with variations in liver biochemical markers, depending on the specific target cells that have been destroyed. NAC, glycyrrhizin, PPC, bicyclol and silymarin are promising hepatoprotective medicines for DILI. However, prospective randomized and controlled trials are still required to demonstrate the definitive therapeutic efficacy of these medications.

MAINTAINING RESPIRATORY PHYSICAL HEALTH

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ABSTRACT

Respiratory home care plays a crucial role in achieving and maintaining respiratory well-being, whether an individual has a respiratory condition or aims to optimize lung function. Through implementing a diverse range of practices in the comfort of one's own homes, individuals can actively support the health of their respiratory system, mitigate the risk of respiratory illnesses, and enhance their lung capacity.

Pulmonary rehabilitation can be offered as a home-based program, providing individuals with the opportunity to receive respiratory care and support in the comfort of their own homes. Home-based pulmonary rehabilitation programs, involving a multidisciplinary team of healthcare professionals, offer valuable benefits to individuals facing challenges accessing or participating in center-based programs. These challenges may arise from factors like transportation limitations or health concerns.

Furthermore, creating a clean and smoke-free environment, and implementing proper nutrition, exercise, and stress management techniques, make individuals can take proactive steps to care for their respiratory well-being at home. Embracing these practices fosters easier breathing, enhanced lung function, and an overall sense of vitality and health.

Keywords: *respiratory physical health, pulmonary rehabilitation, home care*

EXERCISE, DIETS AND NEUROCOGNITIVE

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ABSTRACT

Background: Cognitive capacity is highly dependent on synaptic connections between neurons. These connections are largely determined by the exuberance of neuron structures. Neuroplasticity is the regeneration or structuring of neurons through synaptic growth (dendrite spines). Neuroplasticity is influenced by various factors. It is necessary to explore these factors to improve neurocognitive functions.

Methods: This paper reveals the results of various studies that have been conducted. The results of these studies were analyzed by referring to various relevant literature.

Results: Several studies have been conducted for this. Aerobic exercise has been shown to improve the brain's vascular system and synthesize neurotropic factors. As a result, there are improvements in cognitive function and motoric skills. The recommended exercise is aerobic exercise combined with thought processes such as games. On the other hand, calorie restriction with a balanced diet has the best effect to spur growth and increase neuronal survival.

Conclusion: Neuroplasticity can be boosted by healthy lifestyles such as exercise and calorie restriction.

Keywords: Cognitive, aerobic exercise, caloric restriction, neuroplasticity.

INTRODUCTION

The neuron system consists of four functions, in the form of autonomic, sensory, motor, and integration functions. The integration system is central of all regulatory functions. The neuronal organs involved are the brain, brain stem, hypothalamus, pituitary and cerebellum. In the integration, the neuron system performs various coordination involving intelligence and memory. Integration function is the processes information from the sensory to motor responses. It involves abstraction of thought patterns. This system requires high intellectual capacity and intelligence. Through integration, humans are able to become the most intelligent creatures. Humans can design, plan, build and adapt to the environment. The capacity of the integration depends on a combination of nervous structure and psychological experience. The function of integration largely determines a person's cognitive abilities.[1]

The cerebral cortex is the most important organ related to integration function. The cerebral cortex is the highest part of the CNS. This organ becomes the center of intelligence and the center of voluntary motor and sensory. The cerebral cortex has an area of association. In this area, interactions occur between various sensory centers for further processing involving memory, analytics and emotion. The cerebral cortex also has motor centers related to intelligence. Its control complex movements such as writing, painting and speaking.[2]

METHODS

Information about neurogenesis, neuroplasticity and various influencing factors was written based on the results of studies or research that has been done before. Some of the data that has been obtained was analyzed based on the relationship with each other. In addition, various phenomena that have been revealed were analyzed referring to various relevant literature.

RESULTS AND DISCUSSION

Neurogenesis and Neuroplasticity

Cognitive capacity is highly dependent on synaptic connections between neurons. The connections between neurons are largely determined by the exuberance of neuron structures. Neuron cells are considered a group of post-mitotic (G0 phase) cells. The cells have developed mature (terminally differentiated). Neurogenesis is believed to occur only in the embryonal or at the latest in the first 3 years of life.[3] However, recently, neuron cells have been shown to still be able to grow into old age.

The growth of new neuron cells is called neurogenesis. Neurogenesis in adults occurs mostly in the area of the hippocampal gyrus dentata, subventricular zone, and olfactory bulb. This is because the brain tissue in this area still has neural stem cells (NSC). NSCs will develop into neural progenitor cells and differentiate into neuron cells and glial cells.[4] Neuron cells can grow into dense (neuroplasticity). Neuroplasticity is the anatomical and physiological regeneration or structuring of neurons through the growth of dendrite spines. Neuroplasticity is the inherent capacity of a network of neurons to form new inter-neuronal connections or synapses (synaptogenesis).[5]

The skeletal structure of neurons is the cytoskeleton. The cytoskeleton is dynamic to support connections between neurons. The components of the cytoskeleton can grow to establish connections with other neuron cells.[3] The cytoskeleton consists of three components, microtubules, neurofilaments, and microfilaments. Microfilaments contain actin molecules that polymerize together to form a double helical chain. Actin plays a role in changing the shape of neurons. Actin is constantly changing to undergo polymerization (lengthening) and depolymerization. These changes are regulated by the dynamics of signals in neurons. When neuronal signal intense, actin polymerizes to change the structure of dendrites to lengthen. Then, dendrites form a synaptic system with dendrites of other neurons. Therefore, the microfilament (F)-actin plays a major role in neuroplasticity. F-actin is a major component in the elongation of the structure of dendrite spines.[2]

Factors Affecting Neuroplasticity

Neurons can increase or degrade. Degradation can occur due to hypoxia, oxidative stress, immobilization stress, physical trauma, psychological trauma, infection, aging, undernourishment and toxic.6 For example, toxic effects of aluminum on water consumed by people in mining areas can have adverse effects on neuron systems and cognitive function. They experienced decreased BDNF levels and impaired memory function.[7] Studies have also been conducted on the effect of immobilization stress on neuroplasticity. The immobilization stress significantly decreased levels of post synaptic density-95 (PSD95). PSD-95 is an F-actin protein that is important in the process of neuroplasticity.[8]

Various studies on neurogenesis have progressed. The pioneer researcher in this field is the winner of the 2000 Nobel Prize in Physiology and Medicine, Eric R Kandel. He has studied biomolecular communication in structuring memory capacity and cognitive function. He revealed that the repetition of information between synaptic will activate transcription genes and protein synthesis. This activation spurs the growth of new synaptic structures (neuroplasticity).[9]

Sensitization will take place permanently through the long-term potentiating (LTP) mechanism. Permanent memory compilation occurs when an experience/knowledge stimulates the brain repeatedly. This process stimulates the synthesis of specific proteins and new synapses. The more experience or knowledge is built, the more connections between synapses are formed. When stimulation is fleeting, sensitization of information is lost. Repeated stimulation will trigger structural changes in pre- and post-synaptic. In the early phase of LTP, intense stimulation opens up the non-NMDA glutamate channel. It's also triggering hypo polarization in the postsynaptic. This makes Mg++ exit the NMDA-glutamate channel, and Ca++ enters the cell. Calcium triggers the activity of Ca-dependent kinases, PKC, Ca-calmodulin, and tyrosine kinases. Ca-calmodulin kinase phosphorylates non-NMDA channels. Then this increases the sensitivity of those channels to glutamate and is fed back to the presynaptic. This feedback will increase the release of the transmitting substance from the presynaptic. And also reduce the risk of information transmission failure. Calcium enters the cell and triggers Ca-calmodulin. Thereby, its activating adenyl cyclase and cAMP-kinase. Ultimately, these grooves trigger translation in the cell nucleus. And then, the process of protein synthesis to change the structure of the neuron's membrane and form new synapses will begin.[10] Through this mechanism, experts believe that the LTP process triggers memory formation and neuroplasticity.[2,10]

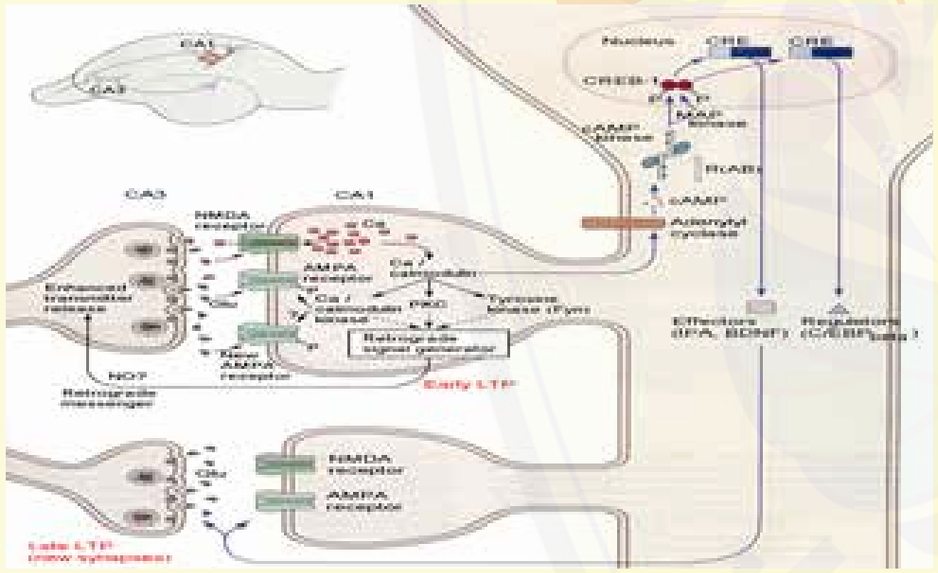

Figure 1. Biomolecular mechanism of neuroplasticity. Source: https://www.nobelprize.org/prizes/medicine/2000/kandel/lecture/[11]

The theoretical foundation has been prepared based on several literature reviews. Neuroplasticity will be driven by at least three mechanisms. The mechanisms include adaptation to conditioned stress, vascular repairment, and environmental enrichment. Healthy life style is believed to increase neuroplasticity through these mechanisms. Neuron cells will adapt better and be able to survive when exposed to conditioned stress. These are preconditioning hypoxia, physical threads and relative caloric restriction. Exercise and fasting are examples of such conditioning. The supply of nutrients and co-factors such as growth factors can run smoothly with vascular repairment. Exercise will also stimulate the repair of the vascular system. Learning and practicing causes a person to be able to master the things he learns / trains. This condition occurs due to adequate synaptic connections. Thus, the delivery of neuron stimulation becomes faster to understand or master the knowledge or skills he learns. Learning activities are a form of enrichment of the environment.[6]

Exercise and Neurogenesis

Several studies have been conducted to explore the influence of exercise on neurogenesis and cognitive function. A group of 7-year-old children were subjected to regular aerobic gymnastics for 8 weeks. Gymnastics was done regularly 3 times per week with guidance from trained instructors. Children are invited to do gymnastics while improving imagination and creativity. They did the Islamic dance, continued with worker gymnastics and animal movement imitation movements. Each session was 45 minutes. For comparison was a group of children of the same age. The comparison group intervened with routine gymnastics once per week. They were not guided by instructors. The results of the study proved that the structured aerobic exercise group had higher Brain Derived Neurotrophic Factor (BDNF). In addition, structured aerobic exercise was also improving executive function abilities, reaction speed, coordination, flexibility and agility. [12, 13]

More in-depth studies were continued. The aims was to prove whether exercise combined environmental enrichment has a better impact on neuroplasticity. A running wheel with obstacle barriers has also been designed. Experimental animals were forced to run at a dose of aerobic intensity. While they were running, they were passing obstacles with volume for 30 minutes, such as turning, jumping and ducking. This type of intervention was based on the hypothesis. The exercise that require strategy and intelligence such as games (basketball, badminton) will spur better cognitive abilities than regular running.[6]

The experiments showed that running with obstacle was able to increase levels of Developmentally regulated brain protein-1 (drebrin-1) in the brain. In addition, it was also able to increase blood flow and spur better neovascularization within the brain. There was an increase in vascular diameter and levels of Vasculo-endothelial growth factor (VEGF). Drebrin is an abundant cytoskeleton that binds to the F-actin protein. F-actin is the main component of the cytoskeleton which becomes the main structure for the elongation of dendrite spines. In addition, exercise with obstacle was able to spur better memory skills than the control group.[14]

The results of this study are in line with recommendations provided by the American College of Sports Medicine (ACSM). ACSM's officially stated that there are valid evidences about the role of exercise or structured physical activity on cognitive function. This includes academic performance and neuropsychological capabilities. The ACSM also recognizes that exercise plays an important role in preventing cognitive decline due to aging. For the reason, ACSM recommends exercise should be one approach to maintaining cognitive function. The ACSM recommends exercise play a role in building the hardware and software elements of neuron systems. For hardware, sports have been shown to build structure and improve the flow quality (diameter) of the vascular system. For software, sports are a form of learning (environment enrichment). During exercise, the fine motor components of the neuron system are trained. These two components together improve the structuring and endurance of neurons. The recommended exercise to build cognitive function are aerobic exercise. The intensity is light to moderate with a combination of movement variations or contain elements of strategy. Aerobic exercise is carried out at a dose of 3-5 times per week. Total exercise volume for 150 minutes for one week. The type is aerobic with more complex movements and

there are elements of strategy. Examples of exercises carried out such as games (basketball, football, gymnastics). Aerobic exercise needs to be combined with elements of coordination and strength such as lifting weights. In addition, exercise is combined with flexibility and balance exercises such as Yoga and Taichi. Weightlifting is carried out 2-3 times per week with a volume of 1-3 sessions, 8-10 reps. While stretching exercises can be done for 10-15 minutes every day.[15]

Dietary Modifications for Neurogenesis

The development of the structure and function of neurons is also inseparable from nutrition. Various dietary patterns have been carried out to maintain nutritional balance. One diet pattern is calorie restriction in the form of fasting and ketogenic diets. A study was conducted to assess the effect of a combination of calorie restriction and ketogenic diet in controlling weight, blood sugar and fat profiles. The combination of fasting and a moderate ketogenic diet turned out to be the most effective in losing weight. In addition, the combination was effective in maintaining HbA1c and fat profile.[16] The study continued by assessing the impact of calorie restriction with a balanced diet and ketogenic diet. Caloric restriction with a balanced diet had just as good an effect as the ketogenic diet on Ki67 expression. The Ki67 protein is dominant in the formation of new neuron cells. However, calorie restriction with a balanced diet has a lower effect than the ketogenic diet on caspase-3 expression. Caspase-3 is a protein that expresses the rate of apoptosis of neuron cells. This has showed that fasting with a balanced diet had the best effect compared to the ketogenic diet in maintaining neuron cell endurance.[17]

A combination of caloric restriction and exercise was also studied against peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1-alpha. This protein plays an important role in energy metabolism from carbohydrates and fats. PGC-1 spurs mitochondrial biogenesis and remodeling of body tissues. It has been proved that exercise combined with calorie restriction was most effective.[13]

A balanced diet is indispensable for brain metabolism. The brain relies heavily on carbohydrates as the main source of energy. The metabolic waste from carbohydrates is CO2 and water which is relatively safe for the body. When the source of nutrients originates from protein causing metabolic waste deamination in the form of NH4. When the source of energy metabolism is dominated by fat sources, then the rest of metabolism is in the form of ketone bodies.[18]

Breast Feeding, Gut Brain Axis and Cognitive Development.

Recently, number of studies have explored the possible role of gut microbiota on memory, learning, anxiety, stress, neurodevelopmental disorders and neurodegenerative processes. The role of microbiota in this brain-gut axis is very important.[19] Breast milk is the main nutrient for newborns. Breast milk contains thousands of variations of bioactive components. The bioactive components of breast milk can provide protection against infection and inflammation. In addition, breast milk spurs colonization of healthy microbes, and contributes to the maturation of immune function and brain development. The bioactive components of breast milk, specifically human milk oligosaccharide/HMO, are assumed to be involved in the regulation of the gut-brain axis via neuro-immuno-endocrine mediators.[20]

HMO which acts as a prebiotic that can stimulate the growth of good bacteria in the digestive tract. Bacterial fermentation produces end products in the form of short chain fatty acid metabolites (SCFA).[21] SCFA is able to create an acidic environment that can inhibit the development of bacteria and fungi that are not good (pathogenic). SCFAs in the intestinal lumen have a local protective effect of the intestine. SCFAs can activate FFAR2 in intestinal epithelial cells to improve gut barrier function. Integrity in the intestinal barrier prevents bacteria from crossing intestinal epithelial cell.[22] SCFAs are absorbed into enteroendocrine cells to induce the release of peptide hormones (including GLP-1, CCK and PYY). In addition, SCFAs trigger the synthesis of neuroactive such as dopamine (DA), 5-hydroxytrypthamine (5-HT), and γ-aminobutyric acid (GABA). These compounds activate neuron signalling. SCFAs modulate neurotrophic factor (FN) by influencing glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) morphologic factor (NGF). SCFA interactions prove the existence of a relationship between microbiota-gut-brain.[23] A meta-analysis study has been conducted. It studies the influence of gut microbiota abundance in cognitive development. *Phylum Bacteroidetes* and family *Lactobacillaceae* are more dominant in the cognitive behaviour enhancement group. The provision of probiotics and anti-biotics affects the abundance of intestinal microbiota.[24]

CONCLUSION

Advances in biomedical science have revealed that quality cognitive is dependent on the connections between synaptic. Connection depends on the development of dendrite spines through the mechanism of neuroplasticity. Neuroplasticity is highly dependent on nutrient supply, oxygen and learning. Exercise provides complete benefits to the process of neurogenesis. Exercise maintains a balance of oxidative stress for neuronal endurance and angiogenesis. Exercise is also a form of learning. This condition then increases the synthesis of neuronal cytoskeleton proteins so as to grow dendrite spines. Improvement of neuron structure will also be more optimal when combined with balanced diet patterns. Currently, ongoing studies are being conducted. Studies focus on the influence of the gut-brain axis on the development of cognitive function. The benefits of breastfeeding and dietary on improving gut microbiota are being examined. And also, how their impact on brain structure and cognitive function.

AUTHORS' CONTRIBUTION

The conceptualization, analysis, and data interpretation: Irfannuddin Irfannuddin. The preparation of the article: Irfannuddin Irfannuddin, Siti Sarahdeaz Fazzaura Putri. The final approval to be published: Irfannuddin Irfannuddin, Siti Sarahdeaz Fazzaura Putri

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MANAGEMENT IN NEURORESPIRATORY DISEASE: FOCUSING ON MYASTHENIA GRAVIS, GUILLAIN-BARRE SYNDROME

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ABSTRACT

Neurorespiratory diseases, also known as neurogenic respiratory disorders, refer to a group of conditions that involve abnormalities in the nervous system and respiratory system, leading to respiratory dysfunction. These disorders can affect various components of the respiratory system, including the muscles, nerves, and brain structures involved in respiration.

The respiratory muscles, including the diaphragm, intercostal muscles, and accessory muscles of respiration, can be affected in GBS, leading to difficulty in breathing. In severe cases, respiratory failure can occur, requiring mechanical ventilation.

ABG analysis should be interpreted in conjunction with the patient's clinical presentation, symptoms, and other diagnostic tests. It helps guide treatment decisions, including the initiation of respiratory support, adjustment of medication regimens, or the need for additional interventions like plasmapheresis or thymectomy.

Interpretation of ABG results should be done by a healthcare professional experienced in the management of neurorespiratory diseases and respiratory failure. Regular monitoring of ABG values is essential to assess respiratory function and optimize patient care.

Arterial Blood Gas (ABG) analysis plays a critical role in the evaluation and management of respiratory failure in patients with neurorespiratory diseases. ABG analysis provides valuable information about oxygen and carbon dioxide levels, acid-base balance, and the overall effectiveness of gas exchange in the lungs.

Interpretation of ABG results and decision-making based on the analysis should be done by a healthcare professional experienced in the management of neurorespiratory diseases and respiratory failure. ABG analysis is one of several tools used to evaluate respiratory function, and it is considered alongside the patient's clinical presentation, symptoms, physical examination findings, and other diagnostic tests to guide appropriate management strategies.

ABG analysis is analyzed and its implications in the evaluation and management of respiratory failure:

1. Oxygenation Status: ABG analysis provides the measurement of arterial oxygen tension (PaO2), which reflects the oxygenation status of the blood. In neurorespiratory diseases related respiratory failure, inadequate ventilation or respiratory muscle weakness can lead to low PaO2 levels, indicating hypoxemia. The analysis helps determine the severity of oxygenation impairment and guides the need for interventions such as supplemental oxygen therapy.
2. Ventilation Status: ABG analysis also measures the arterial carbon dioxide tension (PaCO2), which reflects the adequacy of ventilation and the elimination of carbon dioxide from the blood. In neurorespiratory diseases-related respiratory failure, inadequate ventilation due to respiratory muscle weakness can result in elevated PaCO2 levels, indicating hypercapnia. The analysis

helps assess the severity of ventilation impairment and guides the need for interventions such as ventilatory support.

3. Acid-Base Balance: ABG analysis provides information about the acid-base balance in the blood, primarily assessed by the pH level. In neurorespiratory diseases-related respiratory failure, inadequate ventilation and carbon dioxide retention can lead to respiratory acidosis, characterized by a low pH and elevated PaCO2. ABG analysis helps evaluate acid-base disturbances and guides interventions to restore acid-base balance, such as adjusting ventilatory support or administering bicarbonate therapy.
4. Monitoring Treatment Response: Serial ABG analyses are performed to monitor the response to interventions and guide ongoing management. Monitoring PaO2 and PaCO2 levels helps assess the effectiveness of interventions, such as supplemental oxygen therapy or ventilatory support, and guides adjustments to treatment strategies. ABG analysis is typically repeated at regular intervals to evaluate the patient's progress and ensure appropriate management.
5. Determining the Need for Respiratory Support: ABG analysis helps determine the need for respiratory support in neurorespiratory diseases related respiratory failure. If ABG results indicate severe hypoxemia or hypercapnia that cannot be corrected with less invasive measures, such as supplemental oxygen therapy, mechanical ventilation or noninvasive ventilation may be initiated. ABG analysis is used to guide the initiation, adjustment, and weaning of respiratory support to optimize respiratory function.
6. Assessment of Complications: ABG analysis also helps assess complications related to respiratory failure in neurorespiratory diseases, such as respiratory muscle fatigue, respiratory distress, or the development of respiratory infections. Changes in ABG parameters may indicate worsening respiratory function or the presence of complications, requiring prompt intervention and management.

Pulmonary function tests (PFTs) play a significant role in the management of respiratory failure in neurorespiratory diseases. They provide objective measurements of lung function and help assess the severity of respiratory impairment. Here are the key roles of PFTs in the management of respiratory failure. Pulmonary function tests should be performed and interpreted by qualified healthcare professionals trained in respiratory physiology and lung function testing. They provide objective data that complements clinical assessment and aids in the individualized management of respiratory failure in neurorespiratory diseases patients.

1. Baseline Assessment: PFTs serve as a baseline assessment of lung function in individuals with neurorespiratory diseases. They establish the patient's respiratory status at the beginning of treatment or during follow-up visits, providing a reference point for monitoring disease progression and treatment effectiveness.
2. Detection of Respiratory Muscle Weakness: PFTs can detect respiratory muscle weakness, which is a common manifestation of neurorespiratory diseases. Specifically, spirometry measures lung volumes and airflow rates, enabling the identification of reduced respiratory volumes and flow rates associated with respiratory muscle weakness.
3. Evaluation of Ventilatory Capacity: PFTs, such as forced vital capacity (FVC), can assess the maximal ventilatory capacity of the lungs. A decrease in FVC indicates reduced respiratory muscle strength and impaired ability to generate adequate airflow, highlighting the severity of respiratory involvement in neurorespiratory diseases.
4. Monitoring Disease Progression: Serial PFTs can track changes in lung function over time and help monitor disease progression in neurorespiratory diseases. By comparing follow-up PFT results with baseline measurements, healthcare providers can assess whether respiratory muscle weakness is worsening or stable, guiding treatment decisions accordingly.
5. Assessment of Treatment Response: PFTs are valuable for evaluating the response to treatment interventions in neurorespiratory diseases. Regular monitoring of lung function parameters, such as FVC or peak expiratory flow rate (PEFR), can help determine if interventions like medication adjustments, immunotherapy, or respiratory support are effectively stabilizing or improving respiratory function.
6. Guiding Ventilatory Support: In cases of severe respiratory failure, PFTs can aid in determining the need for and optimal settings of ventilatory support. Baseline lung function measurements, along with changes observed during PFTs, assist healthcare providers in selecting appropriate ventilatory strategies and adjusting support levels as needed.

Guillain-Barré Syndrome (GBS) is an autoimmune disorder that affects the nerves outside the brain and spinal cord, leading to muscle weakness and paralysis. Respiratory distress is a common complication of GBS and can occur due to weakness in the muscles responsible for breathing. Patients with GBS who develop respiratory distress require close monitoring and prompt intervention. Treatment may include supportive measures such as supplemental oxygen and mechanical ventilation to support breathing.

In GBS, the immune system mistakenly identifies components of the peripheral nerves, including the myelin sheath and axons, as foreign and attacks them. This leads to inflammation and damage to the nerves, which can result in muscle weakness, paralysis, and sensory disturbances. The specific immune response involved in GBS is thought to be a T-cell-mediated response, which activates macrophages and other immune cells to attack the myelin and axons. This immune response also leads to the release of cytokines, which can further contribute to nerve damage. The damage to the nerves in GBS typically starts at the myelin sheath and progresses to the axons, leading to loss of nerve conduction and motor function. This damage can occur rapidly and can lead to severe muscle weakness and paralysis, as well as sensory disturbances such as numbness and tingling

Respiratory failure in neurorespiratory diseases typically occurs due to the weakness of the muscles involved in breathing. The diaphragm, which is the primary muscle responsible for inhalation, may become weak and fatigued in individuals with neurorespiratory diseases. As a result, the ability to generate adequate respiratory effort and maintain proper ventilation may be compromised. Respiratory failure can manifest in two primary forms in neurorespiratory diseases.

Acute exacerbation:

This occurs when there is a sudden worsening of respiratory muscle weakness, leading to a significant decrease in respiratory function. It can be triggered by various factors, such as respiratory infections, certain medications (e.g., muscle relaxants), emotional stress, or surgery. Acute exacerbations can be life-threatening and require immediate medical attention. Acute exacerbation of respiratory failure in neurorespiratory diseases refers to a sudden and severe worsening of respiratory muscle weakness, leading to a significant decrease in respiratory function. It is a potentially life-threatening complication that requires immediate medical attention. Acute exacerbations of respiratory failure in neurorespiratory diseases can be triggered by various factors, including:

1. Infections: Respiratory tract infections, such as pneumonia or bronchitis, can trigger an acute exacerbation. Infections put additional strain on the respiratory muscles and can lead to an increased demand for respiratory effort.
2. Medications: Certain medications can interfere with neuromuscular transmission and exacerbate muscle weakness in individuals with neurorespiratory diseases. Examples include muscle relaxants, certain antibiotics (e.g., aminoglycosides), and beta-blockers. It is important for individuals with neurorespiratory diseases to inform their healthcare providers about their condition to avoid medications that may worsen symptoms.
3. Emotional stress: Stressful situations, emotional distress, or extreme fatigue can contribute to the worsening of neurorespiratory diseases symptoms, including respiratory muscle weakness.
4. Surgery: Surgical procedures, particularly those involving the chest or general anesthesia, can increase the risk of acute exacerbation in individuals with neurorespiratory diseases. It is crucial for the surgical team to be aware of the patient's condition and take appropriate precautions during anesthesia and postoperative care.

During an acute exacerbation of respiratory failure in neurorespiratory diseases, individuals may experience the following symptoms: Severe shortness of breath, Inability to speak in complete sentences, Weakness and fatigue in the respiratory muscles, Cyanosis (bluish discoloration of the skin and lips) due to inadequate oxygenation, Use of accessory muscles of respiration (e.g., neck muscles) to aid breathing, Decreased ability to cough effectively, leading to ineffective clearance of secretions.

Arterial Blood Gas (ABG) analysis plays a crucial role in the evaluation and management of respiratory failure in patients with neurorespiratory diseases. ABG analysis provides valuable information about oxygen and carbon dioxide levels, acid-base balance, and the overall effectiveness of gas exchange in the lungs. Here are some key points regarding the role of ABG analysis in respiratory failure in neurorespiratory diseases:

1. Assessment of Gas Exchange: ABG analysis helps assess the adequacy of gas exchange in the lungs. In neurorespiratory diseases, respiratory muscle weakness, particularly involving the diaphragm, can result in inadequate ventilation and impaired gas exchange. ABG analysis provides measurements of arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2), and pH, which help determine the severity of respiratory dysfunction and identify the need for intervention.
2. Detection of Hypoxemia: Hypoxemia, which refers to low levels of oxygen in the blood, can occur in neurorespiratory diseases due to respiratory muscle weakness or impaired lung function. ABG analysis measures the PaO2 level, which reflects the oxygenation status of the blood. Decreased PaO2 values may indicate insufficient oxygenation and the need for supplemental oxygen or other interventions to improve oxygen delivery.
3. Evaluation of Hypercapnia: Hypercapnia, which refers to high levels of carbon dioxide in the blood, can occur in neurorespiratory diseases due to inadequate ventilation. ABG analysis measures the PaCO2 level, which reflects the carbon dioxide retention in the blood. Elevated PaCO2 values indicate a reduced ability to eliminate carbon dioxide, suggesting respiratory muscle weakness. Monitoring PaCO2 helps assess the severity of respiratory failure and guides treatment decisions, such as the need for ventilatory support.
4. Acid-Base Balance Assessment: ABG analysis provides information about the acid-base balance in the blood, specifically the pH level. In neurorespiratory diseases-related respiratory failure, inadequate ventilation can lead to respiratory acidosis, characterized by a low pH and elevated PaCO2. ABG analysis helps identify acid-base disturbances and guides adjustments to respiratory support or other interventions to restore acid-base balance.
5. Treatment Monitoring: Serial ABG analyses can be performed to monitor the response to interventions and guide ongoing management. ABG results can help assess the effectiveness of ventilatory support, such as mechanical ventilation or noninvasive ventilation, and guide adjustments to ventilation parameters or treatment strategies.

Prompt medical intervention is necessary to stabilize the individual and prevent further deterioration. The management of acute exacerbation of respiratory failure in neurorespiratory diseases may include:

1. Hospitalization: Individuals experiencing acute respiratory failure often require hospitalization, preferably in an intensive care unit (ICU) where they can receive specialized monitoring and care.
2. Ventilatory support: Non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation may be initiated to assist with breathing. NIPPV involves the use of a mask or nasal interface to deliver pressurized air to the lungs, while invasive mechanical ventilation requires the insertion of a breathing tube into the trachea.
3. Medications: Immediate administration of medications, such as intravenous immunoglobulin (IVIG) or plasmapheresis, may be necessary to rapidly improve muscle strength and control the autoimmune response.
4. Treatment of triggers: If the exacerbation was triggered by an infection or medication, appropriate treatment or discontinuation of the offending agent is essential.

The overall goal of managing acute exacerbation of respiratory failure in neurorespiratory diseases is to stabilize the individual's respiratory function, optimize muscle strength, and address the underlying cause. Close monitoring and collaboration between healthcare providers, including neurologists, pulmonologists, and critical care specialists, are vital for successful management and prevention of further complications.

Chronic respiratory insufficiency:

In some cases, individuals with neurorespiratory diseases may develop chronic respiratory insufficiency, where the respiratory muscles gradually weaken over time. This can lead to a decrease in lung capacity and impaired gas exchange. It typically occurs in individuals with long-standing and severe neurorespiratory diseases. Respiratory failure can occur as a result of chronic respiratory insufficiency in individuals with neurorespiratory diseases. Chronic respiratory insufficiency refers to a progressive weakening of the respiratory muscles over time, leading to a decrease in lung capacity and impaired gas exchange.

The management of chronic respiratory insufficiency in neurorespiratory diseases focuses on improving respiratory function and ensuring adequate oxygenation. The following approaches may be employed:

1. Medications: Medications aimed at controlling the underlying neurorespiratory diseases, such as anticholinesterase agents and immunosuppressive drugs, can help improve muscle strength and slow down the progression of respiratory muscle weakness.
2. Ventilatory support: Non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation may be used to support breathing and optimize oxygenation. NIPPV can be employed during sleep or periods of increased respiratory demand, while invasive mechanical ventilation may be required for more severe cases.

3. Pulmonary rehabilitation: Physical therapy and respiratory exercises can help improve respiratory muscle strength and overall lung function. These rehabilitation programs may include breathing exercises, chest physiotherapy, and aerobic conditioning.
4. Monitoring and regular follow-ups: Close monitoring of respiratory function is essential to detect changes and intervene promptly. Regular follow-up appointments with healthcare providers, including neurologists and pulmonologists, allow for adjustments in treatment strategies as needed.

It's important for individuals with neurorespiratory diseases to work closely with their healthcare team to manage the condition effectively and minimize the risk of respiratory complications. Regular communication, adherence to treatment plans, and lifestyle modifications may help in optimizing respiratory function and overall quality of life.

Management and treatment of respiratory failure in neurorespiratory diseases involve a multidisciplinary approach and may include the following:

1. Medications: The administration of medications is aimed at managing the underlying neurorespiratory diseases and improving muscle strength. This may involve the use of anticholinesterase agents, immunosuppressive drugs, and, in severe cases, intravenous immunoglobulin or plasmapheresis.
2. Ventilatory support: In cases of respiratory failure, ventilatory support may be necessary to assist with breathing. Non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation may be employed to maintain adequate oxygenation and ventilation.
3. Monitoring and hospitalization: Close monitoring of respiratory function is essential in individuals at risk of respiratory failure. In severe cases, hospitalization in an intensive care unit (ICU) may be required to provide specialized care and monitoring.
4. Thymectomy: Surgical removal of the thymus gland (thymectomy) is often recommended for individuals with neurorespiratory diseases, particularly those with thymoma. Thymectomy can improve symptoms and reduce the risk of neurorespiratory diseases crises, including respiratory failure.

It is important for individuals with neurorespiratory diseases to work closely with their healthcare providers, including neurologists, pulmonologists, and respiratory therapists, to manage the condition effectively and minimize the risk of respiratory complications. Individuals with neurorespiratory diseases should work closely with their healthcare provider, typically a neurologist or specialist in neuromuscular disorders, to determine the suitability and timing of plasmapheresis as part of their treatment plan. Regular monitoring and follow-up appointments are essential to assess the response to plasmapheresis and make any necessary adjustments to optimize muscle strength and manage the symptoms of neurorespiratory diseases effectively.

The role Ventilatory support In cases of respiratory failure in neurorespiratory diseases. Plays a crucial role in the management of respiratory failure in individuals with neurorespiratory diseases. When respiratory muscles weaken due to neurorespiratory diseases, the ability to maintain adequate ventilation and oxygenation becomes compromised, leading to respiratory failure. Ventilatory support helps support and assist the breathing process, ensuring sufficient oxygenation and ventilation. Here are the key roles of ventilatory support in cases of respiratory failure in neurorespiratory diseases:

1. Maintaining adequate oxygenation: Ventilatory support, such as non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation, helps ensure an adequate supply of oxygen to the body. It assists the weakened respiratory muscles by delivering pressurized air to the lungs, improving oxygen exchange and preventing hypoxemia (low blood oxygen levels).
2. Assisting with ventilation: Weakness in the respiratory muscles can result in inadequate ventilation, leading to a buildup of carbon dioxide (CO2) in the blood. Ventilatory support helps remove CO2 from the body by facilitating the movement of air in and out of the lungs. By enhancing ventilation, it prevents the development of respiratory acidosis, which can be a life-threatening complication of respiratory failure.
3. Reducing respiratory muscle workload: Ventilatory support reduces the workload on the weakened respiratory muscles by providing mechanical assistance. This can help alleviate muscle fatigue, allowing the respiratory muscles to rest and recover. By reducing the effort required for breathing, ventilatory support helps minimize the risk of respiratory distress and further deterioration.
4. Supporting during acute exacerbations: Acute exacerbations of respiratory failure can occur in neurorespiratory diseases, often triggered by factors such as infections, medications, or surgery. During these episodes, ventilatory support plays a critical role in stabilizing the individual and preventing life-threatening complications. It provides immediate assistance to ensure adequate ventilation and oxygenation until the underlying cause is addressed and the individual's respiratory function improves.
5. Facilitating recovery and treatment: Ventilatory support can support individuals with severe respiratory failure during the acute phase, allowing time for other treatments to take effect. For example, immunosuppressive medications, intravenous immunoglobulin (IVIG), or plasmapheresis may be administered to control the autoimmune response and improve muscle strength. Ventilatory support ensures that the individual receives the necessary respiratory assistance during this critical phase of treatment.

The specific type and duration of ventilatory support depend on the severity of respiratory failure and the individual's response. NIPPV, which involves the use of a mask or nasal interface, is often employed initially. In more severe cases or when NIPPV is ineffective, invasive mechanical ventilation, which requires the insertion of a breathing tube into the trachea, may be necessary.

It's important for individuals with neurorespiratory diseases to be closely monitored and managed by a multidisciplinary team of healthcare professionals, including neurologists, pulmonologists, and critical care specialists, to determine the appropriate use and duration of ventilatory support. Regular assessments of respiratory function and ongoing adjustments to the ventilatory support strategy are crucial to optimize respiratory function and ensure the best possible outcomes for individuals with neurorespiratory diseases experiencing respiratory failure.

The alternative mode of mechanical ventilation in cases of respiratory failure in neurorespiratory diseases. In cases of respiratory failure in neurorespiratory diseases, when non-invasive positive pressure ventilation (NIPPV) is ineffective or contraindicated, invasive mechanical ventilation is often required. However, in individuals with neurorespiratory diseases, certain considerations should be taken into account when selecting the mode of mechanical ventilation. One alternative mode of mechanical ventilation that can be considered in these cases is intermittent positive pressure ventilation (IPPV), specifically volume-controlled ventilation (VCV).

Volume-controlled ventilation (VCV):

1. Targeted tidal volume: VCV delivers a set tidal volume of air to the lungs with each breath. The ventilator delivers the predetermined volume of air, usually in milliliters, at a set respiratory rate to ensure adequate ventilation. This mode allows precise control over the delivered tidal volume.
2. Fixed inspiratory pressure: VCV also involves delivering air at a fixed inspiratory pressure. The ventilator applies the necessary pressure to achieve the desired tidal volume. This fixed pressure can be advantageous in individuals with neurorespiratory diseases as it avoids excessive inspiratory efforts that can lead to muscle fatigue.
3. Synchronized with patient effort: To prevent asynchrony between the patient's breathing efforts and the ventilator, VCV can be set to synchronize with the individual's spontaneous breaths. This synchronization helps ensure better patient-ventilator interaction and comfort.
4. Inspiratory time limit: It may be beneficial to set an inspiratory time limit to prevent prolonged inspiratory efforts and to avoid muscle fatigue in individuals with neurorespiratory diseases. The inspiratory time limit allows for adequate ventilation while reducing the risk of excessive work on the respiratory muscles.

Other considerations:

1. Low respiratory rate: In neurorespiratory diseases, respiratory muscles can become fatigued easily. Setting a lower respiratory rate can help minimize the workload on the weakened respiratory muscles and reduce the risk of muscle fatigue.
2. Adequate sedation and analgesia: The use of sedative and analgesic medications may be necessary to ensure patient comfort and minimize patient-ventilator asynchrony. Care should be taken to choose medications with minimal respiratory depressant effects.

It's important to note that the choice of ventilation mode and settings should be tailored to the individual's specific needs and closely monitored by healthcare professionals. The decision regarding the mode of mechanical ventilation, including VCV, is made by a multidisciplinary team, including neurologists, pulmonologists, and critical care specialists, with expertise in managing neurorespiratory diseases -related respiratory failure.

It's crucial for individuals with neurorespiratory diseases experiencing respiratory failure to receive appropriate and timely care in specialized settings such as intensive care units (ICUs) or respiratory care units, where close monitoring and expertise in managing respiratory support are available.

The pitfall in the setting of mechanical ventilation in cases of respiratory failure in neurorespiratory diseases. When setting mechanical ventilation in cases of respiratory failure in neurorespiratory diseases, there are potential pitfalls that need to be considered to ensure optimal management. Here are some common pitfalls to be aware of:

1. Over-assistance and excessive tidal volume: Providing excessive ventilatory support with high tidal volumes can lead to increased respiratory muscle workload and potential muscle fatigue. Over-assistance can hinder the ability of weakened respiratory muscles to generate their own efforts, resulting in disuse atrophy and further weakness. It's important to carefully titrate the ventilator settings to avoid excessive tidal volumes and allow for some patient effort.
2. Inadequate synchronization: Asynchrony between the patient's spontaneous breathing efforts and the mechanical ventilator can lead to patient discomfort, increased work of breathing, and inefficient ventilation. Poor synchronization can occur if the ventilator is not properly adjusted to the patient's respiratory pattern, resulting in ineffective support. Close monitoring and adjustment of ventilator settings, including sensitivity and triggering mechanisms, are necessary to achieve optimal synchronization.
3. Insufficient inspiratory time: Insufficient inspiratory time can occur when the ventilator cycling is set too quickly, limiting the duration of inspiratory support. In individuals with neurorespiratory diseases, weakened respiratory muscles may require longer inspiratory times to ensure adequate ventilation. Failing to provide sufficient inspiratory time can result in inadequate ventilation and ineffective gas exchange.
4. Inappropriate sedation and analgesia: While sedation and analgesia may be necessary to ensure patient comfort and minimize patient-ventilator asynchrony, excessive sedation can lead to respiratory depression and reduced respiratory drive. Finding the right balance is crucial to avoid suppressing the respiratory function while maintaining patient comfort.
5. Neglecting to consider non-invasive ventilation (NIV) as an option: In selected cases, non-invasive positive pressure ventilation (NIPPV) can be effective in providing respiratory support, avoiding the need for invasive mechanical ventilation. NIV can help alleviate respiratory distress and support breathing efforts while minimizing the risk of complications associated with invasive ventilation. It should be considered early in the management of respiratory failure in neurorespiratory diseases, particularly in individuals with milder symptoms and preserved airway protection.
6. Delayed recognition of respiratory failure: neurorespiratory diseases-related respiratory failure can develop gradually or occur suddenly during acute exacerbations. Delayed recognition of respiratory distress and failure can lead to delays in initiating appropriate ventilatory support. Early identification of respiratory compromise, such as monitoring for signs of increased work of breathing, decreased oxygen saturation, or inadequate ventilation, is crucial for timely intervention.

To mitigate these pitfalls, a multidisciplinary approach involving neurologists, pulmonologists, and critical care specialists is recommended. Regular assessment of the patient's clinical status, ongoing monitoring of respiratory function, and close collaboration between the healthcare team and the patient are essential to optimize mechanical ventilation and provide appropriate support while minimizing potential complications.

The management weaning in mechanical ventilation in cases of respiratory failure in neurorespiratory diseases. Weaning from mechanical ventilation in cases of respiratory failure in neurorespiratory diseases requires a careful and individualized approach. The process should be guided by the patient's clinical status, respiratory muscle strength, and response to treatment. Here are some key considerations for the technical management of weaning in mechanical ventilation for individuals with neurorespiratory diseases:

1. Monitoring respiratory parameters: Continuously monitor the patient's respiratory parameters, such as tidal volume, respiratory rate, and inspiratory effort, to assess their ability to sustain spontaneous breathing. Parameters such as negative inspiratory force (NIF) and vital capacity can provide insights into respiratory muscle strength and readiness for weaning.
2. Assessing respiratory muscle strength: Regular assessment of respiratory muscle strength is crucial in determining the patient's readiness for weaning. This can be done using bedside techniques such as measuring NIF or through more advanced techniques like diaphragmatic ultrasound. Improvement in respiratory muscle strength is a positive indicator for weaning.

3. Assessing the underlying disease activity: Evaluate the control of neurorespiratory diseases symptoms and the stability of the disease. Ensure that the underlying autoimmune response is well-managed with appropriate immunosuppressive medications or other treatments, such as intravenous immunoglobulin (IVIG) or plasmapheresis, to minimize the risk of disease exacerbation during weaning.
4. Gradual reduction of ventilatory support: Initiate weaning by gradually reducing the level of ventilatory support provided. This can be done by reducing the level of positive end-expiratory pressure (PEEP) or pressure support, or by transitioning from pressure-controlled ventilation to modes that provide greater patient effort and control, such as synchronized intermittent mandatory ventilation (SIMV) or pressure support ventilation (PSV).
5. Assessing tolerance to spontaneous breathing trials: Once the patient shows stability and improvement, conduct spontaneous breathing trials (SBTs) to assess their ability to sustain breathing without ventilatory support. SBTs involve temporarily removing ventilatory support, such as transitioning to T-piece trials or utilizing low levels of pressure support, while closely monitoring the patient's respiratory parameters and clinical response. Successful completion of SBTs indicates readiness for extubation.
6. Extubation and post-extubation management: If the patient passes the SBT and is deemed ready for extubation, carefully manage the post-extubation period. Close monitoring of respiratory function, oxygenation, and the need for supplemental oxygen is essential. Non-invasive ventilation (NIV) may be considered as a transition strategy post-extubation, particularly in individuals at higher risk of respiratory distress.
7. Rehabilitation and respiratory muscle training: Once the patient is successfully weaned from mechanical ventilation, initiate rehabilitation and respiratory muscle training to optimize respiratory function. This may involve physical therapy, breathing exercises, and other interventions to improve respiratory muscle strength and endurance.

The complication in mechanical ventilation in cases of respiratory failure in neurorespiratory diseases. In cases of respiratory failure in neurorespiratory diseases, mechanical ventilation is a critical intervention to support breathing. However, there can be potential complications associated with mechanical ventilation in individuals with neurorespiratory diseases. It's important to be aware of these complications and take appropriate measures to prevent or manage them. Here are some common complications:

1. Ventilator-associated pneumonia (VAP): Prolonged mechanical ventilation increases the risk of developing VAP, which is a lung infection acquired during mechanical ventilation. To minimize the risk, strict adherence to infection control measures, such as proper hand hygiene, sterile techniques during airway management, regular oral care, and elevation of the head of the bed, should be followed. Prompt diagnosis and appropriate antibiotic treatment are essential if VAP occurs.
2. Respiratory muscle weakness and atrophy: Prolonged dependence on mechanical ventilation can lead to respiratory muscle weakness and atrophy. This can occur due to disuse and reduced muscle activity. To minimize this complication, strategies such as regular assessment of respiratory muscle strength, early initiation of weaning protocols, and implementation of respiratory muscle training and rehabilitation should be considered.
3. Ventilator-induced diaphragmatic dysfunction: Mechanical ventilation can lead to diaphragmatic dysfunction, characterized by atrophy and reduced contractility of the diaphragm muscle. This can result in prolonged weaning and respiratory muscle weakness. To mitigate this complication, strategies such as diaphragmatic pacing, early mobilization, and spontaneous breathing trials should be implemented to promote diaphragmatic activity and minimize atrophy.
4. Barotrauma and volutrauma: High ventilatory pressures and excessive tidal volumes can lead to barotrauma (lung injury due to increased airway pressures) and volutrauma (lung injury due to excessive stretch). To prevent these complications, ventilator settings should be carefully adjusted, avoiding excessive pressures and tidal volumes. Lung-protective ventilation strategies, such as low tidal volume ventilation and limiting peak inspiratory pressures, should be employed.
5. Atelectasis: Atelectasis, the collapse or partial collapse of lung tissue, can occur during mechanical ventilation. It is often caused by reduced lung volumes and impaired gas exchange. Strategies to prevent atelectasis include lung recruitment maneuvers, positive end-expiratory pressure (PEEP), and adequate alveolar ventilation.
6. Aspiration: Impaired cough reflex and weakened airway protection mechanisms in neurorespiratory diseases can increase the risk of aspiration. Close attention should be paid to proper positioning, oral care, and cuff management to prevent aspiration of oral or gastric contents. Aspiration precautions, such as elevation of the head of the bed and regular suctioning, should be implemented.
7. Cardiovascular complications: Mechanical ventilation can affect cardiovascular function, leading to hemodynamic instability, decreased venous return, and changes in cardiac output. Monitoring of cardiovascular parameters, such as blood pressure, heart rate, and central venous pressure, is important to detect and manage any potential cardiovascular complications.

It's crucial to closely monitor individuals with neurorespiratory diseases who require mechanical ventilation, and promptly address any complications that may arise. A multidisciplinary approach involving neurologists, pulmonologists, critical care specialists, and respiratory therapists is essential to optimize management and minimize the risk of complications associated with mechanical ventilation in neurorespiratory diseases.

The prognosis in mechanical ventilation in cases of respiratory failure in neurorespiratory diseases. The prognosis of individuals requiring mechanical ventilation due to respiratory failure in neurorespiratory diseases can vary depending on various factors, including the severity of the disease, the presence of comorbidities, the promptness of intervention, and the overall response to treatment. Here are some important considerations regarding prognosis:

1. Disease severity: The severity of neurorespiratory diseases can influence the prognosis of individuals requiring mechanical ventilation. Severe cases with profound muscle weakness and bulbar involvement may have a higher risk of complications and a more challenging recovery. However, with appropriate management and support, including mechanical ventilation, many individuals can experience improvement in respiratory function and overall outcomes.
2. Timeliness of intervention: Early recognition and prompt initiation of mechanical ventilation when indicated are crucial in improving outcomes. Delayed initiation of mechanical ventilation in cases of respiratory failure can lead to increased morbidity and mortality. Therefore, timely intervention and close monitoring are essential in managing respiratory failure in neurorespiratory diseases.
3. Underlying disease control: The prognosis can be influenced by the control of the underlying neurorespiratory disease activity. Adequate management of neurorespiratory diseases with appropriate immunosuppressive medications, such as corticosteroids, immunosuppressants, or other immunomodulatory therapies, can help stabilize the disease and improve overall outcomes. Optimal disease control reduces the risk of disease exacerbations and the need for prolonged mechanical ventilation.

4. Response to treatment: The response to specific therapies, such as intravenous immunoglobulin (IVIG), plasmapheresis, or other immunomodulatory treatments, can impact the prognosis. These treatments aim to modulate the immune response and improve muscle strength. Individuals who show a favorable response to these interventions often have better outcomes, including successful weaning from mechanical ventilation.
5. Presence of comorbidities: The presence of comorbidities, such as cardiovascular disease, respiratory infections, or other chronic conditions, can affect the prognosis. Managing comorbidities appropriately and addressing their impact on respiratory function is important in improving outcomes.
6. Duration of mechanical ventilation: The duration of mechanical ventilation can vary among individuals with neurorespiratory diseases. Prolonged mechanical ventilation may be associated with increased risks of complications, including ventilator-associated pneumonia, muscle weakness, and other complications related to immobility and prolonged critical care stay. Early identification of the patient's readiness for weaning and an individualized weaning approach can contribute to better outcomes.
7. Rehabilitation and post-ventilation care: Following successful weaning from mechanical ventilation, rehabilitation and post-ventilation care, including respiratory muscle training, physical therapy, and supportive care, play a crucial role in optimizing long-term outcomes.

It's important to note that the prognosis for individuals requiring mechanical ventilation in neurorespiratory diseases is highly individualized, and outcomes can vary significantly. Close monitoring, timely intervention, and a multidisciplinary approach involving neurologists, pulmonologists, critical care specialists, and rehabilitation specialists are key in managing respiratory failure in neurorespiratory diseases and improving prognosis.

Chest physiotherapy plays a supportive role in the management of respiratory failure in neurorespiratory diseases. It encompasses various techniques aimed at improving lung function, promoting airway clearance, and maintaining respiratory hygiene. While chest physiotherapy is not a primary treatment for neurorespiratory diseases, it can provide adjunctive benefits to manage respiratory symptoms and prevent complications. Here are the key roles of chest physiotherapy in the management of respiratory failure in neurorespiratory diseases:

1. Airway Clearance: Chest physiotherapy techniques, such as chest percussion, vibration, and postural drainage, can help facilitate the clearance of mucus and secretions from the airways. These techniques involve rhythmic clapping or tapping on the chest wall, using hands or special devices, to loosen and mobilize secretions. Postural drainage positions are employed to assist in the movement of mucus from specific lung segments to larger airways for easier expectoration or suctioning.
2. Breathing Exercises: Chest physiotherapy includes breathing exercises that aim to optimize respiratory mechanics and improve lung ventilation. Techniques such as deep breathing exercises, diaphragmatic breathing, and incentive spirometry can help expand lung volumes, improve oxygenation, and enhance respiratory muscle function.
3. Cough Enhancement: Coughing is an essential mechanism for clearing airway secretions. In neurorespiratory diseases patients with respiratory muscle weakness, an ineffective cough may contribute to retained secretions and an increased risk of respiratory infections. Chest physiotherapy techniques, including assisted coughing and huffing, can assist in enhancing cough effectiveness and promoting clearance of secretions.

4. Mobilization and Postural Support: Chest physiotherapy may involve mobilization techniques and postural support to optimize respiratory function. This includes proper positioning of the patient to alleviate respiratory muscle fatigue, enhance lung expansion, and improve overall ventilation.
5. Education and Self-Management: Chest physiotherapy also plays a role in educating patients and their caregivers about techniques they can perform independently to maintain respiratory hygiene and manage symptoms. Providing guidance on breathing exercises, effective coughing techniques, and self-administered airway clearance techniques empowers patients to take an active role in their respiratory care.

It's important to note that chest physiotherapy should be tailored to the individual needs and capabilities of the patient with neurorespiratory diseases. The specific techniques and frequency of sessions may vary depending on the patient's respiratory status, muscle weakness, and overall clinical condition. A qualified physiotherapist or respiratory therapist with experience in neurorespiratory diseases management can provide appropriate guidance and recommendations for chest physiotherapy interventions.

In the management of respiratory failure in neurorespiratory diseases, there are potential infection-related complications that can arise. These complications are mainly due to the impaired respiratory muscle function, compromised airway clearance, and potential immunosuppression associated with the disease and its treatment. Here are some infection-related complications to be aware of:

1. Respiratory Tract Infections: neurorespiratory diseases patients with respiratory muscle weakness may have difficulty effectively clearing mucus and secretions from the airways. This can lead to an increased risk of respiratory tract infections, such as pneumonia and bronchitis. These infections can further compromise respiratory function and worsen respiratory failure.
2. Aspiration Pneumonia: Impaired swallowing function in neurorespiratory diseases can lead to the inadvertent inhalation of food, liquids, or saliva into the lungs, resulting in aspiration pneumonia. Weakened respiratory muscles may make it challenging to cough effectively and clear the aspirated material from the airways, increasing the risk of infection
3. Ventilator-Associated Pneumonia: In cases where mechanical ventilation is required to support respiratory function, there is a risk of developing ventilator-associated pneumonia (VAP). The presence of an artificial airway and prolonged intubation can provide a pathway for bacteria to enter the lungs, leading to infection.
4. Immunocompromised State: Certain treatments for neurorespiratory diseases, such as immunosuppressive medications, including corticosteroids and immunosuppressants, can suppress the immune system. This can increase the susceptibility to various infections, including respiratory infections. Close monitoring and appropriate infection prevention measures are necessary in individuals receiving immunosuppressive therapy.
5. Urinary Tract Infections (UTIs): neurorespiratory diseases patients with muscle weakness, including the muscles involved in bladder control, may have difficulty emptying their bladder completely. Urinary retention can predispose them to urinary tract infections, which can lead to systemic complications if left untreated.
6. Skin and Soft Tissue Infections: Reduced mobility and weakness in the extremities may result in skin breakdown and pressure ulcers. Open wounds and compromised skin integrity increase the risk of skin and soft tissue infections.

To mitigate the risk of infection complications, it is crucial to implement preventive measures such as: Good hand hygiene practices for healthcare providers, patients, and caregivers, Proper care and maintenance of invasive devices such as endotracheal tubes or tracheostomies to reduce the risk of infection, Adequate oral hygiene to prevent dental and oral infections, Early identification and prompt treatment of respiratory infections with appropriate antibiotics, Vaccination against preventable infections such as influenza and pneumococcal pneumonia, Regular monitoring of vital signs, including temperature, to identify signs of infection promptly.

Consulting with a healthcare professional experienced in the management of neurorespiratory diseases is important to develop an individualized care plan that addresses infection prevention strategies and promptly addresses any potential complications.

Ventilator-Associated Pneumonia (VAP) is a specific type of respiratory tract infection that can occur as a complication in the management of respiratory failure, when mechanical ventilation is required. VAP is defined as pneumonia that develops 48 hours or more after endotracheal intubation. Here are some key points about VAP in the context of managing respiratory failure :

1. Risk Factors: Several factors contribute to the increased risk of developing VAP in neurorespiratory diseases patients requiring mechanical ventilation. These include prolonged intubation and duration of mechanical ventilation, impaired cough reflex, ineffective airway clearance due to weakened respiratory muscles, reduced mobility, the presence of an artificial airway, and potential immunosuppression from medications.
2. Pathogens Involved: The most common pathogens associated with VAP include bacteria such as Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, and Streptococcus pneumoniae. These organisms can colonize the respiratory tract and invade the lungs, leading to infection.
3. Clinical Presentation: The clinical presentation of VAP in Pulmonary function tests should be performed and interpreted by qualified healthcare professionals trained in respiratory physiology and lung function testing. They provide objective data that complements clinical assessment and aids in the individualized management of respiratory failure in neurorespiratory diseases patients. patients may be similar to that in other populations. Common symptoms include fever, increased or purulent respiratory secretions, worsening oxygenation, new or persistent infiltrates on chest X-ray, and worsening respiratory distress.
4. Diagnosis: The diagnosis of VAP in Pulmonary function tests should be performed and interpreted by qualified healthcare professionals trained in respiratory physiology and lung function testing. They provide objective data that complements clinical assessment and aids in the individualized management of respiratory failure in neurorespiratory diseases patients.
5. Patients is based on a combination of clinical signs and symptoms, radiological findings (such as infiltrates on chest X-ray or CT scan), and microbiological analysis of respiratory samples obtained through bronchoscopy, bronchoalveolar lavage (BAL), or endotracheal aspirate. Cultures are obtained to identify the causative pathogens and guide appropriate antibiotic treatment.
6. Prevention: Preventive strategies play a crucial role in reducing the risk of VAP. These include implementing strict infection control measures, such as proper hand hygiene, maintaining endotracheal tube cuff pressure, regular oral care, elevation of the head of the bed to prevent aspiration, and daily assessment of the need for continued mechanical ventilation.
7. Treatment: Prompt initiation of appropriate antibiotic therapy is essential for the management of VAP in Pulmonary function tests should be performed and interpreted by qualified healthcare professionals trained in respiratory physiology and lung function testing. They provide objective data that complements clinical assessment and aids in the individualized management of respiratory failure in neurorespiratory diseases patients.
8. Patients. The choice of antibiotics depends on local antibiotic susceptibility patterns and the individual patient's risk factors and comorbidities. Antibiotic therapy should be guided by the results of respiratory sample cultures and adjusted as necessary once susceptibility results are available.
9. Complications and Prognosis: VAP can lead to significant complications, including sepsis, respiratory failure, prolonged hospital stay, increased healthcare costs, and increased mortality rates. Neurorespiratory diseases patients with VAP may experience a more challenging course due to the underlying muscle weakness and compromised respiratory function. Early recognition, appropriate management, and multidisciplinary care are vital for improving outcomes.

It is important for healthcare providers managing Pulmonary function tests should be performed and interpreted by qualified healthcare professionals trained in respiratory physiology and lung function testing. They provide objective data that complements clinical assessment and aids in the individualized management of respiratory failure in neurorespiratory diseases patients. Patients with respiratory failure to be vigilant for the signs and symptoms of VAP and promptly initiate diagnostic and therapeutic measures. Implementing preventive strategies can help reduce the incidence of VAP and improve patient outcomes.

Guillain-Barré syndrome (GBS) is an autoimmune disorder that affects the nerves outside the brain and spinal cord. The exact pathophysiology of GBS is not fully understood, but it is thought to involve an immune-mediated attack on the peripheral nervous system.In GBS, the immune system mistakenly identifies components of the peripheral nerves, including the myelin sheath and axons, as foreign and attacks them. This leads to inflammation and damage to the nerves, which can result in muscle weakness, paralysis, and sensory disturbances.

The specific immune response involved in GBS is thought to be a T-cell-mediated response, which activates macrophages and other immune cells to attack the myelin and axons. This immune response also leads to the release of cytokines, which can further contribute to nerve damage. The damage to the nerves in GBS typically starts at the myelin sheath and progresses to the axons, leading to loss of nerve conduction and motor function. This damage can occur rapidly and can lead to severe muscle weakness and paralysis, as well as sensory disturbances such as numbness and tingling.

Overall, the pathophysiology of GBS is complex and involves both immune-mediated inflammation and damage to the nerves. Understanding the underlying mechanisms of GBS is important for developing effective treatments and improving outcomes for patients with this condition.

Molecular mimicry is one proposed mechanism of the pathophysiology of Guillain-Barré syndrome (GBS). It suggests that a foreign antigen, such as a bacterial or viral infection, triggers an immune response that also targets self-antigens in the peripheral nerves, leading to nerve damage. The molecular mimicry hypothesis suggests that the antigenic components of certain infectious agents, such as Campylobacter jejuni, resemble the components of peripheral nerve myelin. This similarity between the antigenic components

of the infectious agent and the self-antigens in the peripheral nerves can lead to an immune response that mistakenly attacks the peripheral nerves. The immune response triggered by the infectious agent can lead to the production of antibodies that cross-react with self-antigens in the peripheral nerves, leading to inflammation and damage to the nerves. This can result in muscle weakness, paralysis, and sensory disturbances characteristic of GBS. Evidence supporting the molecular mimicry hypothesis in GBS includes the association of certain infectious agents, such as C. jejuni, with the development of GBS. In addition, studies have shown that patients with GBS have antibodies that react with both the infectious agent and the peripheral nerve myelin. However, the molecular mimicry hypothesis is not the only proposed mechanism of GBS pathophysiology, and the exact role of molecular mimicry in GBS remains a subject of ongoing research. Other factors, such as genetic susceptibility and dysregulation of the immune system, may also play a role in the development of GBS.

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction, leading to muscle weakness and fatigue. Respiratory failure can occur in individuals with MG when the muscles responsible for breathing, including the diaphragm and intercostal muscles, become weak and are unable to support adequate ventilation. Respiratory failure is a severe complication that can occur in individuals with Myasthenia Gravis (MG). Myasthenia gravis is an autoimmune disorder that affects the neuromuscular junction, causing muscle weakness and fatigue. The muscles responsible for breathing, including the diaphragm and intercostal muscles, can be affected in MG, leading to respiratory difficulties.

1. Pathophysiology: MG is an autoimmune disorder characterized by antibodies attacking the neuromuscular junction, leading to muscle weakness, including respiratory muscles. In GBS, the immune system targets the peripheral nervous system, primarily affecting the peripheral nerves' myelin sheath. The weakness in GBS typically begins in the extremities and can progress to involve the respiratory muscles.
2. Pattern of weakness: In MG, muscle weakness tends to be more fluctuating, with symptoms worsening with exertion and improving with rest. Weakness often affects the ocular, bulbar, and proximal limb muscles. In GBS, weakness typically presents as a symmetrical ascending paralysis that progresses over days or weeks, starting from the lower limbs and advancing upward. Bulbar weakness can also occur in GBS but is less common than in MG.
3. Timing of respiratory involvement: Respiratory muscle weakness in MG usually occurs later in the disease course, with patients initially presenting with ocular or bulbar symptoms. In contrast, respiratory involvement in GBS can occur early in the disease progression, particularly in severe cases. It is important to note that the timing and severity of respiratory involvement can vary among individuals.
4. Progression of weakness: In MG, weakness tends to worsen gradually over time, and patients may experience exacerbations and remissions. In GBS, weakness usually progresses rapidly and reaches its peak within a few weeks. The prognosis for recovery is generally better in MG compared to GBS.
5. Response to treatment: In MG, treatment with anticholinesterase medications, such as pyridostigmine, can improve muscle strength and reduce symptoms. These medications have limited effectiveness in GBS. In GBS, treatment often involves intravenous immunoglobulin (IVIG) or plasmapheresis to modulate the immune response and promote recovery. These treatments can also be used in MG but are typically reserved for severe or refractory cases.
6. Weaning from mechanical ventilation: Weaning from mechanical ventilation in MG requires close monitoring of respiratory muscle strength, response to treatment, and careful adjustment of ventilator settings. In GBS, weaning can be initiated once the patient shows signs of improvement in muscle strength and respiratory function. The duration of mechanical ventilation may be shorter in GBS compared to MG.

It's important to recognize that these are general differences, and individual presentations can vary. The management of respiratory failure in both MG and GBS requires a multidisciplinary approach involving neurologists, pulmonologists, critical care specialists, and respiratory therapists to ensure appropriate support and optimize patient outcomes.

Respiratory failure in myasthenia gravis typically occurs due to the weakness of the muscles involved in breathing. The diaphragm, which is the primary muscle responsible for inhalation, may become weak and fatigued in individuals with MG. As a result, the ability to generate adequate respiratory effort and maintain proper ventilation may be compromised. Respiratory failure can manifest in two primary forms in myasthenia gravis:

Acute exacerbation:

This occurs when there is a sudden worsening of respiratory muscle weakness, leading to a significant decrease in respiratory function. It can be triggered by various factors, such as respiratory infections, certain medications (e.g., muscle relaxants), emotional stress, or surgery. Acute exacerbations can be life-threatening and require immediate medical attention. Acute exacerbation of respiratory failure in Myasthenia Gravis (MG) refers to a sudden and severe worsening of respiratory muscle weakness, leading to a significant decrease in respiratory function. It is a potentially life-threatening complication that requires immediate medical attention. Acute exacerbations of respiratory failure in MG can be triggered by various factors, including:

1. Infections: Respiratory tract infections, such as pneumonia or bronchitis, can trigger an acute exacerbation. Infections put additional strain on the respiratory muscles and can lead to an increased demand for respiratory effort.
2. Medications: Certain medications can interfere with neuromuscular transmission and exacerbate muscle weakness in individuals with MG. Examples include muscle relaxants, certain antibiotics (e.g., aminoglycosides), and beta-blockers. It is important for individuals with MG to inform their healthcare providers about their condition to avoid medications that may worsen symptoms.
3. Emotional stress: Stressful situations, emotional distress, or extreme fatigue can contribute to the worsening of MG symptoms, including respiratory muscle weakness.
4. Surgery: Surgical procedures, particularly those involving the chest or general anesthesia, can increase the risk of acute exacerbation in individuals with MG. It is crucial for the surgical team to be aware of the patient's condition and take appropriate precautions during anesthesia and postoperative care.

During an acute exacerbation of respiratory failure in MG, individuals may experience the following symptoms: Severe shortness of breath, Inability to speak in complete sentences, Weakness and fatigue in the respiratory muscles, Cyanosis (bluish discoloration of the skin and lips) due to inadequate oxygenation, Use of accessory muscles of respiration (e.g., neck muscles) to aid breathing, Decreased ability to cough effectively, leading to ineffective clearance of secretions

Prompt medical intervention is necessary to stabilize the individual and prevent further deterioration. The management of acute exacerbation of respiratory failure in MG may include:

1. Hospitalization: Individuals experiencing acute respiratory failure often require hospitalization, preferably in an intensive care unit (ICU) where they can receive specialized monitoring and care.
2. Ventilatory support: Non-invasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation may be initiated to assist with breathing. NIPPV involves the use of a mask or nasal interface to deliver pressurized air to the lungs, while invasive mechanical ventilation requires the insertion of a breathing tube into the trachea.
3. Medications: Immediate administration of medications, such as intravenous immunoglobulin (IVIG) or plasmapheresis, may be necessary to rapidly improve muscle strength and control the autoimmune response.
4. Treatment of triggers: If the exacerbation was triggered by an infection or medication, appropriate treatment or discontinuation of the offending agent is essential.

The overall goal of managing acute exacerbation of respiratory failure in MG is to stabilize the individual's respiratory function, optimize muscle strength, and address the underlying cause. Close monitoring and collaboration between healthcare providers, including neurologists, pulmonologists, and critical care specialists, are vital for successful management and prevention of further complications.

Chronic respiratory insufficiency:

In some cases, individuals with myasthenia gravis may develop chronic respiratory insufficiency, where the respiratory muscles gradually weaken over time. This can lead to a decrease in lung capacity and impaired gas exchange. It typically occurs in individuals with long-standing and severe MG. Respiratory failure can occur as a result of chronic respiratory insufficiency in individuals with Myasthenia Gravis (MG). Chronic respiratory insufficiency refers to a progressive weakening of the respiratory muscles over time, leading to a decrease in lung capacity and impaired gas exchange. In myasthenia gravis, the muscles involved in breathing, such as the diaphragm and intercostal muscles, can become weak and fatigued. As these muscles weaken chronically, individuals may experience difficulties with maintaining adequate ventilation and oxygenation, especially during periods of exertion or when respiratory demands increase.

The development of chronic respiratory insufficiency in MG is typically associated with long-standing and severe disease. Factors that may contribute to the progression of respiratory muscle weakness include:

1. Disease duration: The longer an individual has MG, the higher the likelihood of developing chronic respiratory insufficiency. Over time, the autoimmune processes in MG can lead to ongoing damage and weakness in the respiratory muscles.
2. Disease severity: Individuals with more severe forms of myasthenia gravis, particularly those with extensive muscle involvement beyond the ocular muscles, are at a higher risk of developing chronic respiratory insufficiency.
3. Inadequate treatment or non-compliance: Poorly controlled MG or non-adherence to treatment regimens can contribute to the progression of muscle weakness and respiratory compromise.

The symptoms of chronic respiratory insufficiency in myasthenia gravis may include:

1. Shortness of breath: Individuals may experience persistent or worsening breathlessness, even during minimal physical activity.
2. Fatigue: Chronic respiratory insufficiency can lead to increased fatigue due to the effort required to breathe.
3. Decreased exercise tolerance: Individuals may find it challenging to engage in physical activities or exertion due to respiratory limitations.
4. Morning headaches: Poor oxygenation during sleep can result in morning headaches.
5. Sleep disturbances: Disrupted sleep patterns, including frequent awakenings during the night, may occur due to respiratory difficulties.
6. Cyanosis: In severe cases, inadequate oxygenation may cause bluish discoloration of the skin and lips.

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ULTRASONOGRAPHY IN LUNG INFECTION DIAGNOSTIC

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ABSTRACT

Because the interaction of ultrasound with the lung does not generate a direct anatomical image but rather an artifact-based image, the use of thoracic ultrasound examination has been a comparatively recent development. As a result, ultrasound semantics have been established by the evaluation of pulmonary abnormalities and their correlation with particular diseases. Pneumonia continues to be a major factor in hospital admissions and fatalities today. The ultrasonography properties of pneumonia have been proven in a number of investigations in the scientific literature. Although ultrasound cannot be regarded as the gold standard for diagnosing all lung disorders, it has made great strides and attracted more attention, particularly in the wake of the SARS-CoV-2 pandemic. This article aims to provide crucial insights into the application of lung ultrasound in the study of infectious pneumonia and to explore the differential diagnosis.

Keywords : *lung ultrasound, pneumonia*

Introduction

Due to the difficulties posed by air and bone in the lungs, ultrasound has not historically been used for imaging the lungs. The ultrasonic waves are reflected by the air, creating artifacts and hindering visualization. The ability to investigate artefacts as a basis for lung evaluation has become available through advances in ultrasound technology. In the ultrasound examination of the lungs, pneumonia, a serious and potentially fatal condition gets a lot of attention. To aid the differential diagnosis of pneumonia, specific symptoms and indicators have been devised. Lung ultrasound has seen increased interest and utilization as a result of the SARS-CoV-2 pandemic[1].

Fundamentals of Lung Ultrasound

Lung ultrasonography can be performed using simple ultrasound machines. It is possible to use a variety of transducers, according to the depth of penetration. Depending on their clinical condition, the patient can be evaluated in a variety of positions. Some positions, including lifting the arm or resting it on the shoulder across from it, make it easier to access the intercostal regions[2].

However, ultrasound might have limitation to see other parts of chest, like the retrosternal and retroscapular regions. The posterolateral part is frequently the area of choice for suspected pneumonia, with the precise location depending on the underlying mechanism of the illness. Serial follow-up exams can be performed to monitor changes in the sonographic features of the lung fields over time using a standard procedure and ultrasonography markers[1].

Visualization of Lung Ultrasound

Normal lung in Ultrasound

Using longitudinal scans, layers of the chest wall can be examined. The ribs appear as a hyperechoic line with a shadow cone because they entirely reflect ultrasound signals. The intercostal muscles can be seen as horizontal hypoechoic bundles between the ribs, the sternum, and other structures. The region between the soft tissue interface and the ventilated lung appears on ultrasound as a hyperechoic line (pleural line) with horizontal movement known as "sliding," which is synchronized with ventilation. Artifacts also referred to as reverberation artifacts or A-lines appear as horizontal lines below the thoracic cage. The lung base can be recognized by the "curtain sign," which is produced when the lung base moves while breathing[1].

A-lines, which show horizontal artifacts and are common ultrasound findings, don't always signify a medical condition. Certain pulmonary conditions, such as chronic obstructive pulmonary disease (COPD) or pulmonary embolism, which primarily affect bronchial branches, might still show a "normal" A-line ultrasound pattern. Additionally, in cases of pneumothorax, A-lines might not exist, which would eliminate pleural sliding[3].

Lung Abnormality in Ultrasound

Interstitial Sydrome

The existence of vertical artifacts termed B-lines or "comet tails" that can be seen on ultrasound images using the subpleural air interface. These artifacts show up as vertical, hyperechoic reverberation lines that resemble lasers and come from the pleural line. They move synchronously with lung slide and extend below on the screen without fading. Though the precise underlying process is uncertain, B-lines are related to lung interstitial syndrome. Less than three B-lines per lung area are regarded as normal, particularly in elderly patients. However, if B-lines form a continuous front of hyperechoic lines and take up more than 50% of the studied lung field, it is referred to as "white lung."

Diffuse bilateral B-lines are a sign of interstitial syndrome, which can be brought on by interstitial pneumonia, pulmonary edema or diffuse lung disease. Focal numerous B-lines (more than three) are suggestive of focal interstitial syndrome, which is connected to pneumonia, lung contusion, pulmonary infarction, lung malignancy, or pleural illnesses[2].

On lung ultrasonography, the acute respiratory distress syndrome (ARDS) also shows nonhomogeneous distribution of B-lines and uneven pleural lines. The existence of "spared areas" of healthy lung tissue and anterior subpleural consolidations are further characteristics of ARDS. It's interesting to note that several of the ultrasonography traits linked to ARDS and pulmonary fibrosis have also been seen in patients with COVID-19 pneumonia[3].

Pulmonary Consolidation

Pulmonary consolidation develops as a result of the steady loss of alveolar air and fluid buildup in the lungs. Ultrasound can show the consolidation as a discrete area when it reaches the pleural line without any healthy lung tissue in between. Consolidation shows as a compact, diffusely hypoechoic zone with obvious characteristics like blood arteries and bronchial branches, similar to the liver. Hyperechoic spots or linear pictures known as air bronchograms may be visible within the lung parenchyma if the airways are

still patent. Inflammatory illnesses including pneumonia, as well as neoplastic, granulomatous, infarct, and atelectasis diseases, can all lead to consolidation[4].

Pneumonia

Consolidation appears as a diffusely hypoechoic, compact zone that resembles the liver or splenic tissue. The lung parenchyma may show hyperechoic patches or linear pictures known as air bronchograms if the airways are still patent. Along with inflammatory disorders like pneumonia, neoplastic, granulomatous, infarct, and atelectasis diseases can all contribute to consolidation. Different forms of lung consolidation can be distinguished by examining the margins, quantity, ecostructural elements, and features of air bronchograms. The anatomical subtypes of pneumonia include lobar, bronchopneumonia, interstitial pneumonia, and mixed pneumonia, each having unique histological characteristics. Mixed bronchopneumonia manifests as tiny subpleural consolidations surrounded by B-lines, lobar pneumonia manifests as lobar consolidation on ultrasound, interstitial pneumonia is characterized by B-lines and regions of white lung[4].

The sensitivity and specificity of this "liver-like tissue sign" are very high. The "shred sign," another ultrasonography indicator, depicts a smudged and broken border between the consolidation area and aerated parenchyma. Pneumonia with pleural involvement alters the pleural line and lessens or completely eliminates sliding. Infectious lung consolidations in adults frequently spread to the pleura. Within the consolidation area, air bronchograms or hyperechoic/linear punctate patches are frequent observations(3).

In post-obstructive pneumonia, fluid-filled bronchi, also known as fluid bronchograms, are frequently observed. indicated by the presence of anechoic/hypoechoic branched tubular formations connected to the bronchial tree. In 55% of pneumonia cases, ultrasound can also detect consensual pleural effusion, which is a greater detection rate than a typical X-ray(5). The echo pattern gets denser and less uniform as pneumonia progresses. Reverberation artifacts are typical ultrasonography indicators at this stage. Some investigation reveals that ultrasound test for the diagnosis of pneumonia has a sensitivity and specificity more than 90%[6, 7]. The presence of air bronchograms, liver-like consolidation, and hazy margins were found to be highly indicative of pneumonia.

Tiny subpleural consolidations (5 mm), isolated or diffuse B-line aberrations (the "white lung sign"), tiny pleural effusions, and irregularities in the pleural line (thickness >2 mm) are the hallmarks of viral pneumonia. These anomalies are frequently found in the lower lung fields, especially along the lateral and posterior chest surfaces.

Lung Abscess

Lung abscess, a frequent pneumonia side effect, particularly following staphylococcal infection. Hypoechoic, irregular-fringed focal consolidations are seen on ultrasound imaging; as the condition worsens, they become increasingly isolated. Hyperechoic margins develop in the lung tissue nearby. Contrast-enhanced ultrasonography (CEUS) reveals initial and strong contrast enhancement while color doppler function reveals increased vascularity in the margin area[1].

Pulmonary Tuberculosis

Numerous mediastinal, pleural, and pulmonary alterations, including pleural effusion, rupture of the visceral pleura with subpleural consolidations, the development of cavities or abscesses, might be signs of pulmonary tuberculosis. Lesions from tuberculosis frequently have a homogeneously hypoechoic texture and are ill-defined [64]. Ultrasound imaging of miliary tuberculosis reveals several tiny, hypoechoic subpleural nodules (5 mm). Despite this information, CT is still considered the gold standard for diagnosing probable pulmonary tuberculosis[1].

Lung ultrasound in COVID-19

Irregular pleural line and the presence of B-lines, which are frequently accompanied by tiny subpleural consolidations, are ultrasound findings in COVID-19 pneumonia. An increasing number of B-lines suggest a more severe lung involvement. In the lung fields that have been most seriously impacted, subpleural consolidations are seen. Additionally detectable conditions include atelectasis and bacterial superinfection, particularly in individuals with severe respiratory insufficiency. A less frequent sign called a pleural effusion typically points to a more serious illness. The distribution of COVID-19 pneumonia is often uneven, bilateral, and peripheral, with some lung regions being spared. Indicative of COVID-19 pneumonia is the presence of white lung regions in mid-apical places with basal sparing. An ultrasonography finding in COVID-19 pneumonia is a pattern of bilateral distribution of multiform clusters of B-lines alternating with sparing areas[8, 9]

Aplications of Lung Ultrasound

Lung ultrasonography is a useful substitute for or addition to radiographic examinations since it has been demonstrated to be comparable to or even superior to chest X-ray in the diagnosis of pneumonia. It is especially helpful in situations when avoiding ionizing radiation exposure is recommended, including in pregnant women and patients who are children. Lung ultrasonography can be used as a screening or primary diagnostic tool in cases where a chest X-ray or CT scan is not practical, especially in pediatric cases[10]. When there is a strong clinical suspicion despite a negative ultrasound test, chest radiography may be utilized as a supplement to chest CT, which is still the gold standard.

Conclusion

A technique based on the analysis of artifacts is lung ultrasonography. Different artefactual features are connected to various lung illnesses. The etiology and pathophysiology of pneumonia affect its ultrasonography appearance. The first stages of most viral and atypical bacterial etiologies are characterized by a B-line pattern. Lung consolidations can occur up to the startling appearance of streptococcal lobar pneumonia in bacterial etiologies. In the early stages of viral pneumonia caused by SARS-CoV-2 infection, several B-lines with nonhomogeneous distribution and sparing zones are present; in the most severe cases, consolidations may also be visible. Ultrasound can be helpful in guiding diagnostic-interventional operations, monitoring clinical evolution, and verifying consequences.

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SYMPOSIUM DAY 2

SUNDAY, JUNE 18th 2023

24th INTERNATIONAL MEETING ON RESPIRATORY CARE INDONESIA (Respina) 2023

OSA DIAGNOSIS AND MANAGEMENT

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ABSTRACT

Untreated obstructive sleep apnea (OSA) syndrome is associated with a number of clinical consequences such as daytime sleepiness and reduced quality of life, as well as cardiovascular and metabolic dysfunction including hypertension, heart failure, stroke and diabetes. This is a highly prevalent disorder, with a recent study suggesting a billion people worldwide may have this disorder (1). Obesity, which is increasing world-wide, is a major factor contributing to the development of upper airway obstruction during sleep. However, craniofacial structure and bony restriction can result in OSA at lower body mass indices.

The first step in management is to recognise the potential risk of this disorder in an individual, looking for physical characteristics and symptoms which may suggest the presence of this disorder. A number of questionnaires and symptom scales have been developed to increase the accuracy of pre-screening. Used in an outpatient setting, these questionnaires can be useful in aiding decisions around whether the individual should undergo more extensive sleep breathing testing, such as polysomnography (PSG). While traditionally, the PSG was considered routine practice to diagnose OSA, improvement in technology has moved management of many non-complex OSA patients out of sleep laboratories and into the patient's home. In addition, researchers are now looking beyond the metric of apnea-hypopnea index (AHI) to determine the severity and consequences of OSA. Continuous positive airway pressure (CPAP) is a very effective therapy for this disorder, although other approaches like mandibular advancement splints, positional therapy and weight loss are also additional or alternative therapies. Improvements in daytime sleepiness and sleep-related quality of life are expected with the institution of CPAP, with adherence to therapy a key factor in treatment benefits. There are strong associations between OSA and the development of a range of cardiometabolic disorders. However, a number of large RCTs comparing CPAP to no intervention have failed to show a benefit of CPAP in preventing cardiovascular events (2-5). While these results are disappointing, the patient population primarily recruited into these studies are not reflective of patients shown to benefit from CPAP in observational studies (6), that is sleepy patients with AHI > 30 events/hr. The importance of symptom subgroups when considering the cardiovascular benefits of CPAP treatment has been highlighted (7).

As we move into the era of personalised medicine, how we manage OSA is likely to change over the next few decades. Understanding the heterogeneous nature of OSA in terms of underlying pathophysiology is opening up research into new approaches to identify and manage this disorder, looking beyond AHI and symptoms, to physiology and genetic signatures.

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A MULTIDISCIPLINARY APPROACH IN MANAGING DYSPHAGIA

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ABSTRACT

Dysphagia or difficulty in swallowing is correlated with anatomic abnormalities, neuromuscular dysfunction, and disturbance in behavior as well as sensorimotor function. It is found in stroke, Parkinson's disease, traumatic brain injury, dementia, and children with oropharyngeal maldevelopment or neuromuscular dysfunction. Impaired swallowing function results in health consequences, i.e. respiratory complications, malnutrition, dehydration, low quality of life, and death; psychological problems; and socioeconomic burden. Especially in children, dysphagia causes serious long-term effects on their development, resulting in malnutrition and failure to thrive.

A multidisciplinary approach to diagnostic and therapeutic procedures should be taken to overcome the long-term effects of dysphagia. It requires effective collaboration from a speech-language therapist, dietician, gastroenterologist, otorhinolaryngologist, neurologist, geriatrician, radiologist, occupational therapist, and dentist.

Diagnosis of dysphagia can be made through questionnaires (EAT-10, GUSS, DHI), physical examination, and swallowing evaluation (VFSS and FEES). During swallowing evaluation, Murray secretion scale (MSS) and Penetration Aspiration Scale (PAS) are assessed.

This full paper and presentation give an in-depth and comprehensive explanation of the importance and the need for multidiscipline collaboration and involvement of various important roles in diagnosing and managing dysphagia.

Keywords: *dysphagia, swallowing, multidisciplinary, VFSS, FEES*

Definition of Dysphagia

Per definition, "dys" means difficulty or problem, while "phagein" means swallowing, hence dysphagia is defined as difficulty in swallowing. During the physiological swallowing process, the swallowed bolus is failed to be delivered from the stomach to the gaster. This pathologic condition is associated with different diseases which involve anatomic abnormalities or neuromuscular dysfunction of the oral cavity, pharynx, larynx, and esophagus. Aside from structural and anatomical abnormalities, dysphagia is also correlated with disturbances in behavior, motor, and sensory activity prior to the swallowing process, including cognitive awareness of mealtime, visual recognition of food, and physiological response towards smell and presentation of the food in the form of increased saliva production. [1,2,3]

The burden caused by dysphagia and its complications

Impaired swallowing function may cause considerable and serious medical, psychological, social, and economic burdens. Its true prevalence is difficult to determine. However, in a large survey, 1% of dysphagia

occurs in children, while 10-27% of the cases have been reported among older community-dwelling residents. Among preterm infants and developing children-feeding problems, oropharyngeal dysphagia may cause unexplained respiratory symptoms and failure to thrive due to low intake of nutrition. Oropharyngeal dysphagia is also reported in more than half of acute stroke patients and patients accompanied by traumatic brain injury, such as Parkinson's disease and dementia. The consequences of dysphagia are directly correlated with the overall prognosis. It may lead to various complications, such as aspiration pneumonia, malnutrition, and dehydration, which may lead to low quality of life and death.[3] Aspiration pneumonia elevates infectious complications, especially in Parkinson's disease or stroke patients. The higher mortality rate due to dysphagia in older patients is 65.8% at 1-year follow-up. Among children, dysphagia may cause long-term sequelae effects towards the development of normal swallowing function, thus impairing overall growth and development. In addition, dysphagia may cause psychological effects by causing depression, low mood, anxiety, and panic during eating in public, especially in the elderly. Dysphagia also causes a heavy burden on healthcare resources, especially in stroke-related dysphagia and Parkinson's disease patients which cost nearly 25%. Higher expenses, i.e. 40% are due to Alzheimer's disease-related dysphagia. Higher rate of hospitalization and higher risk of infection cause longer duration of stay in the hospital, hence increasing the cost of medical treatment and equipment.[4]

Dysphagia is a very complex medical problem that needs a multidisciplinary approach for its diagnostic and therapeutic procedures. Many disciplines are involved in managing dysphagia. Otorhinolaryngologists conduct diagnostic evaluations using FEES and laryngoscopy and manage the patient through cricopharyngeal myotomy and tracheostomy. Dietician recommends the right and proper food consistency, nutritional content, and feeding routes. Neurologists manage dysphagia due to neurogenic disease, i.e. stroke, Alzheimer's disease, and Parkinson's disease. Geriatrician takes part in managing multimorbidity, polypharmacy, and comprehensive examination, diagnostic, and management planning. Physical medicine and rehabilitation physicians perform the management of swallowing mechanics, such as muscle strength, positioning, and posture.

Figure 1. Multidisciplinary approach for dysphagia management

Physiology of swallowing

Swallowing is strongly associated with the central nervous system which coordinates the oropharyngeal structures as well as involves nerves and muscles. This complex coordination occurs in several stages. There are 4 main stages of normal swallowing: (1) the oral phase, (2) the pharyngeal phase, and (3) the esophageal phase.

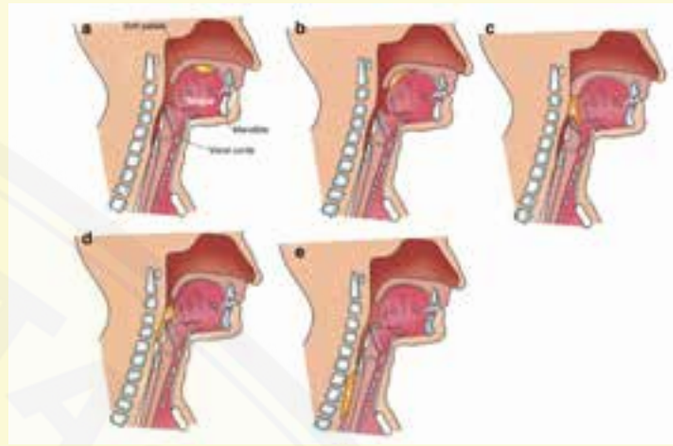


Figure 2. Physiology of swallowing

The oral phase is started with oral preparation, in which the tongue moves the bolus to place them in the right position underneath the teeth. This movement is coordinated by the intrinsic and extrinsic muscles. The intrinsic muscle attaches to longitudinal, vertical, and transversal muscles, whereas extrinsic muscle attaches to hyoid, styloideus process, and other aponeurosis including hyoglossus, styloglossus, genioglossus, and palatoglossus. The tongue movement mixed saliva and bolus to achieve the right consistency to be swallowed. The tip of the tongue meets the anterior part of the palate, hence pushing the bolus backward towards the pharynx. Another structure that Is involved during the oral phase is the velum, which comprises 5 muscles, i.e. tensor veli palatine, palatoglossus, palatopharyngeus, levator veli palatine, and uvula muscle. [5,6]

The pharyngeal phase coordinates two processes, i.e. breathing and swallowing. During swallowing, the mylohyoid muscle automatically involves. Rhythmic muscle contraction occurs to push the bolus toward the upper esophageal sphincter (UES). The involved muscles are the anterior digastric, geniohyoid, stylohyoid, styloglossus, posterior part of the tongue, superior-middle-inferior constrictor, palatoglossus, and palatopharyngeal muscle. After the swallowing process finishes, the UES will be closed due to cricopharyngeal contraction. [6]

There are two valves involved during this phase, i.e. (1) velopharyngeal, (2) laryngeal, (3) tongue base, and (4) cricopharyngeal or esophageal sphincter. The velopharyngeal valve includes the velum and pharyngeal wall which hinder food bolus from moving into the nose. If the valve is impaired, the pressure needed to push the bolus is lacking, thus causing pharyngeal residue. The laryngeal valve functions to ensure the food bolus falls into the pharynx, not the esophagus. The laryngeal valve will be closed at three stages sequentially, firstly the epiglottis and aryepiglottic fold, followed by the false vocal cord and arytenoid cartilage, and lastly the true vocal cord. The third valve is the tongue base which attaches to the posterior part of the pharyngeal wall to mobilize the bolus through the pharynx and gain adequate pressure to push the bolus. Inadequate tongue movement results in food residue in the vallecula.[5] The fourth valve is located near the cricoid-pharynx, called the pharyngo-esophageal sphincter which consists of cricoid cartilage and cricopharyngeal muscle. The sphincter is closed preventing the air to flow into the esophagus. During the swallowing process, the cricopharyngeal muscles relaxes to let the cricoid cartilage moves upwards and

forwards to open the UES, hence the food bolus flows through the esophagus. [7,8] Meanwhile, Logemann (1998) introduced 6-valves-model, which include (1) lips, (2) oral tongue, (3) velopharyngeal sphincter, (4) larynx, (5) tongue base and pharyngeal wall, and (6) cricopharyngeal sphincter.

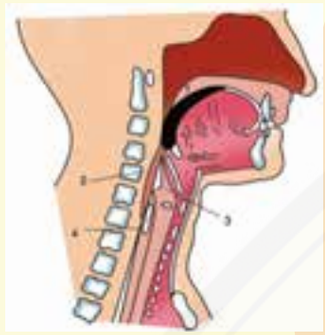


Figure 3. Neuromuscular structure related to swallowing reflex: (1) Closure of the soft palate, (2) peristaltic action, (3) elevation and closure of the larynx and (4) relaxation of the cricopharyngeus muscle

The esophageal phase involves the intrinsic contraction of the esophagus, which is coordinated by the autonomic nervous system, hence it acts involuntarily. Once the food bolus has passed through the UES, it is pushed downwards towards the esophagus by the peristaltic movement. The lower esophageal sphincter (LES) relaxes to let the bolus flows down toward the stomach.[9]

Diagnosis

Diagnosis of dysphagia can be made through questionnaires, physical examination, and swallowing evaluation

Questionnaire

EAT 10

EAT-10 is an eating screening assessment tool developed in the United States in 2008. It measures dysphagia risk to conduct an assessment for patients who need early multidisciplinary intervention. The questionnaire consists of 10 questions that assess the patient's functionality, emotional, and physical symptoms. Each question can be answered using a score ranging from 0 (no problem) to 4 (severe problem) with a total score of 40. After summing up the points, if the score is 3 or higher, then the patient might have a swallowing problem. [10,11]

Based on a study conducted in Brazil with the largest sample size to evaluate the frequency of risk of dysphagia using EAT-10, it was reported that there was a significant correlation between high EAT-10 score with worse functional ability, higher frequency of comorbidities, aging, nutritional risk and malnutrition, and BMI.

Dysphagia Handicap Index (DHI)

Dysphagia handicap index is a diagnostic tool that is commonly used in clinical practice. It consists of 25 items or questions which are divided into 3 main subjects, i.e. 9 items of physical scale, 7 items of emotional scale, and 9 items of functional scale. The answer is presented on a scale from never, sometimes, and always. The score will be summed up and categorized into four levels of severity, i.e. 1 means no difficulty at all; 4 means somewhat of a problem; and 7 means the worse problem you could have.[12]

Gugging Swallowing Screen (GUSS)

Gugging swallowing screen consists of two parts: (1) Preliminary investigation or indirect swallowing test; and (2) Direct swallowing test. During the indirect swallowing test, the observed components are vigilance, cough and/or throat clearing, and saliva swallow in which each component will be scored 1 for "yes" answer and 0 for "no" answer. If the total score is between 1 to 4, then further investigation should be conducted, whereas a score of 5 should be continued by conducting the direct swallowing test. The direct swallowing test comprises several indicators needed to be assessed, i.e. deglutition, cough, drooling, and voice changes. Each indicator will be tested by different food consistency, such as semi-solid, liquid, and solid. Score 0 is given if the patient cannot swallow et al, while score 1 means delayed swallowing, while score 2 is given for a successful swallowing process. While the other indicators, such as cough, drooling, and voice change are scored 0 for a "yes" answer and 1 for a "no" answer. A sum score of 1-4 needs further investigation, while a score of 5 needs additional tests using different consistency. If the total score is 5 out of 5 in each consistency, thus the swallowing process is normal. The score of each step are sum up, a total score of: (1) 0-9 is interpreted as severe dysphagia with a high risk of aspiration which needs NPO, needs nasogastric tube or parenteral; (2) 10-14 is interpreted as moderate dysphagia with a risk of aspiration which needs dysphagia diet using semisolid textures, no liquid medication, needs nasogastric tube or parenteral; (3) 15-19 is interpreted as slight dysphagia with a low risk of aspiration which needs dysphagia diet using puree and soft food, drinking liquid very slowly; 20 is interpreted as slight of no dysphagia with a low risk of aspiration which require normal diet. Further functional swallowing assessment with FEES or VFES should be conducted if the score is below 20. [13]

Examination

Several objective tools can be advised for swallowing evaluation, i.e. Video Fluoroscopic Swallowing Study (VFSS) and Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Video Fluoroscopic Swallowing Study (VFSS)

Video fluoroscopic swallowing study is a radiological assessment or examination which presents the anatomy of the oral cavity and the throat, as well as shows the physiology of swallowing. VFSS evaluates the ingestion process using different consistencies and textures which already mixed with contrast. 14 This test is able to evaluate "silent aspirations", which is a condition where the aspiration happens without activating the cough reflex. However, the downside of VFSS is its inability to evaluate aspiration, penetration, or retentions of the secretion. It shows a more accurate assessment of the oral phase; whereas FEES examination is able to assess the residue secretion during swallowing. [14]

Several indications to perform VFSS are (1) to identify the anatomy and physiology of swallowing; (2) To evaluate the integrity of airway protection before, during, and after swallowing; (3) To evaluate the effectiveness of swallowing maneuvers and its ability to take in different textures and consistencies, as

well as assessing the sensory function of the larynx and lower larynx; (4) To provide recommendations for the most optimal food and fluids delivery route; (5) To acquire the most recommended and optimal swallow techniques; (6) To further assess the swallowing function, especially in patients with neurological disease, degenerative CNS diseases, head and neck cancers, after tracheostomy, spinal cord trauma, COPD, or cerebral palsy. [14]

During the VFSS procedures, the assessments consist of 4 parts, i.e. (1) Assessment of the swallowing phase; (2) Patient's personal data; (3) Consistencies and textures of the food; (4) Therapeutic part. The swallowing phases consist of oral phase, pharyngeal phase, and esophageal phase. During oral phase, the tongue movement, food residues, fragmentary swallowing due to improper processed bolus, mechanism of chewing, and the ability to clear the food from oral cavity.[14]

During pharyngeal phase, silent aspirations are assessed. Aspiration is when food or saliva penetrates below vocal cord; while residue is when a food content is retained in the lower pharynx, base of the tongue, and oral cavity. While residues is a food content that is retained in the lower pharynx, epiglottal fossae, and posterior wall of the throat. [14]

In esophageal phase, the need of collaboration with a gastroenterologist will be assessed. It determines whether the food passes into the esophagus through the stomach or not. The presence of fistula, esophageal diverticula, and reflux can be examined. [14]

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Fiberoptic endoscopic evaluation of swallowing is a procedure to visualize and evaluate nasopharyngeal and oropharyngeal structures by inserting a flexible nasendoscope transnasally. In addition, secretion, sensory response, and pharyngeal swallow function can be assessed. This examination is able to detect dysphagia, aspiration, and penetration during pre and post-swallow. The purpose of conducting FEES is to acquire a better understanding of the physiological, and pathological findings regarding swallowing as well as its etiology and severity. In addition, FEES may also assist the management and therapeutic strategy including the safety of oral feeding to prevent aspiration.[15]

The indication of performing FEES are to evaluate (1) the ability to swallow real foods and fluids; (2) Penetration, aspiration, and airway protection; (3) Laryngopharyngeal residue; (4) Vocal cord mobility; (5) Swallow fatigue over time; (6) Secretion management; (7) Velopharyngeal structures and function; (8) Velopharyngeal sphincter and nasal regurgitation. While the practical indications for performing FEES are to observe the structure and function of the swallowing process which cannot be evaluated by VFS. Patients who are in critical care or on tracheostomy are indicated to undergo FEES examination. [15]

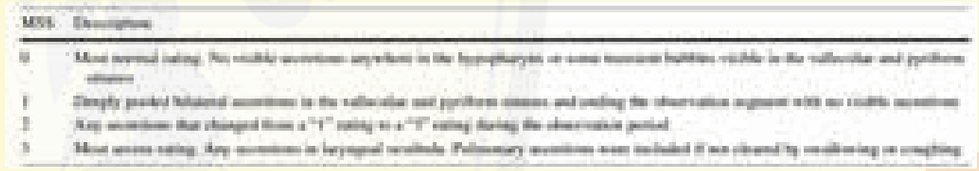
The contraindications of FEES examinations are skull base or facial fracture or surgery within the last 6 weeks, life-threatening epistaxis for the last 6 weeks, nasal cavity trauma due to injury or surgery for the last 6 weeks, nasopharyngeal stenosis, craniofacial anomalies, and laryngectomy for the last 2 weeks. [15]

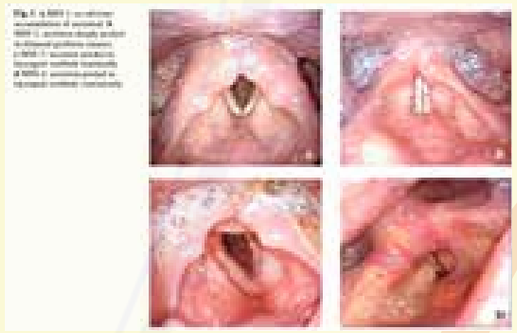
Several adverse effects and complications might happen, both minor and major complications. The minor adverse are patient discomfort, gagging, and vomiting. If the patient is present with nausea, hence the FEES examination should be postponed. The complications of FEES examination are epistaxis, vasovagal response, reflex syncope, allergy to local anesthesia, laryngospasm, and severe aspiration. [15]

Before conducting the examination, the equipment and personnel are prepared. The procedure starts without applying anesthesia since it may interrupt the sensory aspects of the swallowing process. However, local anesthesia may be applied if the patient has poor tolerance toward the endoscope. [15] There is six food bolus with different consistencies, approximately 5-10 cc volume each. The first three consistencies are puree administered using spoon, then followed by three thin liquids (white, fat free, skim milik) which are administered using straw. During every consistency, the evaluation is performed to evaluate the physiology of the swallowing structures, i.e. base of tongue, pharynx, and larynx. [16]

In order to determine secretion status and aspiration, the Murray Secretion Scale (MSS) is used. A patient without any significant saliva accumulation is categorized MSS grade 0; whereas if the secretion pools in the vallecula adan pyriform sinus without any laryngeal penetration, then it is categorized as MSS grade I. If the secrets accumulate in the laryngeal vestibule during the examination, then it is considered as grade II. If the secret is already present in the vestibule at the start of the examination, then it is grade III. [17] (See Table 1)

Table 1. Murray secretion scale (MSS) [17]





The presence of aspiration is assessed using FEES examination based on penetration aspiration scale or PAS. It consists of 8 point-scale, ranging from score 1 (material does not enter airway) to score 8 (material enters the airway, passes below the vocal folds, and no effort is made to eject). The interpretation of the PAS system is presented in Table 2.[17]

Table 2. Penetration – aspiration scale (PAS) [17]

	PAS	Description
Normal	1	Material does not enter airway
Penetration	2	Material enters the airway, remains above the vocal folds, and is ejected from the airway
	3	Material enters the airway, remains above the vocal folds, and is not ejected from the airway
	4	Material enters the airway, contacts the vocal folds, and is ejected from the airway
	5	Material enters the airway, contacts the vocal folds, and is not ejected from the airway
Aspiration	6	Material enters the airway, passes below the vocal folds, and is ejected from the airway
	7	Material enters the airway, passes below the vocal folds, and is not ejected from the airway
	8	Material enters the airway, passes below the vocal folds, and no effort is made to eject

Another criterion using FEES examination to assess the presence of post-swallow pharyngeal residue severity is using the Yale Pharyngeal Residue Severity Rating Scale. These anatomy-based criteria define the residue location (vallecular or pyriform sinus) and its amount (severe, moderate, mild, trace, and none). The presence of pooled secretions in the laryngeal vestibule is highly correlated with aspiration pneumonia in children and prandial aspiration in adults.[16]

Below are examples of FEES findings among neurogenic dysphagia patients.

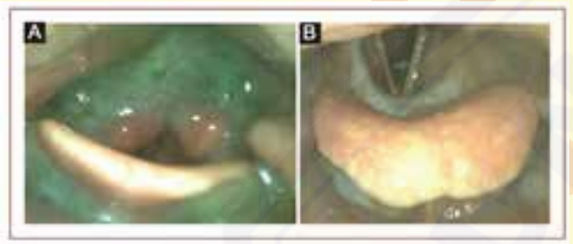


Figure 5. Pathological FEES examination findings in patients with neurogenic oropharyngeal dysphagia. A: residues in vallecula epiglottis and pyriform sinus with penetration/aspiration risk. B: penetration and aspiration of fluid [18]

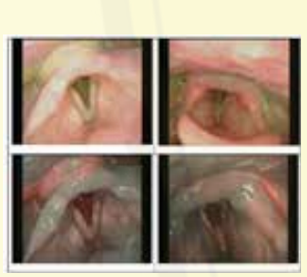


Figure 6. Pathological FEES examination findings in dysphagia: post deglutive findings with green dyed milk (thin fluid level 0). The aspirated milk on true vocal fold an between the vocal fold and trachea[19]

Figure 7. Pathological FEES examination findings in patients with Alzheimer disease and progressive dysphagia. A: Yale score 5/5 for each site. No penetration or aspiration after primary swallow. B: Penetration and aspiration after 2 cued clearing swallows. C: Partially cleared residue after multiple cued swallows. No attempt to cough and clear the aspiration. The black arrow shows the aspirated puree in Subglottis [20]

Swallowing Exercises

There are several swallowing exercises as part of dysphagia management. It consists of indirect and direct exercises. Indirect exercise gives more focus on the movement of the oral organs, such as speed, range of motion, and accuracy; as well as the improvement in respiratory function to expectorate.

a. Posture maintenance

   Ideally, the pattient are seated with their hips low down and their middle and lower back in contact with the back of the chair. Both feet should be put in the ground. The arms should be hang down or at the wheelchair. The patient should breathe deeply in a relax position. The upper body and shoulder muscle should be relaxed by up-and-down movement of the shoulder.

b. Coarse movement of oral organs

   Mandibular depression, mandibular elevation, as well as opening and closing the mouth.

   Effortful swallow is conducted by collecting all the saliva in the mouth and keep it on the center of the tongue. The lips should be close and pretending to swallow a grape whole in one bite.

   Mendelsohn maneuver uses the swallowing saliva to improve laryngeal elevation. Hence, the larynx is kept elevated. At the same time, the patient is asked to hold their breath simultaneously. The exercise starts by pressing the tongue against the roof of the mouth and swallow, then squeeze the floor of mouth and throat muscles to hold the adams apple up for 3 seconds.

   Isometric and isokinetic shaker are done by lying down in a flat surface and ask the patient to lift the chin towards the chest and hold for several seconds.

   Masako maneuver is done by sticking the tounge out of the mouth between the front teeth and gently bite down to hold it in place. Swallow while keeping the tongue between the teeth.

   Tongue range of motion is conducted by protrusion, retraction, and rounding the tounge. Other oral movement exercise is sticking the tongue out and pulling it back in, as well as elevating the tip and the back of the tongue. The patient should touch the corner of the mouth with the tip of the tongue. The tongue range of motion exercise can be applied for lip range of motion.

   Tongue strength exercise is done by pushing the tongue out against the tongue depressor. This can be applied to exercising the tip, middle, and base of the tongue.

   To improve expectoration, breathing exercise is conducted by hard blowing, soft blowing, and other patterns of exhalation. Vocalization exercises are also recommended by reading out loud and repeating meaningless words using labial consonants (p and b), alveolar consonants (t and d), and palatal consonants (k and g). the purpose

Direct exercises for dysphagia patients are using jelly or other thickening agents. The assistance should be provided depending on patients' abilities to swallow and expectorate. After several swallows and voluntary throat clearing, the wet hoarseness is evaluated using an aural scale.

Conclusion

Dysphagia is defined as swallowing difficulties due to many etiologies, which may happen in children, adults, and the elderly. This medical problem may give serious burdens in health as complications, low quality of life, death; and other aspects, such as psychological, social, and economic. A multidisciplinary management approach is very pivotal. Early diagnosis and comprehensive inter-discipline treatment are expected to manage dysphagia.

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RESPIRATORY PREPAREDNESS & MANAGEMENT IN DISASTER

Prof. Dr. Francis Lee Chun Yue, MBBS, FRCSEd (A&E), FAMS

ABSTRACT

A civil emergency is a sudden incident involving actual or potential loss of lives and damage to property on a large scale in excess of which rescue agencies can deal with normally or which may pose grave implications at national, diplomatic or political level. In dealing with a disaster, health institutions will need a disaster plan and train the staff to effectively execute the plan. One of the key concern in managing a disaster is the need to protect staff against any potential hazards. Respiratory hazards are usually associated with the issue of contamination from hazardous materials, dusts and aerosols brought from the scene. Important considerations include the use of personal protective equipment and the decontaminating the casualty. The airway and ventilation management of contaminated mass casualties is difficult not only because of the numbers that are presented but also the challenges for personnel operating in a HazMat environment.

MAINTAINING RESPIRATORY HEALTH

Bulent Tutluoglu

ABSTRACT

The most important thing for maintaining the lung health is to avoid using or exposing to tobacco products. Active or passive smoking is not only a major cause of lung cancer but lung diseases such as Chronic Obstructive Pulmonary Disease ,Chronic Bronchitis, interstitial lung diseases. Vaping is also has some potential harms on the lung health. Drug addiction may cause some severe lung problems. One another important issue for lung health is the quality of the air that we breathe in. Indoor and outdoor air pollution may have some severe effects on both the airways and the lung. Maintaining a healthy body weight is important for lung health . Obese people have less lung capacity and also the lungs have to work harder in order to fulfill the needs of an overweight body. Making regular aerobic and respiratory muscle exercises is very crucial for improving lung health. It is also advised to stay away from respiratory infections. For this purpose influenza , pneumococcal ,herpes, RSV vaccines may be applied to adults for protection.

Key words: *Lung, smoking ,air pollution, exercise*

THE ROLE OF LEVOFLOXACIN IN HOSPITAL ACQUIRED PNEUMONIA/COMMUNITY ACQUIRED PNEUMONIA

Wahyuningsih Suharno

ABSTRACT

Background

Pneumonia and influenza combined is the leading cause of death and the most common cause of infection-related mortality.[1] Streptococcus pneumoniae as the most commonly identified pathogen. The estimated annual economic burden of CAP in the United States exceeds $17 billion.[1,2]

Many microbiologic pathogens can cause CAP. Pneumonia traditionally has been classified as typical, usually caused by S. pneumoniae, or as atypical, caused by Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella species, and respiratory viruses. However, it is often not possible to distinguish typical versus atypical pneumonia solely on clinical grounds.[3,4]

The patient history should focus on detecting symptoms consistent with CAP, underlying defects in host defenses, and possible exposure to specific pathogens. Persons with chronic obstructive pulmonary disease or human immunodeficiency virus infection have an increased incidence of CAP. Patients should be asked about occupation, animal exposures, and sexual history to help identify a specific infectious agent. A recent travel history (within two weeks) may help identify Legionella pneumonia, which has been associated with stays at hotels and on cruise ships. Influenza is often suggested on the basis of typical symptoms during peak influenza season.[5,6]

Definition

Community-acquired Pneumonia (CAP) is pneumonia acquired outside a hospital setting

Community-acquired pneumonia is diagnosed by clinical features (e.g., cough, fever, pleuritic chest pain) and by lung imaging, usually an infiltrate seen on chest radiography.

Hospital-acquired pneumonia (HAP) is defined as pneumonia not associated with mechanical ventilation that occurs at least 48 hours after a patient has been admitted to the hospital and that was not incubating at the time of admission.

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops in patients receiving mechanical ventilation that occurs at least 48 hours after endotracheal intubation.

Initial evaluation should determine the need for hospitalization versus outpatient management using validated mortality or severity prediction scores. Selected diagnostic laboratory testing, such as sputum and blood cultures, is indicated for in patients with severe illness but is rarely useful for outpatients.

Initial outpatient therapy should include a macrolide or doxycycline. For outpatients with comorbidities or who have used antibiotics within the previous three months, a respiratory fluoroquinolone (levofloxacin or moxifloxacin), or an oral beta-lactam antibiotic plus a macrolide should be used. Inpatients not admitted to an intensive care unit should receive a respiratory fluoroquinolone (levofloxacin or moxifloxacin) or a beta-lactam antibiotic plus a macrolide. Patients with severe community-acquired pneumonia or who are admitted to the intensive care unit should be treated with a beta-lactam antibiotic, plus azithromycin or a respiratory fluoroquinolone (levofloxacin or moxifloxacin). Those with risk factors for Pseudomonas should be treated with a beta-lactam antibiotic (piperacillin/tazobactam, imipenem/cilastatin, meropenem, doripenem, or cefepime), plus an aminoglycoside and azithromycin or an antipseudomonal fluoroquinolone (levofloxacin or ciprofloxacin). Those with risk factors for methicillin-resistant Staphylococcus aureus should be given vancomycin or linezolid. Hospitalized patients may be switched from intravenous to oral antibiotics after they have clinical improvement and are able to tolerate oral medications.[5,6]

RADIOLOGIC EXAMINATION

An infiltrate on lung imaging, usually chest radiography, is required for the diagnosis of CAP; therefore, the test should be performed in patients with clinically suspected CAP. includes a tool for identifying patients with respiratory illness who would benefit from chest radiography.[1,3] The extent of radiographic findings may help identify the severity of illness and assist with initial point-of-care decisions. Lobar consolidation, cavitation, and pleural effusions suggest a bacterial etiology. Diffuse parenchymal involvement is more often associated with Legionella or viral pneumonia.1-3

SPUTUM CULTURE AND BLOOD CULTURE

Routine sputum culture and blood culture with nor against routinely obtaining sputum Gram stain and culture in all adults with CAP managed in the hospital setting. Two situations in which we recommend sputum Gram stain and culture: in hospitalized patients with severe CAP, and when strong risk factors for MRSA and P. aeruginosa are identified.[4,5]

ANTIBIOTIC THERAPY

Because the exact causative organism is not identified in many patients with CAP, treatment is usually empiric. All hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population.

Recommendations for antibiotic therapy

For healthy outpatient adults without comorbidities or risk factors for MRSA or pseudomonas. Initial outpatient therapy should include Amoxicillin, doxycycline or macrolide.

For outpatients with comorbidities or who have used antibiotics within the previous three months, a respiratory fluoroquinolone (levofloxacin or moxifloxacin), or an oral beta-lactam antibiotic plus a macrolide should be used. Inpatients not admitted to an intensive care unit should receive a respiratory fluoroquinolone (levofloxacin or moxifloxacin) or a beta-lactam antibiotic plus a macrolide. Patients with severe community-acquired pneumonia or who are admitted to the intensive care unit should be treated with a beta-lactam antibiotic, plus azithromycin or a respiratory fluoroquinolone (levofloxacin or moxifloxacin). Those with risk factors for Pseudomonas should be treated with a beta-lactam antibiotic (piperacillin/tazobactam, imipenem/cilastatin, meropenem, doripenem, or cefepime), plus an aminoglycoside and azithromycin or an antipseudomonal fluoroquinolone (levofloxacin or ciprofloxacin). Those with risk factors for methicillin-resistant Staphylococcus aureus should be given vancomycin or linezolid. Hospitalized patients may be switched from intravenous to oral antibiotics after they have clinical improvement and are able to tolerate oral medications.[5,6]

Conclusions

Most patients with CAP can be adequately treated with regimens that have been used for multiple decades. Patients with CAP who have significant comorbidities and frequent contact with healthcare settings and antibiotics is increasing, and, in some settings, the rates of infection with MRSA or P. aeruginosa are high enough to warrant empiric treatment.

Hospital generate antibiograms to guide healthcare professionals with respect to the optimal choice of antibiotics. Minimize patient harm and exposure to unnecessary antibiotics and reduce the development of antibiotic resistance. The antibiogram data be utilized to decrease the unnecessary use of dual gram-negative and empiric methicillin-resistant Staphylococcus aureus (MRSA) antibiotic treatment. Short-course antibiotic therapy for most patients with HAP or VAP independent of microbial etiology, as well as antibiotic de-escalation.

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THE ROLE OF COMBINATION IMMUNOMODULATOR AND VITAMIN: FOR PREVENTION AND TREATMENT INFECTION

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ABSTRACT

Respiratory infections, including both upper and lower respiratory tract infections, pose a significant global health burden, leading to substantial morbidity and mortality rates. Immunomodulators and vitamins have gained attention for their potential role in preventing and treating respiratory infections by enhancing immune responses. This literature review aims to explore the mechanisms of action and potential benefits of combination immunomodulator and vitamin therapy in the prevention and treatment of respiratory infections. Immunomodulators, such as interferons and cationic host defense peptides, enhance immune responses by activating immune cells and regulating cytokine production. Vitamins, including vitamin A, C, and D, support immune function and strengthen physical barriers against pathogens. The combination of immunomodulators and vitamins shows promise in preventing infection through antioxidant effects and preventing pathogen entry and colonization in the respiratory system. In treatment, it exhibits antiviral, anti-inflammatory, and immunomodulatory effects, thereby reducing pathogen virulence, preventing disease progression, and modulating cytokine production. Examples of combination therapies include quercetin-vitamin C and vitamin D-dipeptidyl peptidase-4 inhibitor (DPP-4i). However, further randomized controlled trials are necessary to establish the efficacy and safety of combination therapy for respiratory infections. Implementing comprehensive strategies that incorporate combination immunomodulator and vitamin therapy may help alleviate the global burden imposed by respiratory infections.

Keywords: *vitamin, immunomodulator, combination therapy, infection*

Introduction

Respiratory infections, including both upper and lower respiratory tract infections, impose a substantial global health burden, contributing to significant morbidity and mortality rates across the world. According to a study conducted by Hay et al. (2021), lower respiratory tract infections were responsible for a staggering number of cases and deaths in recent years. In 2019, the estimated global incidence of lower respiratory tract infections reached approximately 542 million cases, resulting in approximately 2.96 million deaths.1 In addition, upper respiratory infections (URIs) also pose a significant burden, accounting for a substantial proportion of disease incidence. The estimated incident cases of URIs in 2019 reached 17.2 billion, constituting 42.82% of all reported cases of diseases and injuries in the Global Burden of Disease (GBD) 2019 study. These findings highlight the urgent need for effective strategies in both prevention and treatment to address the global impact of respiratory infections on public health[2]

Immunomodulators, substances that modulate or regulate the immune response, and vitamins, essential for optimal immune functioning, have gained attention for their potential role in preventing and treating respiratory infections.[3] Immunomodulators and vitamins have emerged as potential interventions in the prevention and treatment of respiratory infections, holding promise in reducing the burden of these diseases.[4] Understanding their roles and mechanisms of action is essential for developing comprehensive strategies to combat lower respiratory tract infections effectively.

In this literature review, we aim to explore the role of combination immunomodulators and vitamins in the prevention and treatment of respiratory infections. Specifically, we will delve into their mechanisms of action, evaluate the available evidence for combination therapy, and compare their roles in both prevention and treatment settings. By critically examining the current scientific literature, we can assess the potential benefits and limitations of utilizing combination therapy to alleviate the global burden imposed by lower respiratory tract infections.

Immunomodulators in Infection

Immunomodulators play a crucial role in regulating immune responses to infections. They can enhance the immune system's ability to recognize and eliminate pathogens or modulate excessive immune reactions that can lead to tissue damage. Several immunomodulators have shown promise in the prevention and treatment of respiratory infections. One example is interferons, which are cytokines that have potent antiviral properties. They induce an antiviral state in cells, inhibiting viral replication and spread.[3,5] Interferons can also stimulate immune cells, such as natural killer cells and macrophages, to enhance their antiviral activities.[6]

Vitamins in Infection

Vitamins play essential roles in maintaining the integrity and optimal functioning of the immune system. Deficiencies in certain vitamins have been associated with increased susceptibility to respiratory infections. Understanding the role of specific vitamins in infection prevention and treatment is crucial for harnessing their potential benefits. Vitamin A is involved in maintaining the integrity of the respiratory epithelium, which acts as a physical barrier against pathogens.[7] It also plays a vital role in the differentiation and function of immune cells, including T cells and B cells, thus influencing the adaptive immune response.[8] Vitamin C acts as an antioxidant and has been shown to enhance various immune functions, including the proliferation and function of immune cells.[9] Vitamin D, known for its role in calcium homeostasis, has immunomodulatory properties as well.[10] It can modulate both innate and adaptive immune responses, and its deficiency has been linked to increased susceptibility to respiratory infections.[11]

Mechanisms of Action for Immunomodulators in Infection Prevention

Immunomodulators play a key role in strengthening the immune response to prevent respiratory infections. They can act through several mechanisms to enhance the immune system's ability to recognize, target, and eliminate pathogens.[3] One mechanism involves the activation and regulation of immune cells. Immunomodulators can stimulate the production and activity of immune cells, such as natural killer cells, macrophages, and T cells, which play critical roles in recognizing and eliminating invading pathogens. By boosting the immune cell response, immunomodulators help fortify the body's defense against respiratory infections.[3]

Another mechanism is the modulation of cytokine production and inflammation. Immunomodulators can regulate the production and balance of cytokines, which are signaling molecules involved in immune responses. They can dampen excessive inflammation, preventing harmful immune reactions that can lead to tissue damage during respiratory infections. Additionally, immunomodulators can promote the production of specific cytokines that enhance antiviral and antibacterial defenses, further bolstering infection prevention.[3,5,6]

Mechanisms of Action for Vitamin in Infection Prevention

Vitamins play a crucial role in maintaining optimal immune function, which is essential for preventing respiratory infections. They exert their effects through multiple mechanisms that support the immune response against pathogens.One mechanism involves the enhancement of the physical barriers of the respiratory tract. Vitamins, such as vitamin A, contribute to the maintenance of the respiratory epithelium, which acts as a physical barrier against pathogens. It helps prevent the entry and colonization of pathogens in the respiratory system.8 Vitamin C, another important vitamin, supports the integrity of the skin and mucosal tissues, providing an additional physical barrier against infections.[12]

Vitamins also play a role in modulating immune cell function. For example, vitamin D is known to regulate the expression of antimicrobial peptides and enhance the function of immune cells, such as macrophages and T cells. This modulation of immune cell function helps prevent the establishment and spread of respiratory infections.7,10,11 Furthermore, vitamins possess antioxidant properties that can protect immune cells from oxidative damage caused by pathogens. By reducing oxidative stress, vitamins contribute to maintaining the optimal functioning of immune cells and their ability to combat infections.7,10-12

Mechanisms of Action for Immunomodulators in Infection Treatment

Immunomodulators contribute to the management of respiratory infections by regulating immune response. These compounds are designed to enhance the immune response to defense against invading pathogens. For instance, Interferon (IFN) is an immunomodulator that enhances the immune response by directly combating viruses in epithelial cells and promoting the activation, survival, and cytotoxic function of innate immune cells like NK cells.[6,7] IFNs also regulate adaptive immunity, facilitating B-cell activation and class switching during acute viral infections. By activating and enhancing immune cell function, IFNs attenuate viral replication. IFNs signal through a receptor composed of IFNAR1 and IFNAR2 chains, directly impacting NK cell activation, cell cycle entry, and cytotoxic function during viral infections.[7]

Another immunomodulator, cationic host defense peptides (CHDP), combats infections through direct antimicrobial properties and influencing the host's immune responses. The mechanism of CHDP involves complex processes such as peptide uptake into cells, interaction with intracellular protein partners or receptors, modulation of signaling pathways, and engagement of transcription factors.[13] CHDP exhibits various immunomodulatory functions, including recruiting antigen-presenting cells to the site of infection, inducing chemokines for enhanced antimicrobial effects, facilitating neutrophil extracellular traps (NETs), altering endotoxin-mediated signaling pathways, suppressing pro-inflammatory cytokines, promoting phagocytosis and pro-inflammatory responses to nucleic acids, inducing anti-inflammatory cytokines, and influencing the differentiation of dendritic cells and T cell polarization.[13,14]

Mechanisms of Action for Vitamin in Infection Treatment

Vitamins play crucial roles in treating respiratory infections by strengthening the immune system. Vitamin C exhibits antiviral properties and supports both innate and adaptive immune systems.[9] This includes T-cell development and the functions of phagocytosis and chemotaxis of leukocytes. It acts as an antioxidant, protecting cells from oxidative damage, and aiding in tissue repair. Vitamin C reduces reactive oxidative species (ROS) and inflammation by inhibiting the activation of NF- B.[9,15]

On the other hand, vitamin D has several biological mechanisms that are beneficial in the treatment of ARIs. Vitamin D has numerous fundamental functions in the innate and acquired immune response. It enhances immune responses by regulating gene expression and promoting chemotaxis, phagocytosis, and antibody production in B cells.[9,16] It also inhibits pro-inflammatory cytokines (interleukin (IL)-2, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha IL-9, and IL-22) and supports antimicrobial innate immune responses by promoting the production of cathelicidin, an antibacterial peptide. Furthermore, vitamin D protects the lungs by decreasing epithelial cell apoptosis,increasing alveolar type II (ATII) cell proliferation, and inhibiting transforming growth factor-β (TGF-β).[16,17]

Combination Immunomodulator - Vitamin Therapy in Infection Prevention and Treatment

One combination of immunomodulator and vitamin that appears to have benefits in treating respiratory infections is quercetin-vitamin C. Quercetin, along with co-administered vitamin C, demonstrates a wide range of antiviral properties that can interfere with various stages of pathogen virulence, such as virus entry, replication, and protein assembly. This synergistic effect is attributed to their overlapping antiviral and immunomodulatory properties, with vitamin C also enhancing the efficacy of quercetin by recycling it. This multi-drug approach shows promise in disrupting virus activity and bolstering the immune response against respiratory viruses like SARS-CoV-2. Notably, quercetin inhibits viral membrane fusion, targets viral polymerases, and hinders the action of key proteases. In vivo models indicate improved survival rates when treated with quercetin, while vitamin C enhances interferon production and mitigates cytokine-induced organ damage, making it a valuable addition to the treatment strategy. The study also proposes that the combination of quercetin and vitamin C may serve as a promising prophylactic approach for infection prevention, as it exhibits potential antiviral effects and enhances immune responses.[18]

Recommendation cases	Quercetin	Vitamin C
Prophylaxis	250-500 mg BID	500 mg BID
Mild Cases	250-500 mg BID	500 mg BID
Severe Cases*	500 mg BID	3 gr q6 for 7 days

**ARDS-like presentation, require assisted ventilation/intubation, ICU hospitalization*[18]

Table 1. Proposed combination of Quercetin and Vitamin C for prophylaxis dan treatment of infection

Another example of such combinations is vitamin D and DPP-4i. They demonstrate a synergistic effect, exhibiting combined anti-inflammatory and immunomodulatory properties. This combination shows potential in reducing the virulence of SARS-CoV-2, preventing disease progression, and modulating the cytokine storm in COVID-19. It is particularly beneficial for high-risk patients with comorbidities like diabetes, cardiovascular disease, and atherosclerosis. Administering vitamin D and DPP-4i together enhances their anti-inflammatory and immunomodulatory actions compared to using them individually. Additionally, this combination may offer protective effects against endothelial dysfunction, which plays a crucial role in COVID-19 pathophysiology, including the hyperinflammatory state and cytokine storm.[19]

A study conducted by Rondanelli et al analyzed 82 eligible studies to evaluate the effectiveness of combination therapy containing vitamin C, vitamin D, zinc, and Echinacea in prevention and treatment of common cold. The findings suggest that combination of vitamin D, vitamin C, zinc, and Echinacea plays a crucial role in three main immunoreactive clusters: physical barriers, innate and adaptive immunity, with regards to preventing and treating common colds. The current evidence that regular vitamin C supplementation at a dosage of 1 to 2 grams per day can reduce the duration of common cold symptoms in adults by 8% and in children by 14%, as well as alleviate its severity. Zinc supplementation initiated within 24 hours of symptom onset may shorten the duration of colds by approximately 33%. Vitamin D supplementation, particularly in individuals with deficiency and without receiving bolus doses, has shown a protective effect against CC. Prophylactic treatment with Echinacea extract at a dosage of 2400 mg per day for 4 months appeared to be beneficial in preventing and treating common cold These findings indicate that patients with common cold can be encouraged to try these nutrients and botanicals for prevention and treatment, although further research is needed to establish their efficacy conclusively.[20]

Conclusion and Future Recommendations

The roles of combination immunomodulator and vitamin therapy in preventing infection involve bolstering the immune system and minimizing the risk of infection by maintaining the integrity of respiratory epithelium, skin, and mucosal tissues, which act as physical barriers against pathogens. This helps prevent the entry and colonization of pathogens in the respiratory system. Additionally, the combination therapy provides antioxidant properties that can protect immune cells from oxidative damage and maintain optimal immune cell function. In the context of treatment, combination therapy exhibits anti-inflammatory effects and interferes with various stages of pathogen virulence, thereby reducing the virulence of pathogens, preventing disease progression, and modulating cytokine production.

To further validate their efficacy and safety, randomized controlled trials are necessary to determine whether the combination of immunomodulators and vitamins represents a reliable and effective therapeutic intervention for the prevention and treatment of respiratory infections.

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IMMUNE BOOSTING BY EXERCISE

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ABSTRACT

Background: Physical activity (PA) and exercise are one of the best interventions for lifestyle modification. Exercise also inflects the native and specific part of the immune system with a marked intensity-dependent response. The J-curved model suggested that individuals engaging in moderate physical activity are at lower risk of illness compared with sedentary individuals. Conversely, excessive volumes of strenuous endurance exercise may suppress immune function, thereby increasing the risk of illness such as upper respiratory tract infection (URTI). The relationship between URTI and sedentary lifestyle has been strengthened during the COVID-19 pandemic. Therefore, there is a need to raise awareness of the influence of exercise training on the immune system.

Methods: This study is a literature review following PubMed search with custom range of time from 2018-2023.

Discussion: The J-shaped curve model hypothesis is challenged with experimental evidence showing that individual factors such as age, fitness condition, nutritional status, psychological wellbeing, and previous health status that might increase the exposure to pathogens. Exercise training is not only a necessary means to improve the level of exercise, but also an important means to improve the body's immunity. Different time, intensity, items, and forms of exercise training have different effects on the body's immune function.

Conclusion: There is an increasing role of regular and moderate exercise as a preventive and therapeutic tool to improve immunosurveillance against URTI. The optimal dose of PA/exercise may be: at least 150 minutes per week of moderate-intensity aerobic exercise.

Keywords: *exercise, physical activity, immune system, immune function.*

Background

Physical activity (PA) and exercise are one of the best interventions for lifestyle modification. They also aimed to decrease morbidity and mortality linked with non-communicable diseases such as obesity, diabetes, cardiovascular disease, and cancer. Furthermore, exercise also inflects the native and specific part of the immune system with a marked intensity-dependent response. This response might be influenced by sex differences and other factors including age, nutrition status, and overall level of psychological stress.[1]

Back in the 1990s, Dr. Nieman created the contentious "J-shaped hypothesis" to explain the relationship between the intensity of exercise and the acquired risk of upper respiratory tract infections (URTI). This

hypothesis implies that moderate exercise can increase immune function above sedentary levels, at the same time, high intensity exercise lowers the immune system.[2]

The connection between exercise training status and protective acts against URTI has been a progressive scope of research over the past decades. It has been postulated that regular exercise decreases blood circulation of inflammatory cytokines, decreases oxidative stress, and improves function of various immune cells in the resting state, which would potentially reduce the risks for URTI (common cold) cases. More than 200 viruses cause URTI with influenza, rhinovirus, and coronaviruses being the most common.[3-5]

The upper respiratory tract is the main entry of severe acute respiratory syndrome coronavirus (SARS-CoV-2), and SARS-CoV-2 likely interacts with the microbiome inside the upper respiratory tract, and it is seriously imperiled human health worldwide. Evidence in support of the correlation between URTI and sedentary lifestyle has been backed during the coronavirus disease 2019 (COVID-19) pandemic.[6]

Recalling the COVID-19 pandemic in few years back, many studies put PA and exercise as prevention and treatment of COVID-19, it can lower the risk of COVID-19 infection and mortality, promote recovery of physical function, decrease the likelihood of adverse COVID-19 outcomes, lessen the post COVID-19 syndrome, improve patients' psychological well-being.[7-10]

Furthermore, in a recently published study, nearly 200,000 adults showed an association between physical activity and improved COVID-19 outcomes across major demographic groups regardless of whether patients had chronic medical conditions. Black, Hispanic, and Asian patients had a greater risk of adverse outcomes compared with white patients, in line with prior research. However, within each racial and ethnic group, more exercise was still associated with less severe COVID-19 outcomes.[11] Therefore, there is a need to raise awareness of the influence of exercise training on the immune system.

Methods

This study is a literature review study using PubMed as a search engine with custom range of time from 2018-2023 with free full text. The keywords are: ((exercise) AND (physical activity)) AND (immune system) AND (immune function). The matched literatures were 347 results. After further selection of reviews, systematic reviews and meta-analysis studies, 20 references were then handpicked to support the purpose of this paper.

Discussion

J-curve

The term J-curve is used in several fields. In this literature review, it describes the relationship between exercise intensity and its exposure to infections (Figure 1). This model suggests that individuals engaging in moderate physical activity are at lower risk of illness compared with sedentary individuals. Conversely, excessive volumes of strenuous endurance exercise may suppress immune function (lasting between 3 h to 72 h depending on the immune outcome), thereby increasing the risk of illness.[2]

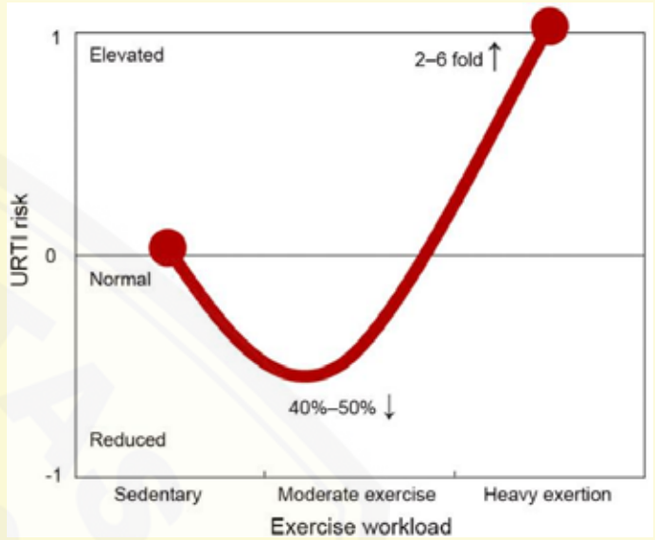

Figure 1. The J-curved model of relationship between varying amount of exercise and risk of URTI.[2]

Although the J-shaped curve hypothesis is generally accepted by consensus, the available experimental evidence is not enough to support it. Not only does exercise intensity or duration seem to be responsible for increasing the risk of URTI, other individual factors such as age, fitness condition, nutritional status, psychological wellbeing, and previous health status increase the exposure to pathogens.[12]

Furthermore, the practitioners should be aware that the right side of the J-curve model may not apply to elite athletes at the highest level, where high training loads are not consistently associated with an increased risk of illness. When competitive athletes are training for an endurance event like a marathon, recovery time and nutrition for performance are essential matters for the athletes that were regarded as important consideration.[12-14] That might lower the risk and consequently change the outcome.

Exercise and Immunity

Exercise training is not only a necessary means to improve the level of physical fitness, but also an important means to improve the body's immunity. Different time, intensity, items, and forms of exercise training have different effects on the body's immune function. As a double-edged sword to improve the body's immune function, there was different reaction mechanism of different immune cells following different exercise training. In addition, the evidence suggests that moderate regular exercise may be beneficial to diminish the risk of URTI.[15]

Aside from that, the regular practice of PA and exercises increases a good quality of life and can act as a booster in the immune response, it also lowers the risk of increasing systemic inflammatory processes and augmenting cellular immunity.[14]

According to a 2019 research review, moderate intensity exercise can stimulate cellular immunity by generating the circulation of immune cells in the body. This helps the body to have better preparation for a future infection by detecting it earlier. Researchers also found that performing aerobic exercise at a moderate to vigorous intensity for less than 60 minutes (an average of 30–45 minutes) increases the recruitment and circulation of the immune system's best defensive cells.[14]

Another systematic review from 2021 studied acute and chronic effects of interval training towards the immune system. The study found that a single session of interval training exercise might provide a temporary disruption on the immune system, followed by decreased immune function. However, if the exercise is done in a regular basis, the interval training exercise is favorable towards the adaptations on immune function, improving immunosurveillance in the short to long term without changing immune cell count.[16]

However, the optimal dose of PA and exercise for maximizing health benefits is lesser known and even 2,500 years ago, Hippocrates taught: "if we could give every individual the right amount of nourishment and exercise—not too little and not too much—we would have found the safest way to health." This suggests that there might be a dose range of physical activity that is optimal for improving wellbeing and life expectancy, with attenuation of these benefits when the amount of exercise is above or below this ideal range.[17, 18]

In general, exercising at a moderate to vigorous intensity for 60 minutes or less is optimal for the immune-boosting benefits of exercise. If the exercise is being done daily or almost every day, the immune and metabolic systems will continue to strengthen, building on previous gains. On the other hand, prolonged high intensity training — especially without appropriate rest between sessions — can suppress the immune system.[14]

Exercise intensity and duration have been demonstrated to have a great impact on immune system function. This beneficial effect of exercise is due to the anti-inflammatory effects of exercise mediated by the downregulation of Toll-like receptors and/or cytokines. Moderate-intensity exercise is considered to enhance immune function and to prevent acute upper respiratory infections and similar conditions.[19]

First and foremost, most studies evaluating the effect of exercise on immune and inflammatory markers at the systemic level are based on acute exercise instead of regular exercise. Therefore, more research is needed on different designs and intensity of exercise among recreational and professional athletes, namely to learn more about the adaptation effect of exercise towards immune function. Current data regarding the effect of acute and chronic regular exercise on systemic inflammation are shown in Figure 2.

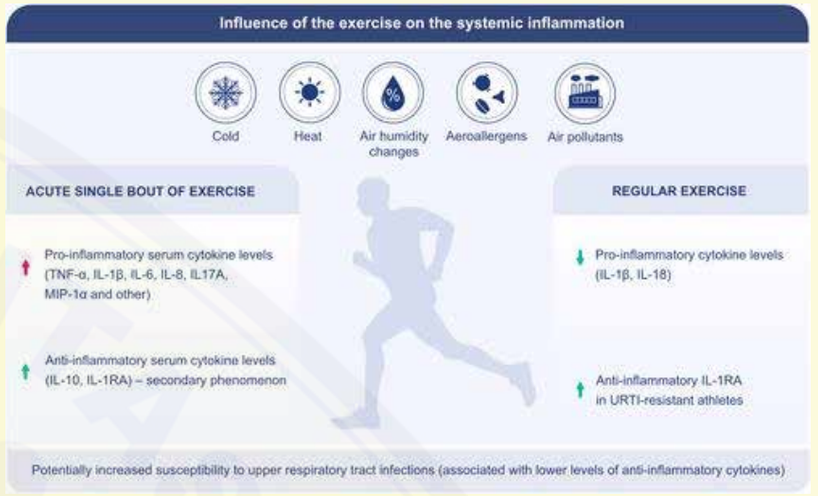

Figure 2. Exercise, both acute and regular, can influence systemic inflammation. Levels of anti- inflammatory mediators vary between athletes susceptible and resistant to upper respiratory infections.[19]

One of the body's immune responses to exercise is the production and secretion of immunoglobulins, whose serum levels and secretion (especially the IgA and IgG) are associated with resistance to infection. It is proposed that secretory IgA provides an immunological barrier by neutralizing and preventing viral pathogens from penetrating the body through the mucosal surfaces. Based on the above mentioned, low concentrations of IgA in athletes may be correlated with the increased susceptibility to URTI.[19]

The results in 2021 systematic review showed that individuals who engage regularly in moderate to vigorous PA/exercise is associated with the increased strength of the mucosal immune barrier (salivary IgA immunoglobulin) and higher concentration of immune cells that prepare, orchestrate, regulate, and effect immunity (CD4 T-cells). In addition, there is evidence that regular moderate to vigorous PA/exercise might contribute to a more effective immune system and response providing enhanced protective immunity to infections.[15]

A systematic review study from 2022 about acute and chronic effects of physical exercise on IgA and IgG levels, as well as its relationship with the susceptibility to develop URTI, stated that acute exercise increases the IgA levels in trained subjects but does not affect its levels in untrained individuals. Such an increase in IgA levels induced by acute exercise is greater in trained individual that performed ultramarathon.[20]

Hence, regular PA/exercise should be promoted in the general population because the regular practice of physical exercises promotes improvements in quality of life and can act in the immune response, reducing the risk of developing systemic inflammatory processes and stimulating cellular immunity.[14] There are some questions to be explored further regarding exercise-induced improvements in immune function that involves the composition and diversity of the gut microbiota. Its applications to human health and immunity are important, in a sense that it may contribute in countering immunosenescence and the development of chronic diseases.[12]

Conclusion

There is an increasing role of regular and moderate exercise as a preventive and therapeutic tool to improve immunosurveillance against URTI. The optimal dose of PA/exercise may be: at least 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes per week of vigorous-intensity aerobic activity, but not more than four to five cumulative hours per week of vigorous (heart-pounding, sweat producing) exercise, especially for those over 45 years of age.

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CASE REPORT FORUM

TUMOR-LIKE MASS IN PATIENT WITH TUBERCULOSIS: A CASE REPORT

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ABSTRACT

INTRODUCTION

Tuberculosis (TB) is not all about chronic cough or hemoptysis. The clinical manifestation of TB could be pulmonary and extrapulmonary, with the later defined as any site other than the lung, affected by the TB.1 The global burden for tuberculosis is still heavy, standing as the second leading infectious killer after COVID-19 (above HIV/AIDS), TB holds the 13th place of the leading cause of death. The World Health Organization (WHO) predicted around 1.6 million people died from TB, and 10.6 million people fell ill with TB worldwide in 2021.[2] Due to the various manifestations and limitations of the diagnostic tools, determining the diagnosis and treatment of TB has been a challenge since a long time ago.[3,4] Here, we report a patient who has tumor-like mass in her thoracic cavity accompanied with pain shoulder pain and weight loss, without history of hemoptysis nor fever.

CASE DESCRIPTION

An 33-year-old lady patient comes to the Sumber Waras Hospital due to left shoulder pain since 3 months prior to admission. Pain described as throbbing pain (VAS 4-5), which felt worse when the left shoulder and arm are moved, and relieved when rested. Pain spreads through left scalps, under the left breast area, to the epigastric area, making it difficult for the patient to perform daily activities. The patient had lost weight lately, and had chronic cough with clear-colored sputum, with no history of hemoptysis and fever. Patient had taken anti-tuberculosis drugs for 3 months but had swelling on her feet and face, so she stopped the medication ever since.

Bloodwork investigations revealed low level of hemoglobin (8.6g/dL), normal total and differential leukocyte counts (7000/ µL; basophils: 0%; eosinophils: 3%; neutrophils: 64%;

Figure 1. Chest x-rays of the patient. Homogenous opacity was found on the first chest x-ray, suggesting a mediastinal mass.

lymphocytes: 23%; monocytes: 10%). The erythrocyte sedimentation rate was 104 mm during the 1st hour. Chest x-ray was done and a mass-like image was found. (Fig. 1)

A Thorax Multislice Computerized Tomography (MSCT) scan with contrast was performed. A paravertebral mass (VTH 5-9) was found with air component inside and ring enhancement after contrast. TB spondylodiscitis (osteoblastic lesion in VTH 6-7) was found along with right lung (S6) collpase and micronodullar branching nodules in the medius-inferior lobe of the right lung and S3 of the left lung which may still be a TB process, but the presence of a malignancy cannot be ruled out just yet.

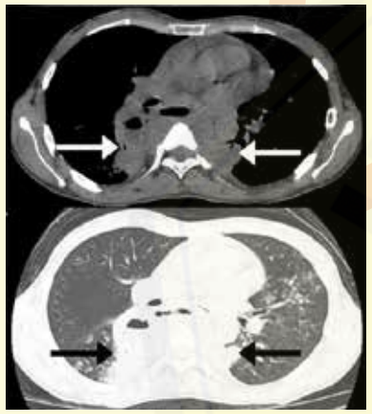
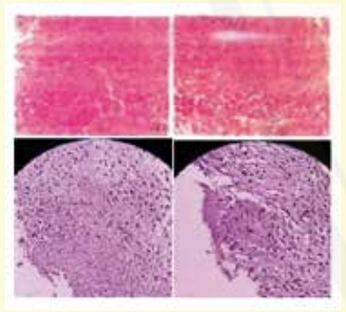


Figure 2. CT-scan of patient's chest. Homogenous mass was found near the vertebrae.

Core biopsy examination was carried out with the guidance of a non-contrast CT scan. Sample tissues were obtained and examined. Chronic inflammatory cells, epithelioid cells and caseous necrosis were found, which suggest that this mass is tuberculous granulomatous inflammation. There were no signs of malignancy found in the preparation.



Anti-tuberculosis therapy (ATT) was given to the patient and the patient was allowed to be discharged. After 6 month of ATT, the patient condition now has improved. Her body weight has increased, the pain has been reduced, and can perform daily activities better.

DISCUSSION

We present this case to highlight the heterogeneous nature of tuberculosis manifestasion. Tuberculosis (TB) can manifests within pulmonary and extrapulmonary. Extrapulmonary tuberculosis (EPTB) was found in 10-42% adults with TB, where females and patients with conditions that impair the host's immunity are more at risk.[1] This is not limited only to adults, but the wide variety of manifestations also applies to children. Other than the usual pulmonary manifestations (weight not increasing or weight loss, malaise, profuse sweating, coughs), children might have neck swelling, restricted movement and pain in the extremities, hematuria, blurred consciousness, vomiting, headache, and growth and developmental delay.[5,6] Most children with EPTB had a single extrapulmonary organ affected. The most frequent site are lymph node, skeletal organs, CNS, and abdominal organs.[7]

Due to the wide variety of manifestations, it is known that tuberculosis, especially the extrapulmonary manifestations, can mimics malignancy both clinically and radiologically.[4] Having similar symptoms like weight loss, fever, cough, hemoptysis, and breathlessness, physician need to take history carefully and detailed examination can help clinician to differentiate TB with lung cancer.[8]

Lung cancers (LC) usually happens to middle aged or elderly patient. Smoking history might be present for TB patient, but usually always present in patient with LC. Fever might be present, usually happens to patient with TB (low grade with evening rise), but no specific pattern for patients with LC. Weight loss for both TB and LC patients are significant, but the weight loss for TB patients tend to have slower pace than the weight loss for LC patients (sudden). Hemoptysis might be present, but for TB patient its usually an early feature, in contrast to LC where hemoptysis tends to be a late feature. Breathlessness for LC patient tends to be vague and dull. Chest pain might be present for both TB and LC patient, but usually more severe for LC patients. Hoarseness rarely happen for TB patient. Backache and paralysis might be present and is associated with Pott's disease. Hoarseness, backache, and paralysis might be present if there are metastasis.[8]

In radiology examination, the chest x-ray anatomical predilection for TB patients are the upper zone. For TB, the usual radiologic findings are parenchymal infiltrates, lymphadenopathy, military, pleural effusion, and cavitation (centric). For LC, the usual radiologic findings are mass, hilar prominence, pulmonary nodule, widening of the mediastinum, total or partial atelectasis of a segment, lobe, or lung, unersolving consolidation (pneumonia), cavitation (eccentric), elevated diaphragm, pleural effusion, and rib erosion.[8]

Cases of a tuberculosis presented with tumor-like mass has been reported before[9,10], where the patients are all presented with cough, fever, anorexia, and weight loss. The symptoms are suggestive to the common tuberculosis, but when a mass was found in the radiologic examination, the presence of malignancy cannot be ruled out just yet. For special cases like these, further examination is needed to confirm the diagnosis.

To give appropriate therapy, accurate diagnosis is important. There are therapies that might be inappropriate even though it's commonly used (e.g. steroids in malignancies are cornerstone, but not in tuberculosis).[4] Radiologic findings alone cannot establish the diagnosis: diagnosis should be confirmed by histopathological and microbiological tests.[8,11] Even though a commonly used biopsy method like fine-needle aspiration cytology (FNAC) is not reliable8, it can help in determining the class of the lung carcinomas, along with salient mutational changes in it.[12] For confusing masses, the best definitive diagnostic method should be

excisional biopsies. However, the gold standards for diagnosis are still histopathological examination and tuberculosis cultures.[11]

Extrapulmonal tuberculosis can affect every other organ, skeletal site included. Spine, being the most common site of TB involvement, still has very little guidance on its management. The infection of tuberculosis in skeletal tissue is different than the common infection, where despite being aerob and thrives best in high oxygen level tissue, the organism can still multiply although not to the same extent.[13] The treatment for spinal tuberculosis are primarily to eradicate the infection and to save life, along with providing stability for the affected spine (correcting spinal deformities) and prevent or treat paralysis.[14]

The spinal TB therapeutic strategies include the holistic treatment for the tuberculosis infection and local therapy for the spine. For the common pulmonary TB, the recommended therapy duration is 6 month, where as TB infection on skeletal and joints, the therapy duration recommendation is 9-12 months.[15] Surgical approach can be considered as supplementary for patients with neurological deficits and patients with "spine-at-risk" (pediatrics) or kyphosis (>60°).[16] Surgical measures include: drainage of the cold abscess; debridement of the focal tuberculous lesion and/or anterior fusion; and surgical decompression.[14] Besides progressive neurological deficit, there are other indications for surgery: progressive increase in spinal deformity (coronal or sagittal); failed conservative treatment including progressive neurologic deficit or increase in spinal deformity or severe pain due to abscess or spinal instability; and uncertain diagnosis (inability to obtain microbiological diagnosis from microscopy, culture, or PCR techniques).[17]

If spinal TB were left unattended, complications might occur, from a solid fusion that could include deterioration, kyphus, and even Pott's paraplegia of late onset.[17] There are three mostly known causes of Pott's paraplegia: compressed cord due to abscess and granulation tissue; compressed cord due to sequestrums and kyphosis with bony protrusion from the vertebral body; and the deformed spine above the level of the kyphosis that makes bony canal stenosis.[14]

Physical therapy could be considered to improve respiratory function, improving the muscle strength and reducing back pain, repair/improve the range of motion (ROM) and sensory function, improve quality of life, and prevent other complications. The therapy mainly focused on alleviating the symptoms like pain, sensory deficits and muscle strength.[18,19] Being generally considered as one of the non-traumatic spinal cord injuries, it is suggested that the patients with spinal should be evaluated as having spinal cord injury.[20]

Patient's clinical status should be evaluated prior to the therapy, including the any presence of paresis or any neurologic involvement, incontinence, and cardiopulmonary and psychological. Early phase is important factor in rehabilitation and will impact on the patient's recovery. For patients with spinal tuberculous with radiologic sign of bony fusion, supporting the body with molded thermoplastic or plaster for 3 months is recommended in along with standard antituberculous drugs regimen as initial treatment. Patient should avoid pain aggravating exercise and should not be exhausted from the exercise program. Patient should have appropriate time for resting after exercise along with compatible diet regimen.[20]

Patients with mild or without neurologic findings, the exercises should include active (or assisted active) ROM and isometric exercises. In the acute phase, exercise should train all joints of the lower extremity. Isotonic exercises should be performed in subacute stage. Isotonic and strengthening exercises are recommended in the chronic stage for atrophic muscles, and mobilization training is continued. Provide a home exercise regimen and follow up evaluation at regular intervals.[20]

Patients with severe neurologic symptoms should have both surgery and medical treatments. In acute phase, exercises need to be performed at least daily to improve the functional capacity of muscles and prevent contractures, including isometric, passive, active (or assisted) exercise. In Subacute phase, active and active assisted exercises are performed. For chronic phase, patients are encouraged for mobilization to regain the previous function and improve quality of life.[20]

CONCLUSION

Radiological and clinical manifestation of tuberculosis frequently mimics malignancy. Physicians needs to be careful in making the diagnosis. The treatment should include multidisciplinary approach and should be done after the diagnosis was made with certainty.

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LINEZOLID-INDUCED BLURRED VISION IN DRUG RESISTANT TUBERCULOSIS PATIENTS: A CASE SERIES

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ABSTRACT

Background: Drug resistant tuberculosis (DR-TB) is a major concern for global health since there is no comprehensive intervention and various side effects during therapy. Linezolid, a second-line anti-TB drug is one of agents for treating multidrug-resistant tuberculosis (MDR-TB). However prolonged use (>28 days) of Linezolid is associated with optic and peripheral neuropathies. The second-line anti-TB drugs are more expensive and toxic than the first-line ones. Global TB Report 2022 estimates that out of 969,000 TB cases in Indonesia 28,000 were DR-TB cases. This case series discusses the importance of side effect management in patients undergoing DR-TB treatment.

Methods: We evaluated MDR-TB patients receiving linezolid as second-line anti-TB therapy from 2021 to 2022 who experienced blurred vision. The clinical data were obtained from history taking and physical examination, while imaging and laboratory data were taken from medical records.

Results: There were 3 patients on DR-TB treatment using linezolid therapy for > 6 months. All of them complained for numbness in their hands and feet along with blurred vision. These symptoms improved after discontinuing linezolid.

Conclusions: Linezolid therapy for DR-TB patients requires closed monitoring as it can lead to optic neuropathy symptom. Stopping and replacing the drug can prevent further damage. Regular ophthalmic screening in these patients is imperative.

Keywords: *DR-TB, linezolid, optic neuropathy, second-line anti-TB drugs*

Background

Drug-resistant tuberculosis (DR-TB) is a major concern for global health due to the lack of comprehensive intervention and its various adverse events during treatment. DR-TB requires longer treatment using second-line anti-tuberculosis drugs, which are more expensive and toxic than first-line drugs. The World Health Organization (WHO) reported that in 2022, 10.6 million people globally will be newly diagnosed with TB. Indonesia has the second-highest number of TB patients in the world, second only to India, followed by China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo, respectively. According to the Global TB Report 2022, DR-TB cases alone were estimated to be 28,000 out of a total of 969,000 TB cases in Indonesia. Total cases of DR-TB in Indonesia are 8268, 5234 of which have started DR-TB treatment. [1–3]

Linezolid is a second-line anti-tuberculosis drug used to treat multidrug-resistant tuberculosis. Linezolid has been shown to be effective for DR-TB, well tolerated, and generally safe. However, the side effects limit

its long-term use for DR-TB. Linezolid-induced toxic ocular neuropathy is characterized by painless bilateral progressive loss of vision and disturbance of color vision. [4,5]

Linezolid has been deemed safe for continuous use for up to 28 days. Longer use is associated with optic and peripheral neuropathy. Patients using linezolid for more than 28 days should be evaluated for signs of peripheral and optic neuropathy. We found that three patients with DR-TB treated with long-term linezolid complained of hands and feet numbness and vision disturbance. [4–6]

This case series is written to discuss the importance of early detection and management of side effects in DR-TB treatment.

Case 1

A 45-year-old man complained for one month of a productive cough and shortness of breath accompanied by weight loss. The patient worked as a janitor for 20 years and actively smokes (moderate Brinkman index). On June 27, 2022, his rapid molecular test for sputum MTB detected ifampicin-resistant MTB. The patient had no history of TB or usage of anti-TB drugs, so the examination was repeated and yielded a consistent result.

The patient was referred to a tertiary health center for further examination and treatment. Based on the examination, the patient was diagnosed with DR-TB. Results of a basic laboratory examination showed a temporary increase in blood glucose levels, while other results were within the normal limit. No significant ophthalmic or psychiatric disturbance was found. A chest X-ray showed cavities and large lesions in the lungs. Individual second-line anti-TB therapy was started on July 7, 2022, consisting of daily bedaquiline 400 mg for four weeks, followed by 200 mg three times a week for six months, levofloxacin 1 x 1000 mg, cycloserine 1 x 750 mg, clofazimine 1 x 100 mg, and linezolid 1 x 600 mg taken simultaneously.

Line probe assays for second-line anti-TB drugs on July 16, 2022, and DST on September 30, 2022, showed high sensitivity for high-dose INH, levofloxacin, moxifloxacin, and second-line injection. After one month of treatment, the patient reported that his cough and shortness of breath had decreased. His microscopic sputum examination for acid-fast bacilli in the third month was negative, and his chest x-ray in the fifth month showed improvement. Monthly blood glucose patients showed hyperclycemia; therefore, they were also diagnosed with uncontrolled diabetes mellitus. We consulted the patient's internist.

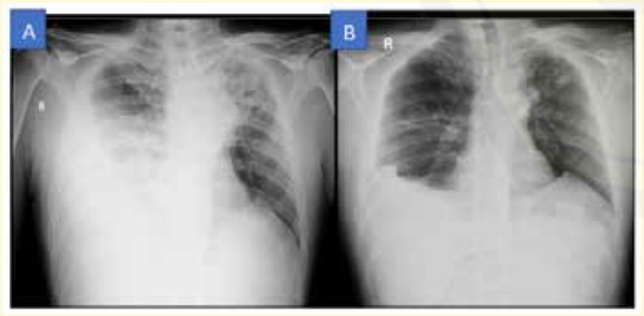

Figure 1. Chest X-ray imaging of patient 1. (A) Chest X-ray on July 2, 2022; (B) Chest X-ray on December 21, 2022

Six months after second-line anti-TB treatment, the patient complained of blurred vision and numbness of fingers and toes. The patient was referred by a primary health facility to a tertiary health facility for an eye examination. Examination showed optic neuritis and papilla edema suspected to be caused by the toxic effects of his anti-TB drugs. A funduscopic examination was done on both eyes.

The patient was treated with methylprednisolone (2x8 mg) and folic acid (1x1 mg) for 7 days, and anti-TB drugs were stopped. The ophthalmologist found right eye (OD) vision of 2/60, left eye (OS) vision of 1/60, and clear lenses in both eyes (ODS), but the Ishihara test could not be assessed. The patient was diagnosed with suspected bilateral toxic optic neuritis and suspected non-proliferative diabetic retinopathy (NPDR).

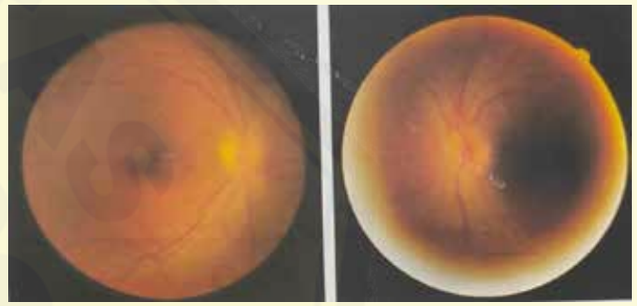

Figure 2. Funduscopy examination of patient 1. (A) Right eye funduscopy; (B) Left eye funduscopy

Description: OD = well-demarcated papillae, CDr cannot be assessed, retina dot (+), blot (+), tubercles (-); OS = blurred margin papillae, CDr cannot be assessed, retina dot (+), blot (+), tubercles (-)

We tried stopping linezolid and continuing other second-line anti-TB drugs. The patient has been taking second-line anti-TB drugs for six months and is currently taking levofloxacin (1x1000 mg), cycloserine (1x750 mg), and clofazimine (1x100 mg). Three wee ks after discontinuing linezolid, the patient reported improved vision.

Case 2

A 44-year-old man complained for two months of a productive cough with a blood streak, shortness of breath, fever, night sweats, and an 8 kg weight loss in two months. The patient was diagnosed with pulmonary tuberculosis in 2020 and treated with FDC first-line anti- TB drugs for six months. There is no past data for bacterial examination at the time the patient was diagnosed or after the treatment. On July 6, 2022, a patient was hospitalized for shortness of breath. The patient underwent a molecular rapid test on July 6, 2022, with the results of MTB detection and high rifampicin resistance detection, and was referred to a DR-TB referral health facility.

The patient worked as a construction worker for 10 years and had a history of heavy smoking. There was no history of other diseases. The patient was diagnosed with DR-TB. Basic laboratory examination results were normal. Ophthalmic and psychiatric examinations showed good results. A chest X-ray showed a cavity in the right lung and consolidation lesions at the apex of the left lung. Short-term second-line anti-TB therapy was given starting July 20, 2022, consisting of bedaquiline 400 mg daily for four weeks, followed

by 200 mg three times a week for six months, isoniazid 1 x 600 mg, levofloxacin 1 x 750 mg, clofazimine 1 x 100 mg, pyrazinamide 1 x 1500 mg, ethionamide 1 x 500 mg, and ethambutol 1 x800 mg.

Line probe assay for second-line anti-TB drugs on July 28, 2022, showed resistance to kanamycin, amikacin and capreomycin. The patient was declared a treatment failure due to disease progression to TB-preXDR. The examination at the start of TB-preXDR treatment was repeated and showed results within normal limits for laboratory, vision, and psychiatric examinations. On August 23, 2022, an individual regimen with bedaquilin 1x200mg three times a week, continuing for up to six months, linezolid 1x600mg, clofazimine 1x100mg, cycloserine 1x750 mg, and levofloxacin 1x750mg

The patient reported improvement in cough and shortness of breath after two months of treatment and gained weight. Acid-fast bacilli in sputum were negative in the fifth month. Every month, the patient was evaluated for treatment results and side effects. A follow-up chest X-ray showed improvement. In March 2023, the patient complained of weakness, nausea and vomiting, blurred vision accompanied by black spots, and numbness in all extremities. We evaluated the side effects of current drugs.

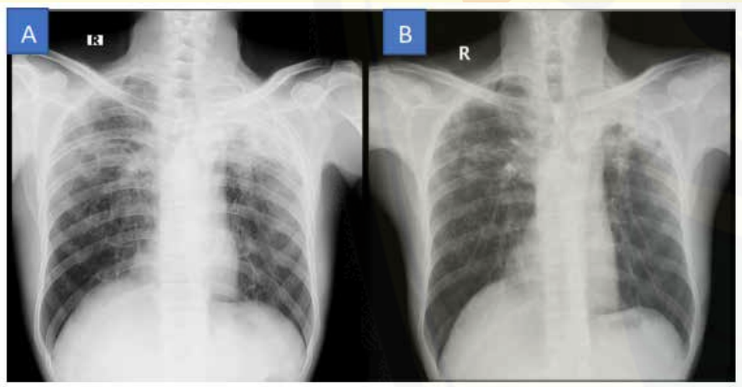

Figure 3. Chest X-ray imaging of patient 2. (A) Chest X-ray on July 18, 2022; (B) Chest X-ray on January 25, 2023

The patient was examined by an ophthalmologist. His vision in the right eye was 4/60 and in the left eye was 1/300; both lenses were normal. The Ishihara test showed dyschromatopsia in the right eye. Funduscopic results showed well-demarcated papillae, CDr 0.3, and no tubercles in both eyes. Ophthalmologists diagnosed patients with suspected toxic optic neuropathy due to anti-TB drugs.

Linezolid was stopped, and other drugs were continued. The patient has been taking second-line antiTB drugs for six months during the intensive phase of TB-preXDR treatment. The patient's drugs in the advanced phase were levofloxacin (1x1000 mg), cycloserine (1x750 mg), and clofazimine (1x100 mg). Two weeks after discontinuing linezolid, the patient's complaints of blurred vision decreased.

Case 3

A 40-year-old man complained for one month of a productive cough accompanied by decreased appetite, weight loss, fatigue, and night sweats. The patient has a history of taking an anti-TB FDC regimen for two months in 2012 and discontinuing the drugs after feeling improvement in his condition. There was no bacteriological examination at that time. A history of diabetes mellitus, hypertension, and other comorbidities was denied. A sputum rapid molecular test for MTB in February 2022 detected MTB with rifampicin resistance. The patient was referred to a DR-TB referral hospital.

The patient worked as a factory worker for 12 years and had a history of smoking a pack daily for 20 years. The patient was diagnosed with DR-TB. Routine blood work and ophthalmic and psychiatric assessment results were within normal limits. A chest X-ray showed fibroinfiltrates in the right lung.

Patient received short-term anti-TB drugs since February 14, 2022, with bedaquilin (1x400mg for two weeks, followed by 1x200 mg three times a week for six months), levofloxacin (1x1000 mg), ethionamide (1x750 mg), ethambutol (1x1200 mg), pyrazinamide (1x1500 mg), isoniazid (1x600 mg), and clofazimine (1x100 mg). Line probe assay on 14 March 2022, showed resistance to high dose of isoniazid (MDR-TB). Treatment was switched to an individual regimen on March 24, 2022, with bedaquilin 1x200 mg continued for 6 months, levofloxacin 1x1000 mg, clofazimine 1x100 mg, cycloserine 1x750 mg, pyrazinamide 1x1500mg, and linezolid 1x600mg.

A drug susceptibility test on June 2, 2022, showed resistance to high-dose levofloxacin, moxifloxacin, pyrazinamide, and isoniazid. The patient was declared a treatment failure (progression to TB-preXDR). Laboratory tests, vision, and psychiatric examinations were repeated. All results were normal. TB-preXDR treatment started on July 13, 2022, with bedaquilin (1 x 200 mg) continued for up to 6 months, clofazimine (1 x 100 mg), cycloserine (1 x 750 mg), linezolid (1 x 600 mg), and ethambutol (1 x 600 mg).

Sputum evaluations in the patient were negative during the first month of preXDR treatment. Cough and shortness of breath, and his appetite improved and he gained weight. The chest X-ray also showed improvement.

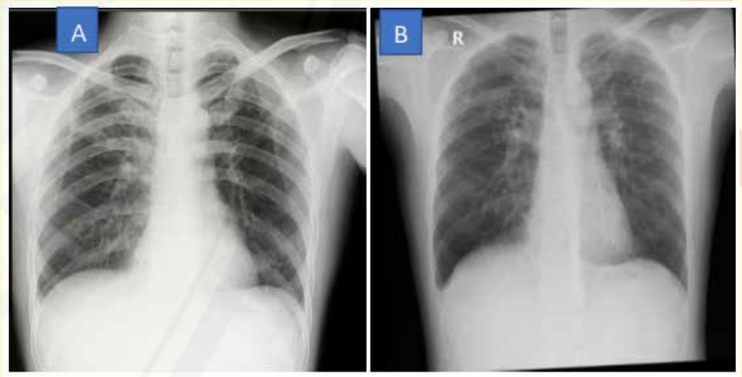

Figure 4. Chest X-ray imaging of patient 3. (A) Chest X-ray on July 11, 2022; (B) Chest X-ray on December 21, 2022

After four months of treatment, the patient complained of numbness in the extremities, pain in the fingertips, black spots, blurred vision, and hearing disturbances. Ethambutol was then stopped for 2 weeks, and treatment continued with linezolid (1 x 600 mg), cycloserine (1 x 750 mg), and clofazimine (1 x 100 mg). After one month, patients' vision worsened. Ethambutol was stopped and replaced with three regimens of

second-line TB therapy.

After six months of treatment, the patient's vision became increasingly blurry; his vision range was less than one meter. The patient decided to transfer to another hospital because it was closer to this house; therefore, we could not continue the evaluation.

Discussion

Toxic optic neuropathy is characterized by gradual, progressive, painless, bilateral symmetrical loss of vision causing a central or centrocecal scotoma. DR-TB is a condition where *Mycobacterium tuberculosis* is resistant to first-line anti-TB drugs; hence, patients must take second-line drugs with longer treatment. [7,8] MDR-TB (multi-drug resistant) is DR-TB resistant to at least two of the most potent anti-TB drugs, namely INH and rifampicin together, or other first- line anti-TB drugs. PreXDR-TB is TB that fulfills the definition of MDR-TB and is also resistant to fluoroquinolones. [1,8]

Table 1. Summary of case series

No	Sex / Age	DR-TB types	Symptoms	Ocular examination	Anti-TB regimen			LPA/ DST	Sputum Conversion	Linezolid	ethambutol
					First	Second	Third	Tuberculosis drug	Months	Months	Months
1	M / 45	MDR-TB	Blurred vision Numb fingertips and toes	Visual acuity OD 2/60 OS 1/60, fundoscopy = OD = well-demarcated papillae, CDr cannot be assessed, retina dot (+), blot (+), tubercle (-); OS = blurred margin papillae, CDr cannot be assessed, retina dot (+), blot (+), tubercle (-)	Bedaquilin Levofloxacin Cycloserine Clofazimine Linezolid				3	6	-
2	M / 43	PreXDR-TB	Blurred vision Numb fingertips and toes	Visual acuity OD 4/60 dan OS 1/300, normal ODS lens, Ishihara: dyschromatopsia OD, OS cannot be evaluated. Fundoscopy = ODS: well-demarcated papillae, CDr 0,3, tubercle (-),	Bedaquilin Isoniazid Levofloxacin Clofazimine Pyrazinamide Ethambutol	Bedaquilin Linezolid Clofazimine Cycloserine Levofloxacin		Kanamycin Amikacin Capreomycin Isoniazid high dose	Resistant Resistant Resistant Resistant	5	6	1
3	M / 40	PreXDR-TB	Blurred vision Numb fingertips and toes	No specific examination by ophthalmologist, patient can only see less than 1 meter.	Bedaquilin Levofloxacin Ethionamide Ethambutol Pyrazinamide Isoniazid Clofazimine	Bedaquilin Levofloxacin Clofazimine Pyrazinamide Linezolid	bedaquilin, clofazimine, cycloserine Linezolid ethambutol.	Isoniazid high dose Levofloxacin Moxifloxacin Pyrazinamide	Resistant Resistant Resistant Resistant	1	12	8

Linezolid, an antibiotic from the oxazolidinone class, shows broad antibacterial efficacy against gram-positive bacteria such as methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA), vancomycin-resistant Enterococcus sp. (VRE), and drug-resistant *Mycobacterium tuberculosis*. Linezolid binds to the 50S subunit of bacterial ribosomes to inhibit protein synthesis. Because the bacterial ribosome resembles the mitochondrial ribosome, linezolid also appears to inhibit mitochondrial protein synthesis, causing side effects related to mitochondrial toxicity, including myelosuppression and peripheral neuropathy. [5,6,9]

This case series described that linezolid, while effective for treating TB, has been shown to be directly correlated with neurotoxicity in a dose-dependent manner. Linezolid has become the first choice for oxazolidinone antibiotic therapy because of its high oral bioavailability and organ penetration with minimal drug resistance. Peripheral neuropathy has been reported to affect 81% of patients in a study at doses up to 1200 mg/day. [5,9] A randomized control study by Zhang X et al. (2015) of 33 MDR/XDR-TB patients receiving an initial daily dose of 1,200 mg linezolid for 4-6 weeks followed by 300–600 mg in the advanced phase reported a significantly higher likelihood of peripheral side effects (24.2%) and optic neuropathy (18.2%). The exact mechanism of linezolid-induced optic neuropathy is unknown. Decreased mitochondrial function in the retinal nerve fiber layer is suspected to be similar to the pathophysiology of other toxic optic neuropathies. [4,10]

Zhang X *et al.* determined that peripheral neurotoxicity occurred in 30% of patients receiving doses of 600 mg/day for 4-6 months. In our case, patients had taken 600 mg/day of linezolid for 6–12 months before the onset of side effects. [10] Age, sex, and mitochondrial DNA polymorphisms are possible risk factors for linezolid poisoning. Linezolid-induced optic neuropathy may be reversible, but the exact duration of symptom resolution after discontinuation of the drug is unknown. Most reported cases of optic neuropathy resolve within 1–3 months after drug discontinuation. [4,6]

Nearly all patients receiving linezolid have been screened using verbal screening, visual acuity, and the Ishihara test by our experts at least once. Immediate access to an ophthalmologist was also provided if there were any vision-related complaints. Similar findings were seen in the visual fields of patients with ethambutol toxicity. Ethambutol may selectively affect traversing fibers in the chiasma, but nerve imaging appeared normal. Ethambutol and linezolid appear to share a similar and specific parameter pattern, which may reflect a toxicity-related mechanism involving mitochondrial dysfunction. Regular ophthalmic screening for suspected neuropathy in patients taking long-term linezolid for DR-TB is imperative.

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SPASTICITY, PAIN, AND WEANING DIFFICULTY: COMPREHENSIVE MANAGEMENT TO SUCCEED WEANING FROM MECHANICAL VENTILATION

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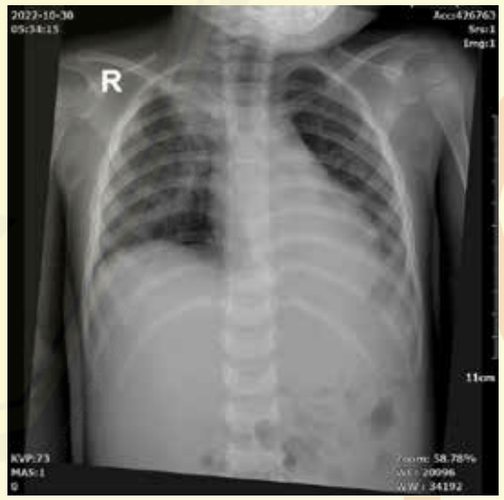
ABSTRACT

Background

A 2-year-old child was referred to Persahabatan Hospital ICU with pneumonia, septic encephalopathy and spastic tetraplegic CP. Patient was unconscious and had history of spastic muscles since childbirth. Systemic inflammation elicited by sepsis can cause acute cerebral dysfunction, characterized by delirium, coma and cognitive dysfunction known as septic encephalopathy, which can develop in 53% patients with sepsis.[1] Patient had leukocytosis of 35.100x103, hypoalbuminemia of 2.77 g/dl, and hyperprocalcitoninemia of 59.08 ng/ml during first days of admission, accompanied with hyperkalemia (5.89) and hyperchloridemia (114.4). Initially, patient was given cefotaxime 3x500 mg IV, which was gradually upgraded to meropenem 3x400 mg IV and amikacin 1x170 mg IV once sputum culture revealed growth of *Acitenobacter baumanii* and consequently newfound spores. No growth of other bacteria was found in cerebrospinal fluid, blood and urine cultures, nor newfound *Mycobacterium tuberculosis* in sputum PCR. Patient was intubated and was attached to mechanical ventilation 2 days after admission, with the setting of SIMV FiO2 70% VT 0.08 Ti 1.2 RR 20 PEEP 5 PS 10. Patient was weaned to CPAP and T piece 30 days after initial intubation and MV application, with vital signs of BP 124/74 (101) mmHg, HR 121 times/minute, RR 43 times/minute, S 37.7ºC. Echocardiography revealed left ventricular ejection fraction of 41%, heart rate decreased to 115 times/minute when spasticity reduced (MAS 4 to 3) while patient was asleep.



Picture 1. Thoracal x-ray during patient's ICU admission: Right upper lobe consolidation, bilateral perihilar and lower right lobe infiltrate, conclusion: pneumonia dd/ lung tuberculosis.

Spasticity as an upper motor sign was elicited since beginning of admission, with MAS scale of 4 at the neck, upper & lower extremity including trunk muscles. Severe spasticity also resulted in severe pain, shown in FLACC 9, along with increasing HR above 200 bpm and RR above 40 every time pain was aggravated due to spasticity. Diaphragm was difficult to inflate when patient's muscles were spastic. Positioning the patient in an upright position to facilitate diaphragm movement was challenging, considering finding of asymmetrical hip due to joint dislocation. Rehabilitation management to enhance mucus clearance and diaphragm movement by mechanical insufflation and exsufflation initiated results in improvement of mucus clearance that showed in adequate O2 saturation (SpO2 99%) in MV mode of PS 10 cmH2O, FiO2 40% PEEP 5cmH2O, TV of 80 ml at the highest, however HR and RR were consistently high (HR 142 beat/minute, RR 38 times/minute). Weaning process was difficult due to limited lung expansion secondary to ineffective chest wall muscle contraction due to spasticity; hence more difficult when pain caused tachycardia.

Material and Methods

Mechanical insufflation and exsufflation was used for training the diaphragm. It was conducted 3 times daily with pressure of +30-40 cmH2O/-30-40 cmH2O, 3 times/day, 5 cycles per session. Positioning to inhibit extensor thrust posture due to spasticity was performed during daytime. Pain management due to spasticity was treated with administration of baclofen 0.5 mg twice daily, alongside training for diaphragm and lung compliance 3 times daily.

Results

Spasticity was reduced from MAS 4 to MAS 2 at day 3 of oral baclofen administration. Pain scale reduced from FLACC 9 to 5. Heart rate also declined to 102 times/ minute; RR declined to 28 times/minute after consumption of baclofen. During weaning at pressure support 6 cmH2O, patient showed sinus rhythm of HR 108 beats/minute, SBP of 92 mmHg, RR of 28 times/minute, FiO2 45%, PEEP 5, and TV of 80 ml. After 4 trials of SBT with duration of 12 hours, weaning was successful and patient was discontinued from mechanical ventilation.

Discussion

This patient experienced gradual worsening of spasticity symptoms on her upper & lower extremities, as well as trunk muscles. Based on examination, patient was diagnosed with cerebral palsy. Cerebral palsy (CP) is defined as a clinical syndrome characterized by a persistent disorder of posture or movement due to a non-progressive disorder of the immature brain.[2] Prevalence of CP is 2 to 2.5 per 1000 live births and its incidence may be increasing secondary due to improved care in neonatal intensive care units and improved survival of low birth-weight infants,[3] as in this case, where patient had a history of PICU admission. Most children with CP will have spasticity as main motor disorder and it can be classified either according to which body areas affected: hemiplegia, diplegia, tetraplegia, or movement disorder type: spastic, athetoid, ataxic and hypotonic cerebral palsy,[4] in this case the patient's condition is tetraplegic CP. Spasticity can result in functional problems with activities of daily living (ADL) such as gait, feeding, washing, toileting and dressing. Over time, spasticity may also cause problems such as muscle pain or spasms, trouble moving in bed, difficulty with transfers, poor seating position, impaired ability to stand and walk, dystonic posturing muscle, contracture leading to joint deformity, bony deformation, joint subluxation or dislocation and diminished functional independence. Shortening and stiffness of soft tissues can cause joints resistant to stretching and prevent normal movement.[5] One of the most important tests in rehabilitation for physical examination of spasticity is the Ashworth scale,[6] in this case, the CP patient's spasticity was found MAS 3-4 during hospitalization, then was given pharmacological and non-pharmacological treatment until it reduced to MAS 2.

Noxious stimuli in this patient are tight upper & lower extremities and trunk muscles, and also a period of urinary tract infection. No pressure injury was ever formed during inpatient period. All of these pain sources have caused spasticity, evolving a vicious circle where spasticity also causes pain, and more pain will cause muscles to be spastic. This condition has caused management of pain to be more aggressive. Besides paracetamol, patient was also administered fenitoin 2x25 mg IV and fenobarbital 2x25 mg IV which resulted in less pain relief (FLACC scale of 6-7). Although pain seemed reduced, patient was still in tachycardia and tachypnea.

Because this patient's body stays in a limited number of positions, the patient will need and benefit from 24-hour postural care.[7] Hip dislocation in children with CP is a major disability, which causes difficulties in sitting and positioning, maintenance of hygiene, and may lead to scoliosis. Inability to pull to stand by the age of 3 years is highly correlated with hip subluxation. Main factors causing progressive subluxation appear to be hip adductor spasticity and shortening, together with lack of normal weight bearing. During ICU admission, the bare minimum approach in preventing progression of subluxation is reducing hip spasticity and inhibiting extensor and adductor superiority by correcting positioning.

From a study done in quadriplegic CP, Siriwat et al found mechanical insufflation-exsufflation (MI- E) could be beneficial in shortening the duration of airway clearance, showing lower-respiratory infections and atelectasis. Regarding effectiveness, MI-E can be a rational alternative for airway clearance, showing fewer adverse effects and reduction in labour hours.[8] MI-E was given with a low dose, continued with gradual increase so as not to cause more spasticity. The purpose of MI-E is to facilitate diaphragm movement, when muscle fibres are not able to contract due to spasticity, passive motion by some pressure applied assists the diaphragm to inflate. In spastic condition, giving low pressure slowly will prevent speed shortening and lengthening of muscle fibres that aggravate the vicious circle of spasticity.

Significant functional impairment in limitation of ADL due to spasticity was given both pharmacological and non-pharmacological therapy. Use of oral muscle relaxants has gained ground and more evidence are available to evaluate its efficacy. Currently, common oral muscle relaxants include baclofen, dantrolene and diazepam.9 Daily administration of 0.5 mg baclofen twice/day was used as anti-spasticity pharmacologic therapy for the patient, aside from its dual role for pain management. Spasticity was reduced from MAS 4 to MAS 2 at day 3 of baclofen administration. The aftermath included reduction of pain scale from FLACC 9 to 5, reduction of HR to 102 bpm, and RR to 38 bpm. Baclofen is commonly prescribed for spasticity in CP; however, despite many years of experience there is a large degree of variability in recent studies evaluating the efficacy of its oral use in patients with cerebral palsy. Current evidence points to an improvement in muscle tone and strength after oral baclofen use, although this effect may be short-term and prolonged use may cause increased weakness in patients.[9] In addition, other muscle relaxants such as tolperisone and tizanidine show similar efficacy to oral baclofen, with less side effects in recent trials.[10] More studies with larger sample sizes and similar treatment protocols need to be conducted to make a definitive recommendation on oral baclofen future use in patients with CP. While promising results show, there is not enough evidence to make a definitive statement in support of its efficacy. It may provide short term relief for patients; however, limited data is yet available on its prolonged use and efficacy in this particular

population. In this case baclofen has shown beneficial effect in reduced spasticity, pain relief and improved strength that resulted in weaning success.

Alongside baclofen administration, training for diaphragm and lung compliance was also conducted regularly 3 times/day. Non-pharmacological management consisting of occupational therapy (OT) and physical therapy (PT) are both fundamental pillars of spasticity management. Consequently, pharmacologic and non-pharmacologic treatment emphasizing on rehabilitation and physical treatments aimed at lengthening the overactive muscles are fundamental in treating spasticity.[11] There are a number of different dynamic occupational and physical therapy approaches, including the Bobath technique, sensory integration therapy,4 proprioceptive neuromuscular facilitation and the Brunnstrom technique.[12] Alongside various techniques, consideration of applying other techniques such as ice (cold), heat, positioning, stretching exercises and use of orthotic devices are very rational. Cold temperature inhibits spastic muscles; however the effect is short-lived, perhaps outlasting the application of the cold by about half an hour. Paradoxically, heat is also used for relaxation of spastic muscle. Positioning the child to stretch spastic muscles will also decrease sensitivity of the stretch reflex & brainstem reflexes that trigger spasticity. Discharge planning include physician's and therapist's roles in the education of proper patient positioning to family members, hence the child will be properly handled while lying and sitting down at home.[13] Massage and stretching muscles may prevent contractures and promote muscle growth, while spasticity decreases with slow and continuous stretching with effect lasting from 30 minutes to 2 hours. Stretching exercises are done beforehand bracing and serial casting to obtain necessary joint positions.[14] Orthoses are generally used in conjunction with occupational therapy and physical therapy with the aims of increasing muscle length (through providing a prolonged stretch), breaking up mass patterns of movement and improving biomechanics and stability. Muscle relaxation after stretching exercises lasts for a short period of time. For lasting effects, stretch on the muscle should be maintained for several hours every day, which is possible with use of rigid splints or serial casting.[15] Spasticity still remains a major challenge for rehabilitation of children with cerebral palsy; therefore, physical treatments aimed at lengthening overactive muscles are fundamental parts of spasticity management alongside passive range of motion exercises on upper & lower extremities such as in this case report.

Difficulty of breathing was found due to spasticity on trunk muscles. Pneumonia was found based on physical and radiological examinations including plain thoracal x-ray showing increased vascular pattern, and consolidation of bilateral perihilar & right paracardial regions. During weaning of pressure support, patient showed sinus rhythm HR 108 bpm, SBP of 92 mmHg, RR of 28 bpm, FiO2 45%, PEEP 5, and TV of 80 ml. After 4 attempts of SBT with 12 hour-long durations, weaning was successful and patient was discontinued of mechanical ventilation. Mechanical ventilation is an indispensable support means for treatment of patients with severe pneumonia, though prone to cause lung injury and bacterial infections which may cause extreme adverse effects on weaning and prognosis.[16] Pulmonary rehabilitation is an integral pillar of management in patients with respiratory diseases, due to its active role in improving patients' pulmonary function and immunity. Introduction of pulmonary rehabilitation therapy was expected

to relieve and even reverse lung injury alongside other complications of severe pneumonia during use of MV. Pulmonary rehabilitation accommodates combined management of patients' exercise capacity, remission of disease, recovery of pulmonary function and psychology, which integrates prevention and treatment. Numerous studies have shown that pulmonary rehabilitation can improve dyspnoea and motor function of patients in an effective manner.[17] Improvement of exercise capacity is crucial to patients' further recovery from disease, not only for enhancing immunity, but also improvement of disease recovery.[18] In this case, patient with spasticity in respiratory muscles succeeded of weaning from mechanical ventilation with usage of muscle relaxant drugs, followed with pulmonary rehabilitation and positioning to improve breathing capability.

In addition, blood gas index of the patient with severe pneumonia were evaluated in this study, where results proved that pulmonary rehabilitation supported remarkable improvement in the patients' PaO_2, $PaCO_2$ and SaO_2, regarding patient's metabolic acidosis in this case. Huppmann et al found that pulmonary rehabilitation in patients with interstitial pneumonia improved blood gas indexes in an effective manner,[19] proving that pulmonary rehabilitation can cause great effects on recovery of pulmonary functions and exchange capacity between oxygen and carbon dioxide. Therefore, pulmonary rehabilitation is beneficial for improving pulmonary functions and blood gas indexes of patients with severe pneumonia during use of MV.[20]

Septic encephalopathy was also acquired by this patient based on chief complaint of altered mental status on first day of hospitalization, accompanied with tachypnea and low blood pressure based on qSOFA criteria. Laboratory findings showed slight anaemia (Hb of 10.3 mg/dl), leucocytosis (18.000), and thrombocytosis (531 10^3). Aspartate aminotransferase (436 IU/L) and alanine transaminase (420 IU/L) values elevated, accompanied with elevated C-reactive protein (CRP) of 56.5 mg/L and Procalcitonin of 2.00 ng/ml. Multi Slice Computerized Tomography (MSCT) showed extensive infarction on cortex, subcortex, deep white matter of bilateral frontal lobes, bilateral temporal lobes, caudate nuclei, internal capsule, bilateral lentiform nuclei, bilateral cerebral peduncle with impression of encephalitis. Sepsis encompasses the top four causes of childhood mortality as reported by the World Health Organization (WHO): severe pneumonia, severe diarrhea, severe malaria, and severe measles. Sepsis-associated encephalopathy (SAE) is one of the most common complications during the acute phase and in later stages after surviving sepsis. It is defined by a diffuse cerebral dysfunction due to the dysregulated host response and absence of a direct central nervous system (CNS) infections.[18]

Long-term deficits of sepsis-associated encephalopathy include cognitive deficits (10%–20%), anxiety and stress disorders (10%–30%), and low quality of life. On average, survivors have 1.6 new functional impairments in activities of everyday life, such as taking medication and getting into bed. Persistent cognitive deficits may be monitored by using the Montreal Cognitive Assessment. Long-term recovery rates have not been assessed, but functional rehabilitation and psychotherapy can reduce symptom severity.21,22 In this case, functional rehabilitation was executed early for the patient.

Conclusion

Severe pain will impact cardiorespiratory status of patient using the mechanical ventilation, especially when pain was related to ventilatory muscles suboptimum contraction due to spasticity. Managing spasticity resulted in pain relief and improvement in work of breathing. Administration of baclofen has shown to support a successful weaning process from MV and cut down the vicious circle of spasticity-related pain.

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BRONCHIECTASIS IN ELDERLY WOMAN ASSOCIATED WITH COPD AND HISTORY OF COVID-19, WHICH ONE IS GUILTY: AN INTERESTING CASE REPORT

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ABSTRACT

Background: The lung damage due to COVID-19 persists even after the disease has receded with fibrotic changes including parenchymal bands, irregular interfaces, and reticular opacities, with or without honeycomb-like changes. Bronchiectasis (BE) in patients with chronic obstructive pulmonary disease (COPD) is associated with increased bronchial inflammation, frequent colonization of pathogenic microorganisms, and airflow obstruction.

Case presentation: a 75-year-old woman came to the ER with chronic shortness of breath getting worse and deterioration of her cough with sputum purulence for about 1 week before admission. Past medical history showed that patient diagnosed COPD for about 5 years and given LABA and LAMA medication. In July 2021 patient had history of severe Covid-19. Honeycomb appearance on chest x-ray and multisegmented widened bronchogenic cyst on chest CT-scan lead to diagnosis of bronchiectasis.

Discussion: Bronchiectasis is defined as permanent dilatation of the conducting airways and is generally associated with symptoms which overlaps with COPD. On the other hand, COVID-19 infection presents a wide variety of complications of acute respiratory failure due to diffuse pulmonary infiltrates, but the formation of BE is still too short to be able to confirmed that associated with COVID-19 infection.

Conclusion: The clinical and radiological finding of BE in patient with COPD and history severe COVID-19 had multi-directional problem that need to be confirmed which one is affect and damage more.

Keywords: *Bronchiectasis, COVID-19, COPD*

Background

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 with high level infectivity has led to a rapid increase in the number of cases and caused a global pandemic. The increasing number of cases worldwide has resulted in a large-scale shortage of medical resources. About 80% of the COVID-19 patients have mild infection and presents a wide variety of complications ranging from self-limiting upper respiratory tract infection to acute respiratory failure due to diffuse bilateral pulmonary infiltrates.[1–3]

Computed tomography (CT) images can objectively show lung changes in patients with COVID-19. Therefore, CT can be used for the rapid diagnosis and assessment of COVID-19 pneumonia. The typical CT feature of ARDS in the acute phase is the opacification that demonstrates an anterio-posterior density gradient within the lungs. In the late phase, the reticulation and ground-glass opacity (GGO) in the anterior part of lungs are the more typical CT findings. When the patients with COVID-19 pneumonia progress to ARDS, CT images show expanded lung involvement, increased density, and consolidation.[1,3]

Bronchiectasis is diagnosed in the presence of airway dilatation and airway wall thickening on imaging (usually computed tomography, CT) and is therefore a structural diagnosis. Clinically significant disease is present when imaging abnormalities are associated with symptoms of persistent or recurrent bronchial infection. Traction bronchiectasis (BE) appears as irregular BE on CT images, which is a common radiological characteristic of patients with ARDS in the acute phase. It is also present in patients with COVID-19 pneumonia. Bronchiectasis is a clinical and radiological diagnosis associated with cough, sputum production and recurrent respiratory infections. The clinical presentation inevitably overlaps with other. respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD).[1,4,5]

Bronchiectasis is diagnosed in the presence of airway dilatation and airway wall thickening on imaging usually on CT and is therefore a structural diagnosis. Clinically significant disease is present when imaging abnormalities are associated with symptoms of persistent or recurrent bronchial infection. COPD and bronchiectasis share common symptoms of cough with sputum production and susceptibility to recurrent exacerbations driven by new or persistent infection. With increasing use of computed tomography in the assessment of people with COPD, the presence of previously unrecognized bronchiectasis is being identified. The prevalence of bronchiectasis in COPD patients has been analysed in several studies with conflicting results ranging from 20% to 69%.[4,6]

This case series is written to discuss the existence of overlapping bronchiectasis in COPD patient with history of Covid-19 infection.

Case Presentation

a 75-year-old woman complained shortness of breath for 5 years getting worse and deterioration of her cough with sputum purulence for about 1 week before admission. The patient had fever and fatigue about 5 days before admission. When came to ER, patient was fully awake but with heavy breathing. On examination in the emergency department, the patient was afebrile though tachycardiac. Heart rate was 107 beats per minute, blood pressure 140/90 mm Hg and the respiratory rate was increased to 24 breaths per minute with the oxygen saturation of 96% while breathing ambient air. Auscultation of the chest revealed crackles and wheezing in both hemithorax. She had oedema on her lower extremities.

We took chest x ray examination to the patient and the result was cardiomegaly with pulmonary oedema and widened mediastinal space suspected with aortic aneurism differential diagnosed with mediastinal mass. From chest x ray did not see any sign of honeycomb appearance or any other bronchiectasis imaging (figure 1A). We continue with contrasted Chest CT scan and the result was multisegmented widened bronchogenic cyst bilateral with some of them had air fluid level lead to infected bronchiectasis. From CT found widened pulmonary artery led to pulmonary hypertension (figure 1B, C, D).

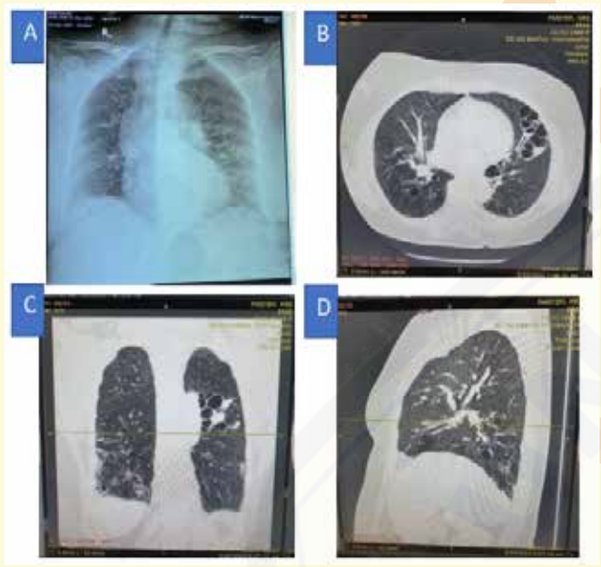

Figure 1 (A) Chest X-ray of patient on March 18, 2023; (B) Chest CT on March 23, 2023 axial view; (C) coronal view; and (D) sagital view.

Past medical history showed that patient diagnosed COPD for about 5 years and given LABA and LAMA medication. The patient did not use the medication regularly. She felt shortness of breath during exertion activity or walking slightly uphill. The patient living along with a smoker husband with history of one pack per day for the past 40 years and she had daily cooking with firewood. During pandemics of COVID-19 in July 2021 patient had confirmed with severe COVID-19. The patient hospitalized in intensive care unit of RSUD Panembahan Senopati for about 2 weeks. After having intensive treatment, the patient moved in ward for about 1 week before discharged. During the hospitalization, she did not have CT examination.

Discussion

Bronchiectasis is a chronic lung disease characterized by a vicious cycle of airway infection and inflammation leading to permanent structural damage to the small airways and sometimes to the surrounding lung parenchyma. Bronchiectasis generally presents as a chronic cough with associated sputum production which occur in most of patients and recurrent lung infections. COPD and bronchiectasis share common symptoms of cough with sputum production and susceptibility to recurrent exacerbations driven by new or persistent infection. In many patients, a history of pulmonary exacerbations, sometimes labelled as bronchitis or pneumonia and treated with antibiotics or anti-inflammatory agents) may be evident before a diagnosis is made. [4,7,8]

A distinct feature of bronchiectasis is the tendency toward exacerbations. A consensus definition of an exacerbation, which was designed for use in clinical trials but is also applicable to clinical practice, was published in 2017. An exacerbation is present when three or more factors in the following categories are present: a deterioration in cough and sputum volume or consistency for at least 48 hours; an increase in sputum purulence, breathlessness or exercise intolerance, fatigue or malaise, or haemoptysis for at least 48 hours; or a determination by a clinician that a change in bronchiectasis treatment is needed. Multiple inciting factors lead to the development of bronchiectasis, which ultimately results in a vicious cycle of remodelling and dilation of the airways. An initial insult leads to airway dysfunction, an inflammatory response, and structural disease and infection. Once the pattern is established, it becomes a progressive process over time and overcomes local and systemic host protective factors. Impaired mucociliary clearance causes mucus retention, airway distortion, and vulnerability to infection. The initial insult varies from patient to patient and often is unknown. In some patients, the airway itself is abnormal because of a pre-existing condition such as infection or ciliary dysfunction; in others, the mucus has abnormal characteristics that lead to stasis and obstruction.[9]

Bronchiectasis is best imaged on high resolution CT scans (HRCT). According to the Fleischner society consensus statement, morphologic criteria on thin-section CT scans include bronchial dilatation with respect to the accompanying pulmonary artery (signet ring sign), lack of tapering of bronchi, and identification of bronchi within 1 cm of the pleural surface. Once bronchiectasis has been confirmed by CT, a systematic workup that is based on the patient's history and clinical symptoms should be undertaken. Radiographically apparent bronchiectasis is sometimes seen in patients whose primary diagnosis is COPD.[8,9]

Substantial number of previously hospitalized survivors of SARS-CoV-2 infection will have abnormalities in a CT scan vary over time, such as ground-glass opacities (GGOs), consolidation, especially those with more severe acute infection can have parenchymal or subpleural bands, reticular abnormalities like honeycombing, pleural thickening, and BE being the most common. CT findings can change as the disease progresses. In the early stage, chest CT shows small lobular and subsegmental patchy GGOs, interstitial changes, and thickening vascular lumens. In the progressive and peak stage, the lesions gradually progress to multiple GGOs and consolidation in the lungs. The presence of traction bronchiectasis is generally considered as the evidence of fibrosis. Traction bronchiectasis may also occur in the acute phase of pneumonia or ARDS and affect the prognosis. It has been reported that traction bronchiectasis is found on the CT images of pneumonia COVID 19 survivors with ARDS.[1–3,10]

Although bronchiectasis has many aetiologies ranging from post-infectious, to congenital and immunologically causes, an association with respiratory diseases such as COPD and COVID-19 has been clearly demonstrated. From a pathophysiological point of view, there are many different potential scenarios can be identified such as COPD leads to the development of bronchiectasis through a variation of the classic "vicious cycle" hypothesis of airway inflammation and repeated infections, bronchiectasis caused by other aetiologies in a non-smoker leads to a fixed airway obstruction. Bronchiectasis could have an impact by impairing mucociliary clearance, causing mucus stasis and increased pathogen colonisation.[11,12]

In humans, ACE2 expression has been found to be increased in the lung of smokers and patients with COPD, and those patients have been reported more likely to have severe COVID-19, implicating a central role of ACE2 in COVID-19 development. The SARS-CoV-2 spike protein demonstrates at least 10 times higher affinity in binding ACE2 than does SARS-CoV-2. High ACE2 expression on host cells increases the susceptibility to SARS-CoV-2, and blocking ACE2 signalling prevents the viral infection in vitro.[13]

We present a COPD patient with history of severe COVID-19 pneumonia who developed progressive bronchiectasis. This case described that COPD, bronchiectasis, and COVID-19 are all related. They influence each other with unclear mechanisms.

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THE RELATIONSHIP BETWEEN IL-6 LEVELS AND THE INCIDENCE OF SEPSIS IN COVID-19 PATIENTS TREATED AT RSUP DR. M. DJAMIL PADANG

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ABSTRACT

Background: The Coronavirus Disease 2019 or COVID-19 pandemic has caused significant alterations to the development of medical science, especially regarding sepsis. Elevated IL-6 levels are associated with a worse prognosis and worsened clinical outcomes in COVID-19 patients. This study aimed to examine the relationship between IL-6 levels and the incidence of sepsis in COVID-19.

Methods: This study was an observational analytic study to determine the difference between IL- 6 levels and sepsis in COVID-19 patients treated at RSUP Dr. M. Djamil Padang from January 2021 to December 2021. Data were collected based on medical record data.

Results: This study involved 492 research subjects, and 68 patients (13.8%) experienced sepsis. The average level of IL-6 in subjects who experienced sepsis and did not experience sepsis reached >7 pg/mL, but the average IL-6 level in subjects who experienced sepsis was much higher than in subjects who did not. The number of subjects who experienced sepsis with IL-6 levels < 7 pg/mL was much smaller than patients with IL-6 levels >7 pg/mL, which is 2.94% compared to 97.06%. The relationship between IL-6 levels and sepsis status in the study subjects was considered statistically significant, indicated by a p-value <0.05.

Conclusion: COVID-19 patient at RSUP Dr. M. Djamil Padang had a small proportion of sepsis. IL-6 levels in COVID-19 patients were significantly associated with the incidence of sepsis.

Keywords: *interleukin, biomarker, prognosis, sepsis*

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has spread rapidly throughout the world and caused millions of cases of infection and death. This disease is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which triggers varying severity of upper respiratory infections between individuals.[1] In some patients, COVID-19 infection can worsen, causing acute hypoxia, acute respiratory distress syndrome (ARDS), multi-organ failure, and even death.[2] Many cases have reported other organ failure accompanying this disease. Although the pathogenesis of COVID-19 is not fully understood, reported hospitalization data show that serum levels of cytokines and chemokines are increased in patients with severe COVID-19, similar to findings in sepsis patients. The COVID-19 pandemic has caused significant alterations to the development of medical science, especially regarding sepsis.[3]

Elevated IL-6 levels are associated with a worse prognosis and worsened clinical outcomes in COVID-19 patients. An increase in IL-6 levels above 80 pg/ml is sufficient to identify a COVID-19 patient with a high risk of experiencing respiratory failure.[4] IL-6 values are known to be more elevated in cases of COVID-19 and sepsis. Remick stated in 2021 that the prevalence of sepsis related to COVID-19 was 77.9% in the ICU and 33.3% in ordinary inpatient rooms; there was a mortality of 33% in COVID-19 patients with sepsis in the ICU.5 Based on the data above, the author was interested in examining the relationship between IL-6 levels and the incidence of sepsis in COVID-19 at RSUP Dr. M. Djamil Padang.

MATERIALS AND METHODS

This study was an observational analytic study to determine the difference between IL-6 levels and sepsis in COVID-19 patients treated at RSUP Dr. M. Djamil Padang from January 2021 to December 2021. Inclusion criteria were all COVID-19 patients undergoing treatment at RSUP Dr. M. Djamil Padang from January 1, 2021, to December 31, 2021, aged over 18 years, and has complete medical record data in the form of IL-6 data, comorbidities and results of blood, urine and/or sputum culture examinations. Exclusion criteria were COVID-19 patients with comorbid autoimmune diseases (Rheumatoid arthritis, Systemic Lupus Erythematosus, Type 1 Diabetes, Myasthenia gravis, Hashimoto's Thyroiditis, Graves' disease, and Multiple sclerosis) and patients who experienced secondary infections within <48 hours of hospitalization. Data were collected based on medical record data. Using the Chi-square test, a bivariate analysis was used to see the relationship between IL-6 levels and sepsis. If the requirements were not met, a Fisher exact test was performed. The two variables are considered to have a significant relationship if the p- value <0.05.

RESULTS

Prevalence of Sepsis in COVID-19 Patients From 612 COVID-19 patients treated at RSUP Dr. M. Djamil Padang from January 2021 to December 2021, 492 patients (80.3%) met the inclusion criteria. There were 120 patients excluded because 106 patients did not have initial IL-6 level data, 13 patients did not have blood, urine, and sputum culture data results, and one patient did not have height data. This study involved 492 research subjects, and 68 patients (13.8%) experienced sepsis.

Description of the Characteristics of Research Subjects

This study obtained data on 492 COVID-19 patients who underwent IL-6 levels from January to December 2021 at RSUP Dr. M. Djamil Padang. Most patients aged <50 years, which was equal to 41.9%. 43.9% male patients and 56.1% female patients. Most of the patients had normal nutritional status (50.4%). The most common secondary infections experienced by the subjects of this study were UTIs accompanied by other infections such as postoperative wound infections, cellulitis, and gynecological infections (18.7%).

Table 1. Description of the characteristics of research subjects

ient Characteristics (n= 492)	Amount (%)	Sepsis n	Sepsis (%)	No Sepsis n	No Sepsis (%)
years	206 (41.9)	16	(23.5)	190	(44.8)
59 years	122 (24.8)	14	(20.5)	108	(25.4)
9 years	100 (20.3)	26	(38.2)	74	(17,4)
years	64 (13)	12	(17,6)	52	(12,2)
er					
	216 (43.9)	33	(48.5)	183	(43.2)
ale	276 (56.1)	35	(51.4)	241	(56.8)
onal status					
utrition	31 (6,3)	5	(7,3)	26	(6,1)
nal	248 (50.4)	39	(57.3)	209	(49.2)
weight	160 (32.5)	18	(26.4)	142	(33,4)
sity	53 (10.8)	6	(8,8)	47	(11,1)
dary Infection					
umonia	56 (11.4)	9	(13,2)	47	(11,1)
ary tract infection (UTI)	60 (12,2)	9	(13,2)	51	(12)
others (postoperative nd infections, cellulitis, cological infections)	64 (13)	6	(8,8)	58	(13,7)
umonia + UTI	47 (9,6)	5	(7,3)	42	(9,9)
umonia + Etc.	78 (15.9)	8	(11.7)	70	(16.5)
umonia + UTI + Etc.	42 (8.5)	7	(10,2)	35	(8,3)
+ Etc.	92 (18.7)	11	(16,2)	81	(19,1)
econdary infection	53 (10.8)	13	(19,1)	40	(9,4)

Culture						
Sputum culture	50 (10,2)	9	(13,2)	41	(9,7)	
Urine culture	57 (11.6)	7	(10,1)	50	(11.8)	
Blood culture	65 (13,2)	7	(10,1)	58	(13,7)	
Sputum + urine culture	43 (8,7)	5	(7,4)	38	(9)	
Sputum + urine + blood culture	47 (9,6)	7	(10,1)	40	(9,4)	0.34
Sputum + blood culture	75 (15.2)	7	(10,1)	68	(16)	
Urine + blood culture	96 (19.5)	12	(17,6)	84	(20)	
Negative culture results	59 (12)	14	(20.6)	45	(11)	
Comorbid						
Without comorbid	308 (62.6)	30	(44.1)	278	(65.6)	0.001*
With comorbid	184 (37.4)	38	(55.9)	146	(34.4)	
Clinical Degree						
Mild	28 (5,7)	1	(1,5)	27	(6,4)	
Moderate	204 (41.5)	11	(16,2)	193	(45.5)	
Severe	114 (23,2)	10	(14,7)	104	(24.5)	0.000*
Critical	146 (29.7)	40	(58.8)	106	(25)	
The total number of research subjects		68	(13,8)	424	(86.2)	

*p-value < 0.05

In this study, 184 (37.4%) subjects had comorbidities, with the most comorbid being hypertension (12%). As many as 62.5% of subjects had one type of comorbid, 29.3% of subjects had two types of comorbid, 7.1% of subjects had three types of comorbid, and 1.1% of patients had four types of comorbid at once. The most positive culture results in the subjects of this study were the results of urine and blood cultures (19.5%). Most clinical degrees in this study were moderate clinical degrees (41.5%). Most of the results of the IL-6 examination of the subjects in this study reached >7 pg/mL (88.4%). Overall, the subjects of this study who experienced sepsis were 13.8%. The results of the univariate analysis of the characteristics of the respondents and the research variables are presented in Table 1.

Of the 68 subjects who experienced sepsis, the largest age range was 60-69 years. The sex of most patients was female but only slightly compared to male (35 vs. 33 patients). Nutritional status, type of secondary infection, and the most positive culture results in the sepsis group patients were similar among the patients. The most comorbid type was diabetes mellitus (23.5%). The most clinical degree in this subject group was the critical clinical degree (58.8%). Table 1 shows several variables with a p-value <0.05: age, comorbidities, and clinical degree.

Correlation between IL-6 levels and sepsis in COVID-19 patients

The average level of IL-6 in subjects who experienced sepsis and did not experience sepsis reached >7 pg/mL, but the average IL-6 level in subjects who experienced sepsis was much higher than in subjects who did not. Because the data on IL-6 levels in this study were identified as not normally distributed, the average IL-6 level was presented in the form of a median value. The median IL-6 level obtained in septic subjects was 80.9 pg/mL (Median: 80.9 pg/mL, Q1-Q3: 28.45 pg/mL – 168.7 pg/mL), and the median value in subjects who were not septic was 29.3 pg/mL (Median: 29.3 pg/mL, Q1-Q3: 12 pg/mL – 94.2 pg/mL). The Spearman Rank test was carried out on the subject's IL-6 level data and obtained a p-value of 0.01.

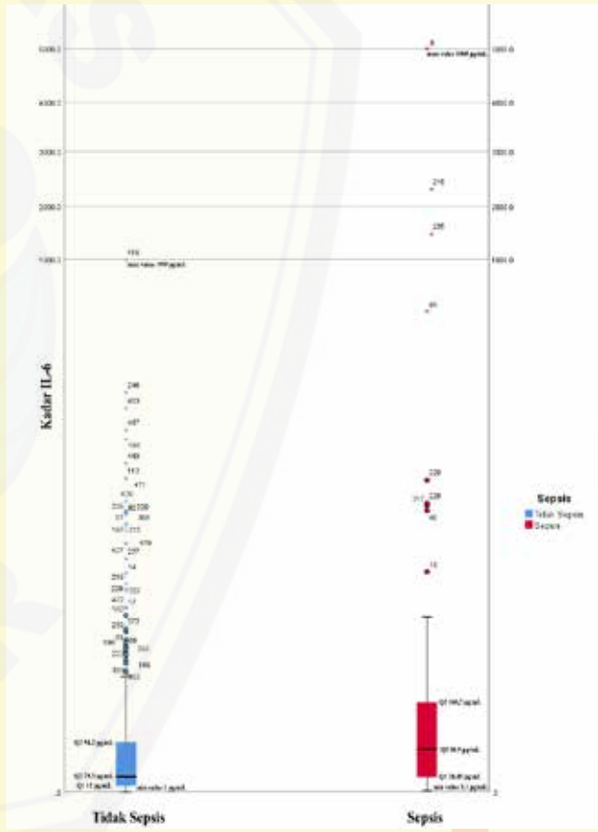

Figure 1. Box plot of the distribution of data on IL-6 levels in research subjects

The number of subjects who experienced sepsis with IL-6 levels < 7 pg/mL was much smaller than patients with IL-6 levels >7 pg/mL, which is 2.94% compared to 97.06%. The relationship between IL-6 levels and sepsis status in the study subjects was considered statistically significant, indicated by a p-value <0.05.

The bivariate analysis results of the incidence of sepsis in subjects on IL-6 levels using the chi-square test can be seen in Table 2 below.

Table 22. Relationship between IL-6 levels and sepsis status in research subjects

Sepsis state	IL-6 levels				*p-values*
	<7 pg/mL		≥7 pg/mL		
	n	f(%)	n	f(%)	
Sepsis	2	(2.94)	66	(97.06)	0.028*
No sepsis	55	(12.97)	369	(87.03)	

*p-value<0.05

DISCUSSION

Prevalence of Sepsis in COVID-19 Patients

Overall, the subjects in this study were 492 subjects, and 68 subjects (13.8%) had sepsis. These results were almost similar to the study by Abumayyaleh et al. in 2021 at the University of Heidelberg, Germany, which calculated the prevalence of sepsis in COVID-19 patients at 11%.[6]

Shappell et al., in 2022 at Harvard University, United States of America, had results quite different from the results of this study, which had a prevalence of sepsis in COVID-19 patients of 32.5%.[7]

This difference in results is probably due to the small number of study subjects by Shappell et al., namely only 200 subjects, compared to Abumayyaleh et al.'s study subjects, which included 5,837 patients.

Characteristics of Research Subjects

The age range for most COVID-19 patients was < 50 years; it is probably due to the high mobility of the population aged < 50 years, so the risk of exposure to and infection with COVID-19 is greater. The largest age range for COVID-19 patients with sepsis showed different results, namely 60-69 years old. Age is known to affect the outcome of the infection process experienced by patients. Ginde et al. found that levels of inflammatory cytokines were higher in elderly septic patients.[8]

The gender of the study subjects indicated that there were more female COVID-19 patients than male subjects (56.1% female subjects and 43.9% male subjects). The result of this study aligned with the research of Setiadi et al., where the prevalence and epidemiology study of COVID-19 in Jakarta also had more female subjects than male subjects.[9]

The overall nutritional status of the study subjects and the sepsis group showed similar results, in which most had good nutritional status. The 2020 Center for Disease Control and Prevention (CDC) report explained that undernourished status and obesity have a higher risk of worsening the course of the COVID-19 disease.[10] It was not seen in this study population.

Secondary infections experienced by most of the research subjects were UTIs accompanied by other infections such as postoperative wound infections, cellulitis, and gynecological infections. Thess secondary infections were thought to occur due to an immunosuppressive effect due to ongoing viral infection and due to medical therapy in COVID-19 patients.[11] The Kruskall-Wallis test showed that secondary infection did not significantly influence the occurrence of sepsis in the subjects of this study.

The most common comorbidity in the subjects of this study as a whole was hypertension, while the most common comorbidity in patients with sepsis was diabetes mellitus. Abumayyaleh et al.'s study of 5,837 patients also found that hypertension was the most common comorbid in their research subjects.[6]

The highest clinical degree in the subjects of this study was a moderate clinical degree, but the most clinical degree in the group of subjects with sepsis was a critical clinical degree. There were a small number of research subjects with mild clinical degrees, but all of them had comorbidities. The Kruskall-Wallis test of the clinical degree of COVID-19 on the prevalence of sepsis in this study obtained a p-value of 0.000, indicating that in this study, the clinical degree of the subjects affected the risk of progression of COVID-19 to sepsis. The pathophysiology underlying this degree is driven by the inflammatory response and coagulopathy due to direct viral infection, so that multiple organ damage can occur quickly and is difficult to treat.[12]

Correlation between IL-6 levels and sepsis in COVID-19 patients

The mean IL-6 level in this study showed a striking disparity compared to the subjects who had sepsis and those who did not (80.9 pg/mL vs. 29.3 pg/mL). The Spearman Rank test gave a p-value of 0.01, proving that in the subjects of this study, the prevalence of sepsis resulted in a statistically significant relationship between IL-6 levels and sepsis status. By grouping IL-6 levels based on a cut-off of 7 pg/mL, it was observed that only 11.6% of research subjects had IL-6 levels < 7 pg/mL, and as many as 88.4% of study subjects had IL-6 levels > 7 pg/mL. Infection by SARS-CoV-2 in all subjects of this study could trigger an increase in IL-6 levels.

There was a significant relationship between IL-6 levels in COVID-19 patients and the incidence of sepsis. Interleukin 6 is a proinflammatory cytokine that plays an important role in the inflammatory process. It was first identified in the late 1980.13 SARS-CoV-2 infection can induce an abnormal hyperinflammatory response due to the virus starting to infect monocytes, macrophages, and dendritic cells (DC), thus increasing the secretion of proinflammatory cytokines, including IL-6.14 IL-6 is known to cause multi-organ injury in COVID-19 cases.[15]

The result of this study aligned with the results of Huang et al.'s study of COVID-19 patients who had ARDS showing increased concentrations of IL-6, IL-1β, and tumor necrosis factor (TNF)-α. This abnormal increase in cytokine levels is described as a cytokine storm. This condition results in excessive immune system activation, thus encouraging the production of too many cytokines and chemokines.[16] This phenomenon will continue to the process of immunothrombotic,[17] which in turn causes organ damage.

Research by Kalligeros et al. also explained that IL-6 levels increased threefold in COVID-19 patients who experienced complications compared to patients who did not experience complications. IL-6 levels have the potential to be a reliable prognosticator and indicator of disease progression and/or death in hospitals.[18] The results of the studies mentioned above are strong evidence that IL-6 levels play an important role in the progression of COVID-19 disease. Infection in the human body will activate the host response, humoral elements (complement cells, acute-phase proteins or APPs and cytokines), and cellular elements

(monocytes, macrophages, and anti-inflammatory mediators). Some of these components will spread in the systemic circulation and can be considered as biomarkers to detect sepsis, including IL-6.[19] IL-6 is a cytokine that plays an important role during the acute phase of the body's response from inflammation to sepsis.[20]

CONCLUSION

COVID-19 patient at RSUP Dr. M. Djamil Padang had a small proportion of sepsis. Characteristics of COVID-19 patients that had significant differences between the septic and without sepsis groups were age, comorbidities, and clinical degree of COVID-19. IL-6 levels in COVID-19 patients were significantly associated with the incidence of sepsis.

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LUNG FUNCTION OF USUAL INTERSTITIAL PNEUMONIA PATTERN OF INTERSTITIAL LUNG DISEASE ASSOCIATED SJOGREN'S SYNDROME TREATED WITH MYCOPHENOLATE SODIUM: CASE REPORT

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ABSTRACT

Background:

Interstitial lung disease (ILD) is a common complication and significant cause of death in Sjogren's syndrome. Usual interstitial pneumonia type is rare in Sjogren's syndrome. We report a case of lung function of usual interstitial pneumonia pattern of interstitial lung disease associated Sjogren's Syndrome (SS-ILD) treated with mycophenolate sodium. Parameters of lung function test are vital capacity (VC), predicted VC, forced vital capacity (FVC), predicted FVC, FEV1, predicted FEV1, FEV1/FVC, and diffusing capacity (DLCO).

Methods:

A retrospective cohort study was performed using electronic health record and diagnosed as SS- ILD. Patient has been treated with mycophenolate sodium and has been performed lung function test, diffusing capacity test, and high-resolution computed tomography (HRCT) to evaluate progressivity ILD.

Results:

Lung function measurements for SS-ILD patients 1 month after treatment were as follows: VC 1200 mL, predicted VC 47%, FVC 1280 mL, predicted FVC 50%, FEV1 1020 mL, predicted FEV1 46%, and FEV1/FVC 79%. Six months after treatment, the measurements were: VC 1370 mL, predicted VC 53%, FVC 1400 mL, predicted FVC 55%, FEV1 1240 mL, predicted FEV1 56% and FEV1/FVC 88%. Fifteen months after treatment, the measurements were: VC 1310 mL, predicted VC 51%, FVC 1140 mL, predicted FVC 45%, FEV1 1000 mL, predicted FEV1 45% and FEV1/FVC 88%. Diffusing capacity test in 1 month, 6 months, and 15 months revealed 26%, 29%, and 34% respectively.

Conclusion:

A rare usual interstitial pneumonia pattern of SS-ILD with mycophenolate therapy, FVC% slope change tended to increase 1,6% per month after 6 months therapy but decreased 2% per month after 15 months therapy. FEV1% slope change tended to increase 1,6% per month after 6 months therapy but decrease 1,2% per month after 15 months therapy. DLCO% slope change tends to increase steadily 1,9% per month after 6- and 15-months therapy.

Keywords: *Interstitial lung disease, Sjogren's syndrome, Mycophenolate therapy*

Background

Sjögren's syndrome is the second most common autoimmune disease after rheumatoid arthritis. Sjogren's syndrome (SS) is a chronic multisystem autoimmune disease, characterized by focal lymphocytic infiltration of the lacrimal and salivary gland resulting in dry eyes and dry mouth.1 SS can occur as primary disease as known as primary SS (pSS) or may occur be associated with connective tissue disease such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), dermatomyositis, or systemic sclerosis (SSc).[2] pSS predominance in female (9:1) and peak incidence at approximately 50 years of age.[3] The prevalence in the general population is estimated between 0,02% and 2,7%[4], based on diagnostic criteria used and ethnic background of the population. In 9–20% of cases, Sjögren's syndrome is associated with various respiratory symptoms. The most typical manifestations are chronic interstitial lung disease (ILD) and tracheobronchial disease. The most common manifestation of ILD is nonspecific interstitial pneumonia (45%) in its fibrosing variant. Other types of ILD, such as organising pneumonia (11%), usual interstitial pneumonia (16%), and lymphocytic interstitial pneumonitis (15%), are rare. ILD is a significant cause of death in Sjögren's syndrome.[1] We report a case of lung function of usual interstitial pneumonia pattern of interstitial lung disease associated Sjogren's Syndrome (SS-ILD) treated with mycophenolate sodium. Parameters of lung function test are vital capacity (VC), predicted VC, forced vital capacity (FVC), predicted FVC, FEV1, predicted FEV1, FEV1/FVC, and diffusing capacity (DLCO).

Material and methods

A retrospective cohort study was performed using electronic health record and diagnosed as SS- ILD. Patient has been treated with mycophenolate sodium and has been performed lung function test, diffusing capacity test, and high-resolution computed tomography (HRCT) to evaluate progressivity ILD. The following parameters were evaluated at ILD diagnosis: vital capacity (VC), forced VC (FVC), and diffusing capacity for carbon monoxide (DLCO). Lung function was considered abnormal when volumes were ≤79% of the predicted values and when DLCO was ≤75% of the predicted value.

Results

A 35-year-old woman was consulted to immunology and ILD division due to HRCT features revealed ground glass opacity, fibro-infiltrate, infiltrate reticula granular, signet sign in both lung, peri bronchial thickening and tree in bud pattern, suggesting ILD pattern (Figure A). From anamnesis, patient had persistent exertional shortness of breath, cough with white phlegm sputum, multiple peripheral joint pain, fatigue, malaise and dry eye. During examination, we found oxygen saturation 89% room air and bilateral basal late inspiratory crackles on chest auscultation. We did laboratory examination and the results were positive for Antinuclear Antibody, and rheumatoid factor were negative. We diagnosed as ILD-CTD (SS) dd/ SLE. We treatment with mycophenolate sodium 2 x180mg. We consult to ophthalmologist for dry eye. Ophthalmologist performed schirmer's test and the results were OD 0 mm and OS 0 mm. Ophthalmologist diagnosed dry eye ODS ec Sjogren's syndrome. One months later the shortness of breath worsened, oxygen saturation 90% room air, we added mycophenolate sodium dosis to 360mg-0-180mg. In 3rd months therapy, shortness of breath decline, patient didn't need oxygen in home, oxygen saturation 94-96% room air. In 5th months later, patient infected with Covid-19 and self- isolated for 14 days. Patient was still taking mycophenolate sodium during self-isolation. In 6th months therapy mycophenolate sodium dose was titrated up to 2x180 mg. In 9th months therapy, we additionally laboratory examination, and the result were rheumatoid factor positive. We diagnosed patient as ILD mixed CTD dd/ Sjogren's syndrome, SLE and Rheumatoid Arthritis. We consult to rheumatologist. In 10th months therapy, dose up to 2x360mg, and titrated up to 360mg-0-180mg in 15th month, dose up to 2x360mg, and the dose up to 2x720mg followed RA treatment.

Patient had spirometry test and DLCO 1, 6, and 15 months after treatment. Lung function measurements for SS-ILD patients 1 month after treatment were as follows: VC 1200 mL, predicted VC 47%, FVC 1280 mL, predicted FVC 50%, FEV1 1020 mL, predicted FEV1 46%, and FEV1/FVC 79%. Six months after treatment, the measurements were: VC 1370 mL, predicted VC 53%, FVC 1400 mL, predicted FVC 55%, FEV1 1240 mL, predicted FEV1 56% and FEV1/FVC 88%. Fifteen months after treatment, the measurements were: VC 1310 mL, predicted VC 51%, FVC 1140 mL, predicted FVC 45%, FEV1 1000 mL, predicted FEV1 45% and FEV1/FVC 88%. Diffusing capacity test (DLCO) in 1 month, 6 months, and 15 months revealed 26%, 29%, and 34% respectively. Follow up HRCT obtained 6 and 15 months later. HRCT 6 months treatment showed a reduction of ground glass opacity, fibro-infiltrate, infiltrate reticula granular, signet sign in both lung, peri bronchial thickening and tree in bud pattern relative steadily, suggesting ILD pattern improvement (Figure B). HRCT 15 months treatment showed usual interstitial pneumonia bilateral relative steadily (Figure C). After 20 months of therapy, she remains stable with mycophenolate sodium 50 mg 2x720mg.

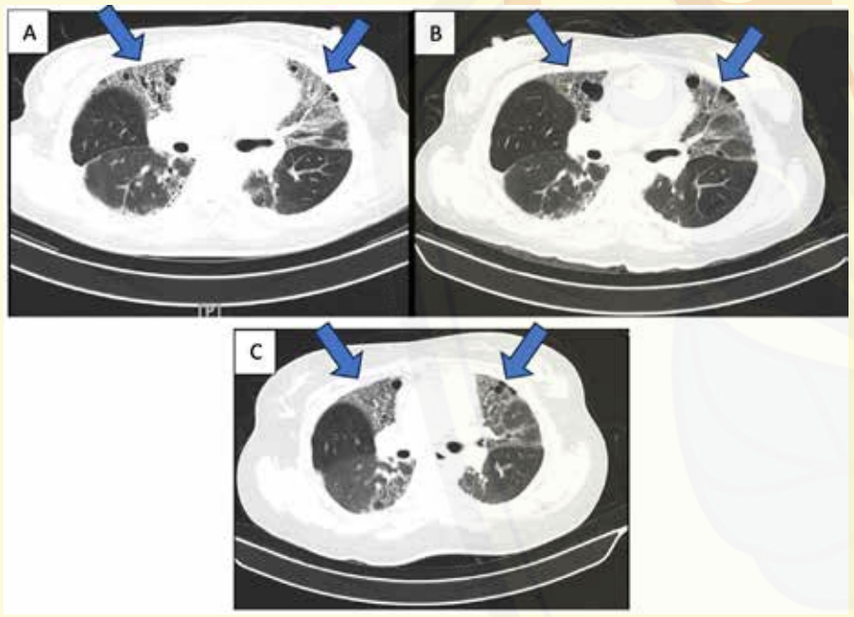

Figure 1. HRCT of the patient **(A)** Axial slice. Note ground glass opacity, fibro-infiltrate, infiltrate reticula granular, signet sign in both lung, peri bronchial thickening and tree in bud pattern, suggesting ILD pattern. **(B)** Axial slice. Note reduction of ground glass opacity, fibro-infiltrate, infiltrate reticula granular, signet sign in both lung, peri bronchial thickening and tree in bud pattern relative steadily, suggesting ILD pattern improvement. **(C)** Axial slice. Note usual interstitial pneumonia bilateral relative steadily **(arrows)**.

Discussion

In this patient, we conclude that patient had secondary Sjogren's syndrome and rheumatoid arthritis (RA). Overall, sSS is a common extra-articular manifestation of RA. Within Mediterranean [5–8] A large cross-sectional study in Spain estimated the prevalence of sSS at 17% in 788 RA patients over a 10 year period. countries, the highest prevalence of sSS in RA is reported in Greece, ranging from 26%–31%.[9] A similar prevalence rate of 17.5% was noted in a prospective study of 587 consecutive RA patients in Italy.[10] In Chile, sSS in RA patients is reported at 29%. other hand, lower rates of sSS in RA have been reported; 4%–7% in Norway, Turkey,[14] and 7% in the UK.[15]

Clinical presentation of SS can vary considerably, ranging from classic sicca symptoms, to mild constitutional symptoms (such as fatigue, malaise, arthralgias), to systemic symptoms (such as neuropathy or vasculitis). Sicca symptoms are nonspecific and may be seen in several medical conditions or as the result of medications or aging, and SS can often present with relatively nonspecific symptoms, thus requiring a high level of suspicion for detection.[16] In this patient, had many and atypical symptoms such as shortness of breath, cough with white phlegm sputum, multiple peripheral joint pain, fatigue, malaise and dry eye.

Up to 59%–85% of patients with pSS, like in this patient, are noted to have an elevated ANA titer.[17] ANA positivity is associated with a higher prevalence of anti-SSA and anti-SSB antibodies, antiphos- pholipid antibodies, RF, and hypergammaglobulinemia. The presence of ANA in pSS is associated with a higher risk of cutaneous vasculitis, articular and renal involvement, and higher utilization of corticosteroids.[17]

RF positivity is fairly common, like in this patient, reported in 36%–74% of patients with pSS.[17] Anti-cyclic citrullinated peptide antibodies have been reported in 3%–10% of patients with pSS. A prospective Italian study of 141 consecutive patients with pSS patients described positive anti- cyclic citrullinated peptide antibodies in 9.9% (14/141) of patients, and their presence was associated with higher rates of synovitis. [18]

The final classification criteria of Sjogren syndrome are based on the weighted sum of 5 items: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm^2, each scoring 3; an abnormal ocular staining score of ≥5 (or van Bijsterveld score of ≥4), a Schirmer's test result of ≤5 mm/5 minutes, and an unstimulated salivary flow rate of ≤0.1 ml/minute, each scoring 1. Individuals with signs and/or symptoms suggestive of SS who have a total score of ≥4 for the above items meet the criteria for primary SS.[19] But, in this patient, there is only Schirmer's test result of OD 0 mm and OS 0 mm. So the scoring is 1.

Patient had spirometry test and DLCO 1, 6, and 15 months after treatment. Lung function measurements for SS-ILD patients 1 month after treatment were as follows: VC 1200 mL, predicted VC 47%, FVC 1280 mL, predicted FVC 50%, FEV1 1020 mL, predicted FEV1 46%, and FEV1/FVC 79%. Six months after treatment, the measurements were: VC 1370 mL, predicted VC 53%, FVC 1400 mL, predicted FVC 55%, FEV1 1240 mL, predicted FEV1 56% and FEV1/FVC 88%. Fifteen months after treatment, the measurements were: VC 1310 mL, predicted VC 51%, FVC 1140 mL, predicted FVC 45%, FEV1 1000 mL, predicted FEV1 45% and FEV1/FVC 88%. Diffusing capacity test (DLCO) in 1 month, 6 months, and 15 months revealed 26%, 29%, and 34% respectively. Follow up HRCT obtained 6 and 15 months later. HRCT 6 months treatment showed a reduction of ground glass opacity, fibro-infiltrate, infiltrate reticula granular, signet sign in both lung, peri bronchial thickening and tree in bud pattern relative steadily, suggesting ILD pattern improvement (Figure B). HRCT 15 months treatment showed usual interstitial pneumonia bilateral relative steadily (Figure C).

Conclusion

A rare usual interstitial pneumonia pattern of SS-ILD with mycophenolate therapy, FVC% slope change tended to increase 1,6% per month after 6 months therapy but decreased 2% per month after 15 months therapy. FEV1% slope change tended to increase 1,6% per month after 6 months therapy but decrease 1,2% per month after 15 months therapy. DLCO% slope change tends to increase steadily 1,9% per month after 6- and 15-months therapy.

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Appendix

Interstitial lung disease

Sjögren's syndrome

Usual Interstitial Pneumonia

Mycophenolate sodium

FREE PAPER

EFFECTIVITY OF TELEMONITORING TOWARDS QUALITY OF LIFE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: As the fifth most frequent cause of morbidity worldwide, Chronic Obstructive Pulmonary Disease or COPD often makes the patients who contracted the disease experience distress in their everyday lives. Several patients developed either or both physical and psychological problems in the period of their therapy. Some examples of these problems include dyspnea, which reduces patient's exercise tolerability, and daily activities in general and worsens overtime if left untreated. Anxiety and depression are also significantly associated with COPD. These exemplars are significantly great argument to suspect a lower quality of life in these patients.[1] Currently, guidelines produced by many medical organizations in the world recommends supportive therapy as the main option in dealing with COPD, such as oxygen therapy, inhaler use, and several mucolytic and antibiotic tablets.[2] However, treatment plans are often burdening for the patients who have severe exacerbations of the disease, especially taking into consideration the fact that 29-47% of patients at least experience one exacerbation annually. This prolonged length of stay and increased both hospitalization cost and risk of death during their care.[3]

As this problem continues, COPD remains as a public health problem in Indonesia with 3,72% of the population having the disease.[4] Nonetheless, government programs are still in the work to reduce exacerbations in patients with COPD. Telemonitoring has become one of the most potential programs available nowadays. Telephone-based monitoring is currently being studied to allow hospital staff or health care providers to oversee disease progression, especially in the context of preventing or responding quickly to signs of exacerbations. Furthermore, conversations with the health care providers might be therapeutic as the case of psychological symptoms may be relieved throughout the process of monitoring. This add up to the goal of telemonitoring itself, by providing greater quality of life for patients.[5] Several studies completed in the past years have shown this achievement throughout various methods, but some remains unsure about the effectiveness of the program.[6,7] Further studies and long-term follow up are in demand to solidify the evidence of telemonitoring programs and quality of life of patients with COPD.

The goal of this study was primarily directed to evaluate several effects on patients' quality of life who received telemonitoring programs, using frequently used questionnaires such as SGRQ, HADS, and EQ-5D QoL Questionnaire.

Materials and Methods

This meta-analysis was based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions. Reporting of results followed the Preferred Items of Systematic Reviews and Meta-Analyses (PRISMA) proposal guidelines. Three independent reviewers identified articles eligible for analyses, extracted data and assessed the risk of bias. Disagreements were resolved through discussion or consultation with a fourth reviewer.[8]

Searching Strategies

The following six electronic databases were searched for articles from inception to 15 March 2023: PubMed,

EMBASE, Scopus, Proquest, Cochrane Library, and Google Scholar. Search terms included combinations of text word terms and medical subject headings (MeSH) or EMTREE terms using all possible combinations using Boolean logical operators (AND, OR, and NOT). The search keywords were 'chronic obstructive pulmonary disease', 'COPD", 'telemonitoring', 'telehealth', 'telemedicine', 'telecommunication', 'remote consultation', 'randomised controlled trial', 'randomized controlled trial', 'RCT', and any matched subject or MeSH terms. To avoid missing potentially applicable articles, comprehensive searches were conducted using the keywords above and similar terms. The identified articles were managed using Google Sheets.

Eligibility Criteria

To determine the eligibility of studies, the participants, intervention, comparison, outcomes, and study design (PICOS) framework was used. The target population (P) was adult patients 18 years and older who were diagnosed with COPD. The intervention (I) was defined as telemonitoring. The comparison (C) was defined as usual COPD care other than a telemonitoring intervention. The outcomes (O) included the quality of life. The study design (S) included randomised controlled trials (RCTs) along with a control group. Only original research articles written in English with full texts were included. No restrictions on the publication time period were imposed.

The major inclusion criteria were: (a) studies on patients with COPD, (b) randomized controlled trials (RCTs) comparing telemonitoring with non-telehealth supported usual care and (c) studies that reported at least one outcome of interest. Non-original articles, abstracts, and pre-clinical studies were excluded. Articles not published in English were also excluded.

Data Extraction

All articles extracted from the six databases were independently reviewed and selected by three reviewers (investigators J.J., K.R., and K.E.U.). After excluding duplicate studies, the reviewers chose articles based on the titles and abstracts, including study designs and objectives, according to predefined selection criteria. Only original research articles with full texts were included. The review results of the three reviewers were compared, and any disagreements were discussed to reach a consensus. When there were any unresolved discrepancies between reviewers at any stage of the study extraction process, a fourth reviewer (A.P.V.) was consulted. Finally, all four reviewers (J.J., K.R., K.E.U.) reviewed the full articles again. The study extraction processes were reviewed and verified by all reviewers again.

Risk of Bias

The risk of bias and methodological study quality were assessed using the Cochrane risk of bias tool, RoB 2.0. Each domain in the evaluation tool was rated as low, high, or of some concern. Three investigators (J.J., K.R., and K.E.U.) independently evaluated the quality of all the included studies and compared their own assessment results. A fourth investigator (A.P.V.) was consulted if there were any discrepancies between the three investigators.

Statistical Analysis

Meta-analysis was conducted by using Review Manager version 5.4.1 software (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020). Statistical heterogeneity was tested by using Cochran's Q test and I2 statistics. A fixed-effects model was applied for all outcomes. The results were expressed Mean Difference (MD) and 95% confidence intervals (CIs) for continuous variables, and as weighted mean differences or standardized mean differences and standard deviations for continuous outcomes. We used a two-tailed test of significance ($p < 0.05$). The p-value for the test of significance of the total overall estimate was presented. Forest plots were visually inspected to reveal heterogeneity among studies. Statistical heterogeneity of treatment effects among the studies was assessed using estimated effect (I2) statistics based on the Cochrane threshold, with cut-off limits of 0%, 25%, 50%, and 75% as insignificant, low, moderate, and high heterogeneity, respectively. If appropriate, subgroup analyses for study follow up also been done. We used the inverse variance for the statical method as suggested by Bender et al.9 We considered that illegible heterogeneity could be discovered from studies.

Results

Study Selection and Characteristics

A total of 1,345 studies were identified through five database searches, with details listed in Table 1. After deduplicating and excluding irrelevant studies, 21 records were checked for eligibility criteria. Finally, 10 studies were included for quantitative analysis (Figure 1). The characteristics of the included studies are listed in table 1.

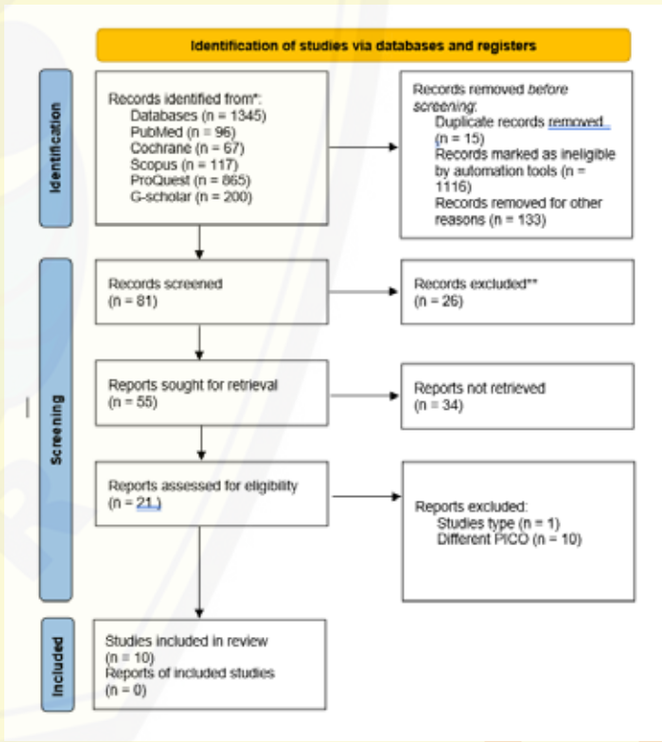

Figure 1. Prisma Flow Diagram.

Table 1. Characteristics of study used

Author, Year	Study Location	Study Interval	Sample Size (n)	Mean Age [Mean(SD)]	Gender (F/M)	Outcome							
						SGRQ		HADS Anxiety		HADS Depression		EQ-5D	
						Telemonitoring	Control	Telemonitoring	Control	Telemonitoring	Control	Telemonitoring	Control
Kopfli, 2023	Denmark	6 months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A
Boer, 2019	Netherlands	12 months	[illegible]	[illegible]	[illegible]	N/A	N/A	N/A	N/A	N/A	N/A	[illegible]	[illegible]
Landeskrankenanstalten-Betriebsgesellschaft, 2018	Austria	12 months	[illegible]	[illegible]	N/A	[illegible]	[illegible]	N/A	N/A	N/A	N/A	N/A	N/A
Farmer, 2017	England	6 and 12 Months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A	N/A	N/A	N/A	N/A
Walker, 2017	Europe	9 months	[illegible]	[illegible]	[illegible]	N/A	N/A	N/A	N/A	N/A	N/A	[illegible]	[illegible]
Chatwin, 2016	England	6 months	[illegible]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[illegible]	[illegible]
Vianello, 2016	Italy	12 months	[illegible]	[illegible]	[illegible]	N/A	N/A	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A
McDowell, 2015	Ireland	6 months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A	N/A	N/A	[illegible]	[illegible]
Jódar-Sánchez, 2013	Spain	4 months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A	N/A	N/A	[illegible]	[illegible]
Pinnock, 2013	Scotland	12 months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A	N/A

M: Male, F: Female, SD: Standard Deviation, T: Telemonitoring, C: Control, N/A: Not Available

A total of 1,677 patients from all studies were involved in this systematic review. Almost all of the included studies were conducted in the Europe continent. Treatments that we analyze are telemonitoring to the patient's quality of life. We use some scoring such as Saint George's Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Scale (HADS) for anxiety and depression, also EuroQol 5 Dimensions (EQ-5D). For SGRQ, there are six studies that we can compare. Other than that, there are four studies that we can assess for HADS and five studies for EQ-5D.

Quality Assessment

Most of the randomized controlled trials included in this study have a low risk of bias based on Cochrane risk of bias 2.0 (Figure 2).

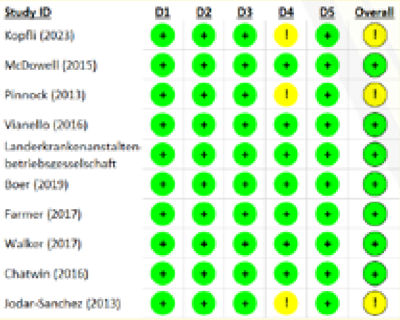

Figure 2. Bias Assessment.

SGRQ

SGRQ was observed in 6 studies.5,10–14 The qualitative analysis found a mean difference of -1.13 [95% CI-4.23, 1.97; p=0.47]. The result also shows that 6 months of intervention is more significant than 12 months of intervention even though the p is above 0.05. Other than that, there is a low heterogeneity in these six studies (Figure 3).

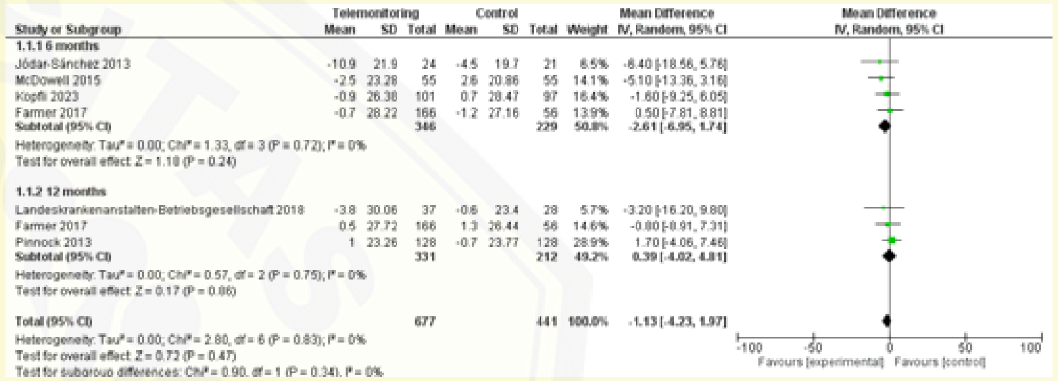

Figure 3. Forest Plot for SGRQ.

HADS

Four studies have been observed to analyze HADS for anxiety and depression.[5,10,14,15] A mean difference of -0.16 [95% CI -0.96, 0.63; p=0.69]. Low heterogeneity is found in this qualitative analysis (Figure 4A). On the other hand, HADS for depression shows a more insignificant effect with a mean difference of 0.04 [95% CI -0.64, 0.72; p=0.69] with also a low heterogeneity (Figure 4B).

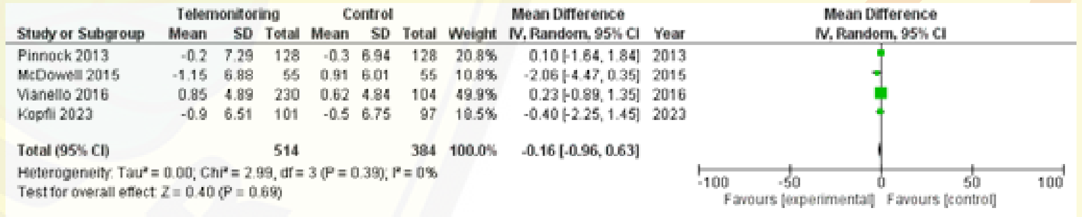

Figure 4A. Forest Plot for HADS Anxiety.

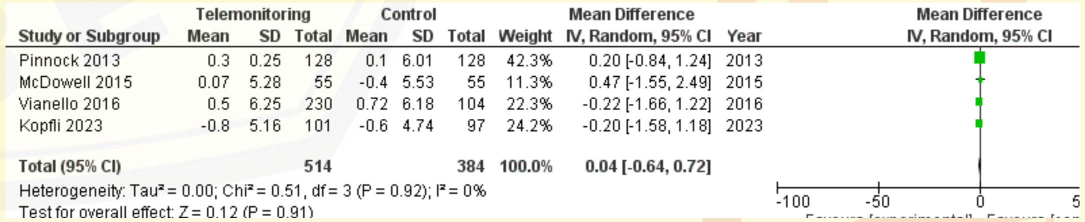

Figure 4B. Forest Plot for HADS Depression.

EQ-5D

EQ-5D is analyzed with five pieces of literature and we found an insignificant result with a mean deviation of 0.01 [95% CI -0.04, 0.06; p=0.63] although there is low heterogeneity in the result (Figure 5).[10,11,16–18]

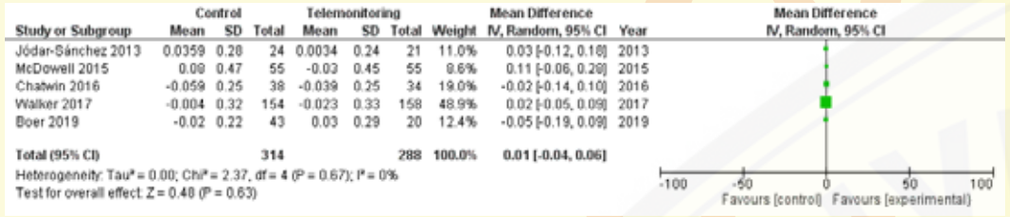

Figure 5. Forest Plot for EQ-5D.

Discussion

Home-Based Telemonitoring in Improving Quality of Life of COPD Patients

COPD patients frequently experience severe physical and psychological distress that leads to a decline in quality of life (QoL). The technological advancement that has been integrated into health systems, such as Telemonitoring, is intended to assist healthcare services from a distance. This uses telecommunication technology to transfer healthcare information between patients and healthcare professionals. Home telemonitoring of symptoms and physiological parameters may enable hospital staff to respond to signs of a COPD exacerbation which may necessitate treatment and in some cases hospitalization. Therefore, this can hopefully improve the provision of healthcare services resulting in improving the patient's quality of life (QoL). Related to the patient's QoL, Rixon L, et al indicated that in comparison to the control group, individuals who got telemonitoring exhibited greater emotional functioning which increased with time. Moreover, Sul AR, et al., found that telemonitoring reduced exacerbation rates and length of hospital stay.[5,19]

The Reported Quality of Life Score for COPD Patient

Studies reporting the intervention of home-based telemonitoring vs control for improving COPD patient's quality of life were evaluated in SGRQ Score and HADS.

SGRQ is a validated and widely used scoring system for measuring quality of life among patients, especially COPD patients. It constitutes a variety of aspects of disease's overall impact on general health, daily life, and well-being. This questionnaire consists of 50 items with 3 overall domains with scores ranging from 0 to 100. Higher scores indicate more limitations in daily living. We observed significant results better than previous meta-analyses which incorporate small-scale population in the study. Thus, more reliable results can be made throughout this study.[20,21]

The HADS is a 14-item instrument with seven items for measuring anxiety and depression and seven items for measuring depression. Anxiety and depression are evaluated independently, with each item having four choices with scores ranging from 0 to 3, for a total score between 0 and 21. Cut-off values are 0–7 for absence of cases, 8–10 for cases that are borderline or mild, and 11 for cases that are moderate or severe.5 Our meta-analysis shows that home-based telemonitoring is able to improve the quality of life of the patients with COPD. This analysis is statistically enough due to significance and low subgroup heterogeneity.

Furthermore, another scale used to assess the quality of life was EQ5D. EQ5D is a simple questionnaire which has two-page consisting of five descriptive questions. Each question has one of three-level answers and visual analog scale (VAS). The mentioned 5 dimensions consist of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients can answer each question with one of three levels of functioning, namely no problems, some problems, or unable to/extreme problems. In our meta-analysis, five studies were assessed and we found that telemonitoring improves COPD patients' quality of life insignificantly. The result is probably due to the small number of studies provided in this meta-analysis. Other than that, different modalities in each study are most likely the reason for different results that could affect the significance.[22]

The reason HADS and EQ-5D were not significant may be due to the little number of studies that were provided in this analysis. Other than that, different modalities in each study are most likely the reason for different results that could affect each result .

Cost Effective of Home-Based Telemonitoring Interventions for COPD

Since home telemonitoring enables healthcare clinicians to evaluate patients' clinical data more regularly, cost and time efficiently, this may lead to improved clinical outcomes, greater patient self-management and less costly interventions, especially in a long-term perspective. However, things regarding cost effectiveness are not yet obvious and the outcome was varied. Study by Cruz J, et al (2014) found that there is a trend to reduce healthcare costs in the telemonitoring group. This, was also supported by a study by De San Miguel et al that reported a total cost savings of 112,439 US dollars (USD) in the home telemonitoring group as well as the study by Koff et al and Pare et al. which found that home telemonitoring reduced healthcare-related costs when compared with usual care, although the difference was not statistically significant.6 Besides, according to a study by Van der Burg, et al, the healthcare costs were significantly lower, about 54% lower in COPD patients after the telemonitoring intervention's intervention began.[23] However, it was different from the studies by McDowell JE, et al., Pedone C, et al., dan Hofer F, et al., that observed significantly higher costs due to the use of telemonitoring in COPD patients over one to two year follow up.[11,24] Even though there was an increase in patients with telemonitoring survival rate, study by Hofer F, et al. found an increase in the survival rate of patients with telemonitoring. Therefore, more detailed research is needed to fully understand the correlations.[19]

Strength and Limitation

The strength is that we have a higher population in assessing the quality of life so it can represent the general population. Other than that, new studies also complied to give the best result. However, different modalities and types of telemonitoring of each study were different from each other. These studies also haven't compiled a large-scale population so the definitive results were not found properly.

Conclusion

Telemonitoring benefits patients with COPD. Lower exacerbation and length of stay in the hospital intervened by telemonitoring can be very beneficial. Some studies also suggest that telemonitoring has a better cost-effectiveness than usual care. Through this meta-analysis, we found that there is an improvement of telemonitoring on the quality of life, especially as seen from the SGRQ score. However, the HADS and EQ-5D scores were insignificant. This may happen due to the small size of the population.

We suggested a larger scale of research to give a better understanding of the effect of telemonitoring on depression and anxiety in patients with COPD.

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RESPONSES AND SIDE EFFECTS POST RADIOTHERAPY FOR MANAGEMENT OF SUPERIOR VENA CAVA SYNDROME EMERGENCY OF THORACIC MALIGNANCIES IN PERSAHABATAN HOSPITAL

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ABSTRACT

Background: An oncological emergency from superior vena cava syndrome (SVCS) requires immediate radiotherapy to reduce the emergency symptoms that arise. There is litte data available of responses and side effects in treating SVCS at Persahabatan Hospital.

Material and Methods : This research is a descriptive retrospective. The study were on 62 patients with thoracic malignancies who experience SVCS emergency and undergo immediate radiotherapy at Persahabatan Hospital within 2021-2022, 6 subjects were excluded due to incomplete data and only 56 subjects were included and analyzed. Evaluation of clinical response, hematological and non hematological si de effects post radiotherapy were carried out.

Result : Based on gender there were 49 men (87.5%) and 7 women (12.5%). Subject characteristics on age, aged 40 years and over 29 subjects (51.8%) and less than 40 years were 27 subjects (48.2%). Symptoms of SVCS founded were dyspnea in 55 subjects (98.2%), facial edema in 16 subjects (28.6%), arm edema in 17 subjects (30.4%), venectation in 5 subjects (8.9%), cough in 30 subjects (53.6%) and pain in 36 subjects (64.3%). Type of malignancy were lung cancer in 28 subjects (50%), mediastinal tumour in 27 subjects (48.2%) and metastatic cancers in 1 subject (1.8%). Dose of radiotherapy were 1000 cGy in 49 subjects (87.5%) and more than 1000 cGy in 7 subjects (12.5%). Clinical responses after radiotherapy were improved in 45 subjects (80.4%) and no changes in 11 subjects (19.6%). Hematological side effect after radiotherapy were anemia in 36 subjects (64.3%) and normal haemoglobin level in 20 subjects (35.7%), leukopenia in 4 subjects (7.1%) and normal leucocyte level in 52 subjects (92.9%), trombocytopenia in 6 subjects (10.7%) and normal platelet level in 50 subjects (89.3%). Non hematological side effects after radiotherapy were cough in 15 subjects (26.8%), dyspnea in 22 subjects (39.3%) and pain swallowing in 2 subjects (3.6%).

Conclusion : Radiotherapy are efective to obtain improvement responses in management of SVCS emergency with minimum side effects.

Key words : *SVCS, radiotherapy, responses*

Background

The incidence malignancy of the thoracic cavity is increasing from year to year. Thoracic cavity malignancies include lung cancer, mediastinal tumors, lung metastases, chest wall tumors, mesothelioma. The National Cancer Institute estimates that 14.5 million people in the United States suffer from cancer, this number is expected to rise to 19 million in 2024.[1] Data in the United States estimates that new cases of lung and bronchial cancer in men are around 119,000 cases or 12% which is the second rank after prostate cancer. In women there are around 116,660 cases or 13% which also the second rank after breast cancer. Superior vena cava syndrome (SVCS) occurs in approximately 15,000 people in the United States each year. [2,3] As the incidence of malignancy of the thoracic cavity increases, the risk of emergency events in the disease also increases. The oncological emergencies found included SVCS, central airway obstruction, massive pleural effusion, myasthenia gravis and massive blood coughing. The incidence of SVCS is quite high, around 75% in patients with lung adenocarcinoma and 25% in squamous cell carcinoma at Dr. Soetomo General Hospital in 2016-2017.[4] Emergency oncology conditions such as SVCS requires immediate radiotherapy to reduce pressure on the superior vena cava so that improvement occured on this emergency condition.[5] A previous study at the same place by Azmi F on 140 inpatients from March 1st, 2009 to February 29th, 2010, obtained an efficacy of 69.7% with a decline in subjective symptoms of 70% and an improvement in clinical objective signs of 60%.[6] With this study we hope that this will become an additional reference regarding the efficacy of radiotherapy in managing SVCS emergencies in Indonesia.

Materials and Methods

This study is a retrospective cohort study to determine the efficacy of radiotherapy in treating SVCS in patients with thoracic malignancy. This research was conducted at Persahabatan Hospital in Jakarta, period 2021-2022. Population of the study was all patients with thoracic cavity malignancy with SVCS undergoing radiotherapy at Persahabatan Hospital in Jakarta. Samples were from medical records that met the inclusion and exclusion criteria. Total sampling is the sampling technique used in this study. The data will be presented in a descriptive table and analyzed using the SPSS program.

Result

This study is a retrospective descriptive study in 62 people with thoracic malignancy who experience an emergency SVCS and undergo immediate radiotherapy during 2021-2022. We did analysis of clinical response's efficacy, post-radiotherapy hematological and non- hematological side effects was carried out. A total of 56 people met the research criteria and 6 people did not meet the research criteria. So that the total subjects of this study were 56 people.

General and Clinical Characteristics

This study succeeded in examining 56 people, most of the subjects were 49 men (87.5%) and 7 women (12.5%), as shown in table 1. Most of the subjects age ≥40 years were 29 people (51.8%) and age less than 40 years were 27 people (48.2%). Subjects with lung cancer malignancy were 28 people (50%), mediastinal tumors were 27 people (48.2%) and lung metastases tumors was 1 person (1.8%). Subjects with doses received of radiation 1000 cGy were 49 people (87.5%) and doses >1000 cGy were 7 people (12.5%). The clinical characteristics of the study in distribution of SVCS symptoms as shown in Figure 1., including dyspnea in 55 people (98.2%), facial edema in 16 people (28.6%), arm edema in 17 people (30.4%), venectation of 5 people (8.9%), coughed 30 people (53.6%) and chest pain were 36 people (64.3%).

Table 1. General characteristics

Characteristic	N	%
Gender		
Men	49	87,5
Women	7	12,5
Age		
< 40 years	27	48,2
≥ 40 years	29	51,8
Type of Malignancy		
Lung cancer	28	50
Mediastinal tumour	27	48,2
Metastatic cancer	1	1,8
Dose of radiotherapy		
1000 cGy	49	87,5
>1000 cGy	7	12,5

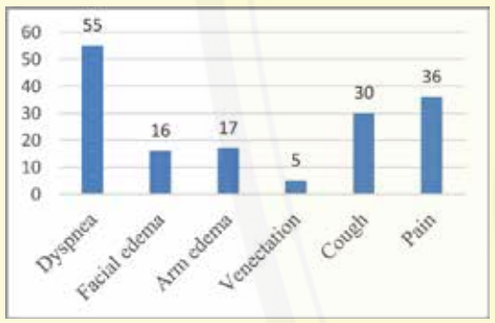

Figure 1. Distribution of SVCS symptoms

Post Radiotherapy Clinical Response

Post-radiotherapy clinical response were experienced improvement in 45 people (80.4%) and 11 people (19.6%) settled, as shown in table 2.

Post-Radiotherapy Hematological and Non-Hematological Side Effects

Post-Radiotherapy hematological side effects were found anemia in 36 people (64.3%) and did not have anemia in 20 people (35.7%), had leukopenia in 4 people (7.1%) and did not have leukopenia in 52 people (92.9%) had thrombocytopenia in 6 people (10.7%) and 50 people (89.3%) did not experience thrombocytopenia. Post-radiotherapy non-hematological side effects included coughing in 15 people (26.8%), dyspnea in 22 people (39.3%) and swallowing pain in 2 people (3.6%), as shown in table 3.

Table 2. Clinical response

Characteristic	N	%
Lung cancer		
Improvement	21	75
Settled	7	25
Mediastinal tumour		
Improvement	23	85,2
Settled	4	14,8
Metastatic cancer		
Improvement	1	100
Settled	0	0

Table 3. Post-Radiotherapy Hematological and Non-Hematological Side Effects

Characteristic	Lung cancer	Mediastinal tumour	Metastatic cancer	Total
Hematological Side Effects				
Anemia	17 (30,3%)	18 (32,1%)	1 (1,7%)	36 (64,3%)
Leukopenia	1 (1,7%)	3 (5,3%)	0	4 (7,1%)
Thrombocytopenia	3 (5,3%)	3 (5,3%)	0	6 (10,7%)
Non Hematological Side Effects				
Cough	5 (8,9%)	9 (16,1%)	1 (1,7%)	15 (26,8%)
Dispnea	10 (17,8%)	12 (21,4%)	1 (1,7%)	22 (39,3%)
Swallowing pain	0	1 (1,7%)	0	2 (3,6%)

Discussion

In this study, the number of subjects who met the inclusion criteria and participated in this study were 56 people, in the 2021-2022 period. Our study found that radiotherapy was effective in producing an improved response of 80.4% in the management of SVCS emergency with 64.3% anemia as a side effect. This study supports that radiotherapy is effective in the management SVCS emergencies.

Post radiotherapy clinical response

This study found that post radiotherapy clinical response had improved in 45 people (80.4%) and settled in 11 people (19.6%). The results of this study are slightly different from previous studies in the same place

by Azmi F in 140 hospitalized patients from March 1st, 2009 to February 29th, 2010, obtained an efficacy of 69.7% with a reduction in subjective symptoms of 70% and clinical objective signs improvement of 60 %.6 Research by Mose S, et al obtained an improvement response of 85.7% in 35 patients who underwent radiotherapy.[7] Retrospective analysis, radiotherapy can be given immediately without considering the histological diagnosis can also be given in conditions that do not allow surgery. Reduction of post-radiation symptoms can be felt within 72 hours and will usually be maximum in 2 weeks, with an average of 5-9 days.[8] Complete response of improvement of SVCS obstruction symptoms, were SCLC in 78% of patients and 63% of NSCLC patients within 2 weeks and a rapid improvement response within 72 hours.[9]

Post-Radiotherapy Hematology Side Effects

Radiotherapy can cause a decrease in the process of forming blood cells, although it is rare. Blood cells play a role in fighting infection and preventing bleeding. If blood cell levels are low, radiation needs to be stopped for several weeks until blood cell levels are normal again. The side effects that arise are similar to the side effects of chemotherapy.[10] In this study, hematological side effects were found anemia in 36 people (64.3%), leukopenia in 4 people (7.1%) and thrombocytopenia in 6 people (10.7%). The results of this study showed a lower incidence of anemia compared to research by Sun M, et al in 48 hospitalized patients with SVCS during 2015 to 2020 were anemia in 80% in the group who received radiotherapy alone.[11]

Post-Radiotherapy Non Haematological Side Effects

Non-hematological side effects from radiotherapy can include fatigue, skin changes, painful swallowing, coughing, dyspnea. In this study, non-hematological side effects were found coughing in 15 people (26.8%), shortness of breath in 22 people (39.3%) and swallowing pain in 2 people (3.6%). The results of this study are similar to the study by Sha S, et al in 126 NSCLC patients with SVCS during 2018 to 2020, found that 35.71% of patients experienced coughing and dyspnea.[12] Research by Sun M, et al showed lower results in the incidence of dysphagia and sore throat by 10% in 48 inpatients with SVCS during 2015 to 2020 in the group that received radiotherapy alone.[11] Coughing and shortness of breath are the effects of radiotherapy which causes an inflammatory reaction in the lungs that can occur up to 3 months after radiation.

Conclusion

Radiotherapy is effective in producing an improved response in the management of SVCS emergencies in thoracic malignancies by 80.4%. Haematological side effects that occured was anemia in 64.3% and non-hematological was dyspneu in 39.3%.

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RISK FACTOR ANALYSIS OF MULTIDRUG-RESISTANT ORGANISM BACTERIA IN COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRACT

BACKGROUND

Pneumonia is a global health concern. Community acquired pneumonia (CAP) is associated with significant morbidity and mortality. Pneumonia is the leading infectious disease causing mortality in the United States, with an estimated 5-6 million cases of CAP, 1.1 million patients admitted to hospital, and 45,000 patients died annually. In Asia, CAP resulted from bacterial infections is the primary cause of death and frequently results in sepsis. Community- acquired pneumonia is estimated to affect 0.2-1.1% of adult patients, with a mortality rate of 2-14% in developing nations and 7.3% in Asia. In Indonesia, 4.5% of people have been diagnosed with pneumonia, and the country has a crude fatality rate (CFR) of 7.6%.[1-4]

Multidrug-resistant organism (MDRO) is defined as pathogens which are resistant to two or more classes of antimicrobial agents. Pneumonia therapy for MDRO infections is difficult. Resistance to antibiotics is a significant determinant of clinical nonresponse to treatment and rapid progression to sepsis and septic shock. Patients with sepsis and MDRO infections have an increased risk of in-hospital mortality. Gram-negative infections frequently exhibit drug resistance. In CAP, Gram-negative bacterial infections frequently result in respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, and septic shock. Multidrug-resistant organism bacteria require antibiotics that differ from the initial empiric antibiotics recommended by guidelines for CAP. The subsequent empiric antibiotics administered for MDRO bacteria are antipseudomonal and anti-MRSA. It is essential to identify the proportion of MDRO as the cause of CAP. This study analysed MDRO as the cause of CAP and its associated risk factors among patients treated in Dr. Moewardi Hospital.[2,5]

MATERIAL AND METHOD

We conducted a retrospective analytic observational cohort study using medical record data of patients with community-acquired bacterial pneumonia treated in Dr. Moewardi hospital, Surakarta from January to December 2022. The sample collection used total sampling technique, with the inclusion criteria of age >18 years old, hospitalized with the diagnosis of CAP, and having sputum culture findings as well as with antibiotic resistance. We excluded patients whose medical records were incomplete.

Pneumonia was defined as the presence of pulmonary opacity on the chest x-ray during hospitalization associated with more than one of the following signs and symptoms: new or worsening cough with or without sputum production; fever (37.8 C) or hypothermia (35.6 C); or an abnormal number of white blood cells (leucopenia or leukocytosis). Community-acquired pneumonia defined as an acute infection of the pulmonary parenchyma associated with at least some acute infection symptoms, accompanied by the presence of an acute opacity on a chest radiograph or auscultatory findings consistent with pneumonia in a subject who has not been hospitalized or residing in a long-term care facility for 14 days prior to the onset of symptoms.[4] MDRO pathogens are pathogens that are resistant to two or more classes of antimicrobial agents. The MDRO Criteria were based on the Republic of Indonesia's Ministry of Health definition.[6]

Frequency distribution tables were used to illustrate data features. On categorical variables, the Chi-square test was used to analyze differences in demographic and clinical characteristics, while numerical data meeting the normality requirements of unpaired group were subjected to the independent t test and numerical data that did not meet the normality requirements of unpaired group were subjected to the Mann whitney test. The Shapiro Wilk test was used to determine normality, and the difference was determined as significant if the test generated $p<0.05$. The MDRO risk factors with a $p<0.05$ in bivariate analysis were subjected to multivariate analysis with logistic regression.

RESULT

This study involved 446 subjects diagnosed with CAP. Based on the results of bacterial culture and antibiotic resistance testing, they were classified into 2 groups, namely, the MDRO group as many as 190 subjects (42.6%) and non-MDRO as many as 256 (57.4%). Klebsiella pneumonia was the most common cause of MDRO (18,4%) followed by Pseudomonas aeruginosa (12.6%), Escherichia coli (11.6%), Acinetobacter baumannii (8.9%), Enterobacter cloacae (8.9%), Staphylococcus haemolyticus (8.4%), Streptococcus mitis (7.4%), Staphylococcus aureus (5.3%), and other MDRO bacteria (18.4%). (Figure 1)

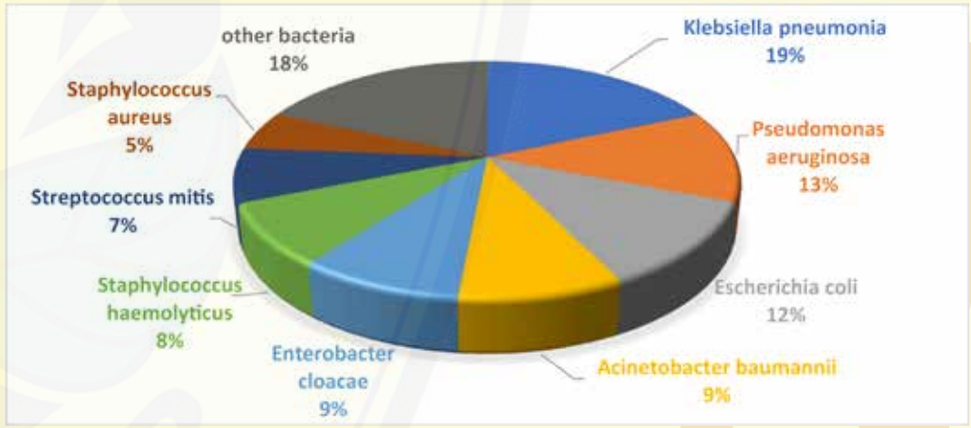

Figure 1. MDRO bacteria that are the etiology of community acquired pneumonia (in percentage).

We analysed the patterns of antibiotic resistance in 190 MDRO causative bacteria of CAP. The resistance level of most antibiotics was greater than its sensitivity of MDRO bacteria except for Tigecyline, Amikacin, Meropenem, Cefepime, Piperacilin/ Tazobactam, Gentamicin, Ertapenem, Trimethoprim/ Sulfamethoxazole, Linezolid, Vancomycin, and Chloramphenicol. (Figure 2).

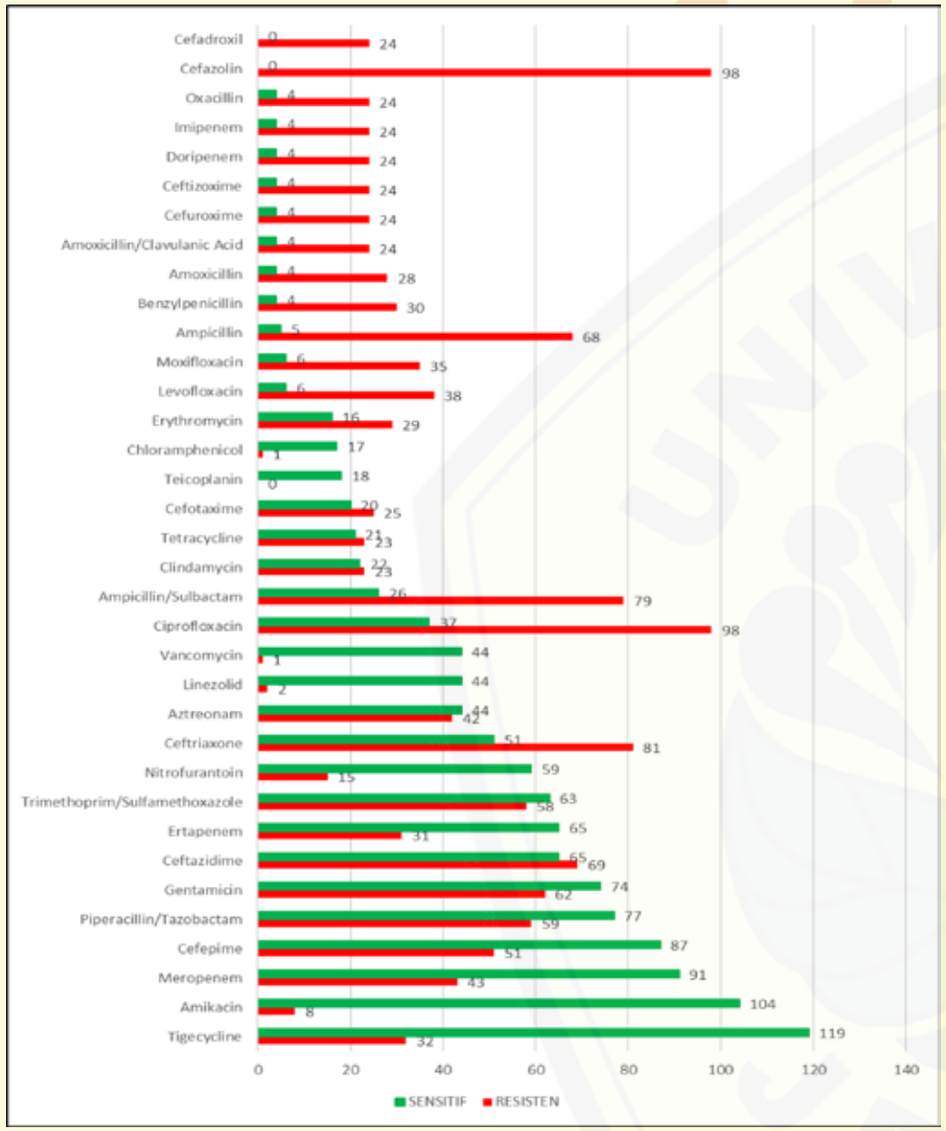

Figure 2. Antibiotic Resistance Patterns in MDRO bacteria

There were no differences in age, sex, length of treatment, type of infection, empirical antibiotics given, clinical symptoms, vital signs, routine blood results, blood gas analysis results of the subjects in both MDRO and non-MDRO groups. The differences between MDRO and non- MDRO groups were found in the type of intensive and non-intensive care (p=0.011), PSI score (p=0.016), history of antibiotic use in the previous 3 months (p=0.000), and smoking status (p=0.002). Clinical improvement on the third day of treatment was significantly different between the two groups (p=0.005). Regarding the outcomes, the two groups did not differ significantly (p=0.124). (Table 1)

Table 1. The Characteristics of the study subjects

Characteristic	Group		p-value
	MDRO	Non MDRO	
N	190 (42.6%)	256 (57.4%)	
Age (Mean±SD)	56.63 ± 15.95	55.16 ± 14.03	0.206
Age			0.008*
≥ 65 years	62 (13.9%)	55 (12.3%)	
< 65 years	128 (28.7%)	201 (45.1%)	
Sex			0.947
Male	126 (28.3%)	169 (37.9%)	
Female	64 (14.3%)	87 (19.5%)	
Type of care			0.011*
Intensive care unit	84 (18.8%)	83 (18.6%)	
Non-intensive care unit	106 (23.8%)	173 (38.8%)	
Length of stay (LoS)	10.51 ± 6.36	10.03 ± 6.10	0.288
Type of infection			0.328
Dual infection	38 (8.5%)	42 (9.4%)	
Single infection	152 (34.1%)	214 (48.0%)	
PSI score	89.94 ± 24.39	86.58 ± 22.06	0.016*
Empirical antibiotics			0.121
Combination antibiotics	25 (5.6%)	22 (4.9%)	
Single antibiotic	165 (37.0%)	234 (52.5%)	
History of antibiotic use			0.000*
No	131 (29.4%)	214 (48.0%)	
Yes	59 (13.2%)	42 (9.4%)	
Symptoms			
Shortness of breath			0.870
Yes	157 (35.2%)	210 (47.1%)	
No	(33 (7.4%)	(46 (10.3%)	
Characteristic	Group		p-value
	MDRO	Non MDRO	
Cough			0.992
Yes	150 (33.6%)	202 (45.3%)	
No	(40 (9.4%)	54 (12.1%)	
Chest pain			0.875
Yes	42 (9.4%)	55 (12.3%)	
No	148 (33.2%)	201 (45.1%)	
Fever			0.143
Yes	28 (6.3%)	26 (5.8%)	
No	162 (36.3%)	230 (51.6%)	
Vital Signs			
GCS	13,74 ± 3,11	14,26 ± 2,36	0.150
Systole	126,73 ± 28,00	124,86 ± 24,92	0.308
Diastole	77.56 ± 14.12	78.70 ± 14.34	0.051
Respiration	23,64 ± 4,05	24,11 ± 8,62	0.266
Pulse	97.55 ± 18.07	98.81 ± 19.29	0.678
Temperature	36,50 ± 0,71	36,52 ± 0,56	0.573
Saturation	97.15 ± 3.97	97.09 ± 3.76	0.902
Routine blood			
Hb	12.13 ± 2.38	11.85 ± 2.53	0.536
Leukocytes	17,01 ± 10.91	16,89 ± 9,61	0.151
Platelets	328.39 ± 164.25	327.63 ± 153.16	0.819
Erythrocytes	4,16 ± 0,88	4,16 ± 0,89	0,680
Blood gas analysis			
pH	7.44 ± 0.12	7.41 ± 0.29	0.312
pCO2	43,47 ± 18,40	42,92 ± 17.76	0.701
pO2	107.18 ± 58.42	93.85 ± 51.39	0.050
BE	4,97 ± 7,91	4,63 ± 8,67	0.378
HCO3	29.54 ± 7.58	32.35 ± 24.71	0.863
Comorbidities			
Diabetes	25	18	0.030*
Cardiovascular Disease	21	31	0.731
Liver Disease	4	4	0.728
Neoplasms	92	136	0.326
Chronic lung disease	49	39	0.006*
Chronic kidney disease	2	1	0.578
Characteristic	Group		p-value
	MDRO	Non MDRO	
Neurologic disease	24	22	0.166
Smoking status			0.002*
Smoker/passive smoker	97 (21.7%)	94 (21.1%)	
Non/ex-smoker	93 (20.9%)	162 (26.3%)	
DPH-3 clinical improvement			0,005*
Improvement	111 (24.9%)	182 (40.8%)	
No improvement	79 (17.7%)	74 (16.6%)	
Outcome			0.124
Survive	138 (30.9%)	202 (45.3%)	
Not-survive	52 (11.7%)	54 (12.1%)	

Note : Percentages represents categorical data on a nominal scale. The descriptive statistic data were presented in mean and standard deviation. Chi square test or Fisher exact test was applied for categorical data from unpaired groups. For the unpaired groups, the independent t test was applied for numerical data fulfilling the normality criteria and those which did not meet the normality requirements were analysed with Mann-Whitney test. Shapiro-Wilk test was used to test the normality, and the difference was deemed statistically significant if p<0.05.

We assessed patients' comorbidities obtaining significant differences between MDRO and non-MDRO groups in diabetes (p=0.030) and chronic lung disease (p=0.006). Meanwhile other comorbidities such as cardiovascular disease (p=0.731), liver disease (p=0.728), neoplasm (p=0.326), chronic kidney disease (p=0.578), and neurological disease (0.166) were comparable. (Table 1).

Table 2 presents multivariate analysis for MDRO bacteria risk factors. Multivariate analysis using logistic regression test obtained age ≥ 65 years (p=0.003, OR=1.946, 95% CI 1.252-3.025), history of antibiotic use within 3 months (p=0.005.OR=1.976, 95% CI 1.225-3.188), diabetes mellitus (p=0. 031, OR=2. 070, 95% CI 1.070-4.005), chronic lung disease (p=0.044, OR=1.673, 95% CI 1.014-2.761), and smoking (p=0.017, OR=1.622, 95% CI 1.092-2.411) were risk factors for MDRO bacterial infection in CAP patients. (Table 3)

Table 3. Multivariate analysis of risk factors for MDRO bacteria as the cause of CAP

Variables	Bivariat	Multivariat			
	p-value	p-value	OR	95% CI	
				Lower	Upper
Age > 65 years	0.008	0.003*	1.946	1.252	3.025
History of antibiotic use in the previous 3 months	0.000	0.005*	1.976	1.225	3.188
Diabetes mellitus	0.030	0.031*	2.070	1.070	4.005
Chronic lung disease	0.006	0.044*	1.673	1.014	2.761
Smoker	0.002	0.017*	1.622	1.092	2.411

Note: logistic regression test. Significant at p < 0.05.

DISCUSSION

Millions of people around the world are affected by pneumonia, which poses a substantial threat to public health. As a potential cause of pneumonia, the presence of MDRO has become an increasing source of concern. Infections caused by MDRO bacteria such as methicillin- resistant Staphylococcus aureus (MRSA) and Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBL) are notoriously difficult to treat.

This study found that 42.6% of patients had MDRO-caused CAP. This figure is significantly greater than those found by Prina E et al., 2015 and Capsoni N et al., 2019, which indicated a prevalence of MDRO infections in CAP were 6% and 17%, respectively. Dr. Moewardi Hospital is a tertiary referral hospital which receive many patients suffering from chronic conditions such as neoplasms, chronic lung disease, heart disease, and chronic kidney disease. A significant number of these individuals require several admissions to the hospital, thus the incidence of MDRO infection is high.[7,8]

Klebsiella pneumonia and Pseudomonas aeruginosa are the most common bacteria detected in this study (18.4% and 12.6%, respectively). The Gram-negative bacteria known as Klebsiella pneumonia is responsible for severe cases of pneumonia in people whose immune systems are compromised. In the last two decades, there has been a rise in the prevalence of antibiotic resistance among Klebsiella pneumonia isolates all across the world. There have been reports of MDR crises as well as strains of hypervirulent Klebsiella pneumonia in immunocompromised individuals as well as healthy people.9 The primary mechanisms of antimicrobial resistance in Klebsiella pneumonia are the expression of extended spectrum β- lactamases (ESBLs), which confer resistance against penicillins, cephalosprins, and monobactams, and the expression of carbapenemases, which are resistant to all β-lactams, including carbapenems. Hypervirulent Klebsiella pneumonia strains generate a hypercapsule, also known as a hypermucoviscous membrane. The capsule, a polysaccharide matrix coating the cell, is essential for the virulence of K. pneumoniae and is arguably its most extensively studied virulence factor. Although hypervirulent Klebsiella pneumonia strains are typically less resistant to antimicrobials than non-hypervirulent Klebsiella pneumonia strains, there have been recent reports of hypervirulent Klebsiella pneumonia strains which are more resistant.[9,10]

Pseudomonas aeruginosa is a Gram-negative, non-fermentative, opportunistic bacterium that inhabits soil and surfaces in aqueous environments. It is particularly difficult to treat due to its high innate antibiotic resistance, metabolic versatility, and adaptability. Multiple studies have demonstrated that the morphological characteristics (phenotype) of Pseudomonas aeruginosa isolates from chronic infections, such as cystic fibrosis, and acute infections, such as pneumonia, are varied. Mutations in the mucA gene on the chromosome can convert a non-mucous phenotype to a mucous phenotype. Pseudomonas aeruginosa's adaptation, which involves intricate physiological changes, confers a selective advantage because it is better in adapting to various habitats.[11,12]

Patients' severity of illness, functional disability, advanced dementia, dialysis, diabetes mellitus, renal failure, structural lung disease, and chronic obstructive pulmonary disease (COPD), liver failure or other organ failure and surgical procedures, indwelling devices (urinary catheters and/or feeding tubes), fecal incontinence, previous antibiotic exposure, and recent hospitalization have been shown to predispose patients to MDROs infection in previous study.[13] In this study we found age ≥ 65 years, history of antibiotic use in the last 3 months, diabetes mellitus, chronic lung disease, and smoking as risk factors for MDRO bacterial infection in CAP patients.

This study revealed no statistically significant relationship between MDRO bacteria and hospital mortality. This finding differs from that of Capsoni N et al., 2019, which reported that MDRO infection is one of the independent risk factors associated with hospital mortality in sepsis patients. Given that we did not find any association between antibiotic resistance and hospital mortality, it is possible that other variables besides antibiotic resistance are responsible for hospital mortality. Possibly the existence of sepsis, the severity of sepsis, or the severity of comorbid conditions all play a role in the hospital mortality rate measured in this study.[8]

CONCLUSION

The incidence of CAP due to MDRO bacteria in Dr. Moewardi hospital is relatively high. Klebsiella pneumonia is the MDRO bacterium responsible for the majority of cases of CAP. Age over 65 years old, a history of antibiotic usage in the past three months, diabetes mellitus, chronic lung diseases, and smoking are all factors contributing to increased risk of MDRO bacteria.

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SURVIVAL RATE ANALYSIS OF LUNG ADENOCARCINOMA PATIENTS RECEIVING EGFR-TKI TREATMENT WITH CARBOPLATIN AND PACLITACLE CHEMOTHERAPY IN THE COVID-19 PANDEMIC AT Dr.Hi. ABDUL MOELOEK REGIONAL PUBLIC HOSPITAL, BANDAR LAMPUNG

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ABSTRACT

Background: The benchmark for the success of cancer treatment is the survival rate. Although the hope for survival is increasing, there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third generation EGFR-TKI target therapy (osimertinib).

Method : Analytic descriptive with retrospective cohort design processed with SPSS 25 with log rank test and shown with Kaplan Meier product limit curve. Data was taken at Dr.Hi.Abdul Moeloek Hospital from January 2020 to December 2022 during the Covid 19 pandemic.

Results : Group of Lung adenocarcinoma treated by EGFR-TKI 39 subjects. The lung adenocarcinoma group was treated with paclitaxel-carboplatin 53 subjects.The median survival time of the group treated with EGFR-TKI was 7 (95% CI: 3.805-10.195) months, while the group receiving paclitaxel carboplatin was 5 months (95% CI: 3.788- while the overall median survival was 6 months (95% CI: 4.836- 7.164) there is no significant difference with the p value: 0.209.

Conclusion: The median survival rate of two groups at 6 months was not significantly different Keyword: Adenocarsinoma, survival rate, EGFR-TKI, carboplatin-paclitacle, covid 19

INTRODUCTION

Regional General Hospital Dr. Hi.Abdul Moeloek (RSUDAM) is a Type A Referral and Education Hospital in Lampung Province. Data on lung cancer cases at RSUDAM from Fransiska's research results in 2018-2021 found 244 cases with the number of cases: women around 3:1. Based on the age category, the most cases of lung cancer were between 35-65 years old, 173 people (70.9%), and based on the stage of lung cancer, most cases of lung cancer came in stage IV B with a total of 92 people (37.7%), stage IV A 91 people (37.3%), stage III B 38 (15.6%) and stage III A as many as 23 people (9.4%).[1(2)]

Treatment of lung cancer with multimodality therapy. The choice of therapy is based on histological/ cytological type, stage, appearance of the patient, availability of drugs in the hospital and the economic capacity of the patient. Surgery and radiotherapy are local treatments while chemotherapy and targeted therapy are systemic treatments. The management of lung cancer non-small cell carcinoma subtype adenocarcinoma (non squamous) which has mutations in the epidermal growth factor receptor (EGFR) in exons 19 and 21 can be given treatment with the first generation of EGFR-tyrosine kinase inhibitors (TKI) (gefitinib, erlotinib) or the first generation of tyrosine kinase inhibitors (TKI). two (afatinib), whereas those with mutations in exon 18, 20, L861Q) will respond well to second and third generation EGFR-TKI (osemertinib). Currently the era of national health insurance (JKN) is managed by the Social Security

Administration Agency (BPJS), the requirement to get EGFR-TKI chemotherapy drugs must have EGFR examination results which not all patients are able to carry out.[2(4)]

The benchmark for the success of cancer treatment is the survival rate. Survival in cancers with high malignancy such as lung cancer is 1 year survival, 2 year survival and 3 year survival.[3(5)]Although survival expectations are increasing there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third generation EGFR-TKI target therapy (osemertinib).

Supriadi Kasum's research at the Friendship General Hospital(RSUP Persahabatan) for lung cancer cases between 2010 - 2013 concluded that the survival time of non-small cell lung cancer patients of the adenocarcinoma type (non-squamous) treated with EGFR-TKI was slightly longer than first-line chemotherapy (263 days vs. 260 days).4(6) Hasan Nyambe's retrospective study at Wahidin Sudirohusodo Hospital Makassar in 2017-2019 survival in non-small cell lung cancer (KPKBSK) patients who received EGFR-TKI had a significantly higher survival rate than those who received first-line chemotherapy (conventional chemotherapy).[5(8)]

Research on survival rates of lung cancer patients at RSUD Dr. Hi. Abdul Moeloek has never done. This study aims to determine the characteristics and survival rates of lung cancer patients with subtype adenocarcinoma who received EGFR-TKI therapy and who received conventional chemotherapy with carboplatin and paclitaxel. Survival analysis provides great benefits not only for predict survival chances, but also for better management of lung cancer patients.

METHODS

This research is a descriptive analytic study using a retrospective cohort design. The research sample was obtained from medical record data of patients diagnosed with lung cancer of non-small cell carcinoma of the adenocarcinoma type who received conventional chemotherapy (Karboplatin and paclitaxel) and EGFR-TKI therapy from January 2020 to December 2022 at Dr. Hi. Abdul Moeloek Bandar Lampung, using the total sampling method (consecutive sampling).The data were processed using the SPSS 25.0 program, then survival analysis was carried out using the Kaplan-Meier product limit method. Log-rank test is used to get the difference between the sub-variables. Significance was determined with a p value <0.05.

RESULTS

1. Basic data on the characteristics of research subjects

The characteristics of adenocarcinoma lung cancer patients can be seen in Table 1. Research subjects collected from January 2020 to December 2022 in the adenocarcinoma type lung cancer group who received EGFR-TKI therapy were 39 subjects out of a total of 48 subjects, with 12 male subjects (30.8%), 27 female subjects (69 ,2%). The mean age of the subjects was 58.08 (SD 12.31) years, with the youngest being 32 years and the oldest 88 years. Subjects in the adenocarcinoma type lung cancer group who received carboplatin - paclitaxel therapy were 53 subjects consisting of 35 males (66%) and 18 females (34%). The mean age of the subjects was 54.11 years (SD 10.13) with the youngest being 31 years and the oldest being 77 years.

Smoking status in the EGFR-TKI group 26 subjects (66.67%) did not smoke and 13 subjects (33.33%) smoked, while in the group treated with carboplatin - paclitaxel 15 subjects (28.3%) did not smoke and 38 subjects (71.7%) smoked. Lung cancer staging in the EGFR-TKI group obtained data from 5 subjects (12.8%) stage 3B, 32 subjects (82.1%) stage 4A and 2 subjects (5.1%) stage 4B. Staging in the carboplatin - paclitaxel chemotherapy group obtained data from 8 subjects (15.1%) stage 3B, 34 subjects (64.2%) stage 4A, 11 subjects (20.7%) stage 4B. The p value > 0.05 indicates the distribution of the data is normal.

Tabel.1 Data on the characteristics of the two groups of research subjects

VARIABLE	CATAGORY	EGFR-TKI (N = 39)	p (Shapiro-wilk)	KEMOTERAPI KARBOPLATIN – PAKLITAKSEL (N = 53)	p (Kolomogorof-Smirnof)
AGE	Mean	58,08 ± 12,3	0,980	54,11 ± 10,13	0,140
	Median (min-max)	53,33 (32-84)		56,25 (31 – 77)	
GENDER	Male	12(30,8 %)	0,581	35(66 %)	0,420
	Female	27(69,2 %)		18(34 %)	
SMOKING STATUS	Non-Smokers	26(66,67%)	0,497	15(28,3 %)	0,460
	Smokers	13(33,33%)		38(71,7 %)	
STAGING	3B	5(12,8 %)	0,077	8(15,1 %)	0,412
	4A	32(82,1 %)		34(64,2 %	
	4B	2(5,1 %)		11(20,7%)	
EGFR MUTATIONS	No data	20(51,3 %)	0,748	34(64,2 %	0,518
	Ex 18	1(2,6 %)		0	
	Ex 19 Del	13(33,3 %)		0	
	Ex 21	5(12,8 %)		0	
	WT	0		19(35,8 %)	

Research subject data from the age variable were grouped into 4 categories, namely age < 45 years, 46 – 60 years, 61 – 75 years and > 75 years. In the group of subjects with EGFR-TKI therapy, the highest number of subjects was in the age range between 46-60 years, with 20 subjects (51.3%), as well as in the group of subjects with carboplatin-paclitaxel therapy with 31 subjects (58.5%). This data is shown in table 2.

Tabel 2. Description of the basic data on the characteristics of research subjects by age group

Age	EGFR-TKI therapy	Carboplatin-paclitaxel therapy
<45	7(17,9%)	11 (20,8%)
46 - 60	20(51,3%)	31(58,5%)
61-75	8(20,5%)	9(17%)
>75	4(10,3%)	2(3,8%)

2. Survival rate in the adenocarcinoma lung cancer group receiving EGFR-TKI therapy

In the table of statistical analysis results with SPSS 25 (table 3) in the EGFR-TKI treatment group with Kaplan Meier the mean survival rate (mean) in women was 11.53 months with a 95% confidence interval between 7.29 to 15.78 (95% CI: 7 ,29-15,78). The mean survival rate for males was 8.13 months with a 95% confidence interval between 4.66 months and 11.60 (95% CI: 4.66-11.60). Statistically, there is no significant difference in the average survival rate with a value of p = 0.370 for men and women.

The survival rate in the EGFR-TKI group based on the age group was 14.52 months at the longest in the age group <45 years with a 95% confidence interval between 8.01 and 21.03 (95% CI = 8.01-21.03). The mean longer survival rate in this therapy group was also found in the non-smoking group, the 3B stage group and the exon 19Del mutation status group. There was a significant difference in mutation status with p = 0.046. From the results of the analysis in table 4.3 it shows that the Exon 19 Del mutation status has an average survival rate of 15.20 months (95% CI 7.938 – 22.450). However, overall the average survival rate based on age, sex, smoking status, staging and mutation status in the EGFR-TKI treatment group was not significantly different with an average of 10.50 months with a 95% confidence interval between 7.28 and 13.72.

Table 3. The survival rate of the EGFR-TKI treatment group is based on independent variables

VARIABLE	CATAGORY	Mean			Median			P
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
			Lower Bound	Upper Bound		Lower Bound	Upper Bound	
AGE	<45	14.518	8.011	21.025	17.000	8.530	25.470	0.195
	46-60	12.049	6.215	17.883	7.000	4.389	9.611	
	61-75	6.375	2.545	10.205	7.000	2.199	11.801	
	> 75	5.750	.000	13.715	1.000	-	-	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
GENDER	MALE	8.130	4.656	11.604	7.000	.386	13.614	0.370
	FEMALE	11.533	7.285	15.782	7.000	3.532	10.468	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
SMOKING STATUS	NON SMOKERS	12.419	7.980	16.858	7.000	3.664	10.336	0.088
	SMOKERS	7.000	3.764	10.236	7.000	.000	14.105	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
STAGING	3B	16.000	6.066	25.934	11.000	.000	23.413	0.614
	4A	9.803	6.279	13.326	7.000	4.545	9.455	
	4B	10.000	10.000	10.000	10.000			
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
MUTATION STATUS	No Data	9.022	5.154	12.889	7.000	4.951	9.049	0.046
	Wild Type	-	-	-	-	-	-	
	Exon 18	1.000	1.000	1.000	1.000	-	-	
	Exon 19 Del	15.194	7.938	22.450	13.000	8.221	17.779	
	Exon 21	7.133	.223	14.044	5.000	1.681	8.319	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	

3. Survival rate in the adenocarcinoma lung cancer group receiving carboplatin – paclitaxel therapy

In the carboplatin – paclitaxel therapy group, the results of survival rate analysis using the Kaplan Meier test mean survival rate was 11.21 months with a 95% confidence interval between 7.03 and 15.39 (95% CI 7.029 – 15.388) based on independent variable factors, age group < 45 years. There was no significant difference in the mean survival rate in this group based on age, sex, smoking status, staging or mutation status with an average of 7.84 months, with a 95% confidence interval between 5.84 and 9.84 (95% CI 5.840 – 9.836). The results of the analysis of survival rates in the carboplatin – paclitaxel group are presented in the table 4.

Table 4. Survival rate in the carboplatin-paclitaxel group based on independent variables

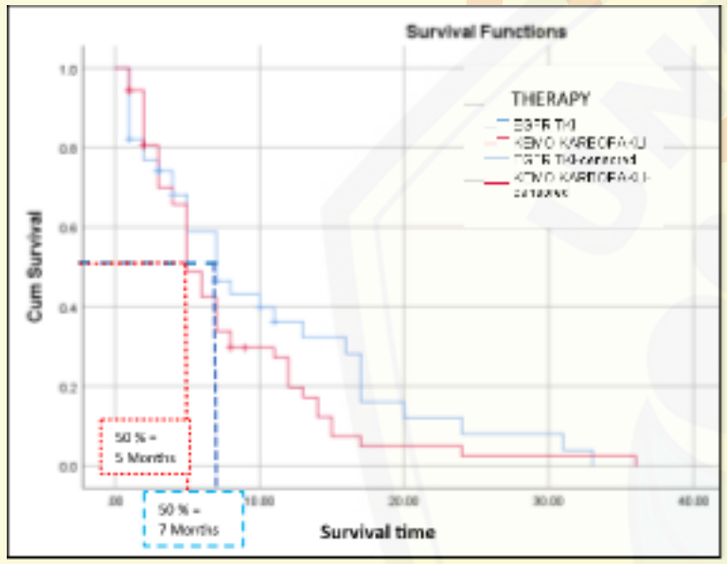
VARIABLE	CATAGORY	Mean			Median			p
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
			Lower Bound	Upper Bound		Lower Bound	Upper Bound	
AGE	<45	11.208	7.029	15.388	14.000	.000	31.344	0.084
	46-60	6.661	4.722	8.599	5.000	3.270	6.730	
	61-75	9.111	2.248	15.975	5.000	4.026	5.974	
	> 75	3.500	2.520	4.480	3.000	-	-	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
GENDER	MALE	7.981	5.276	10.686	5.000	3.788	6.212	0.978
	FEMALE	7.500	4.971	10.029	7.000	3.245	10.755	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
SMOKING STATUS	NON SMOKERS	8.000	5.375	10.625	7.000	4.273	9.727	0.738
	SMOKERS	7.888	5.188	10.588	5.000	3.577	6.423	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
STAGING	3B	9.375	3.894	14.856	6.000	3.228	8.772	0.245
	4A	6.818	4.147	9.490	5.000	4.136	5.864	
	4B	9.515	6.151	12.880	12.000	6.477	17.523	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
MUTATION STATUS	No Data	7.805	5.310	10.301	6.000	4.180	7.820	0.668
	Wild Type	7.820	4.964	10.676	5.000	2.720	7.280	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	

4. Analysis of differences in survival rates between the EGFR-TKI treatment group and the paclitaxel carboplatin therapy group of subjects with lung adenocarcinoma

The average survival rate in the EGFR-TKI group was 10.50 months with a 95% confidence interval between 7.28 and 13.72. The mean survival rate for the carboplatin-paclitaxel group was 7.81 months with a 95% confidence interval between 5.80 and 9.81. The mean survival rate for the two groups was 8.90 months with a 95% confidence interval between 7.10 and 10.66 and was not significantly different with a p value > 0.05 (p = 0.209). Data analysis results are shown in table 5.

Table 5. Analysis of differences in survival rates between the EGFR-TKI group and the paclitaxel carboplatin group for subjects with lung adenocarcinoma

THERAPY	Mean			Median			p
	Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
		Lower Bound	Upper Bound		Lower Bound	Upper Bound	
EGFR-TKI	10.498	7.280	13.715	7.000	3.805	10.195	0.209
CHEMOTHERAPY	7.807	5.799	9.814	5.000	3.788	6.212	
Overall	8.875	7.094	10.656	6.000	4.836	7.164	



Fugure 1. Kaplan Meier curve comparison survival rate EGFR-TKI group with carboplatin paclitaxel group of subjects with lung adenocarcinoma

In the Kaplan Meier chart in Figure 1. it is shown that 50% survival rate in the EGFR-TKI group is 7 months. Whereas in the paklitaxek carboplatin therapy group 50% survival rate was 5 months. Overall 50% survival rate is 6 months.

DISCUSSION

Data on the characteristics of study subjects in the EGFR-TKI therapy group found that subjects with lung adenocarcinoma cancer were more common in women, non-smokers, mean age 58.08 ± 12.3. The age group between 45-65 years has the most lung cancer in both groups. The most common EGFR status mutations occurred in Exon 19 Del 13 (33.3%). In this study there were 20 subjects who received EGFR-TKI therapy but their mutation status was not recorded in the subjects' medical records. This result is different from the results of Novita's research at Adam Malik Hospital, data from 1 January 2014 - 31 December 2016 that the highest number of cases of EGFR mutations were exon 21.[17] The results of the same data as this study were obtained from Hendra Taufik's research on tissue biopsies and plasma ctDNA in several hospitals in Medan from April 2018 – February 2019 the highest number of Exon 19 Del mutations from the two examinations.[18]

Based on gender, the smoking status of the results of this study differed from Novita's research from data on the characteristics of subjects with EGFR mutation lung adenocarcinoma at Adam Malik Hospital, males and more smokers. Based on the age group, the youngest subject was 32 years old and the oldest was 84 years old, in contrast to the results of Novita's study, there were no data obtained at ages <40 years. [17]

Lung adenocarcinoma subjects in the carboplatin – paclitaxel therapy group were mostly male and smoked according to the results of a study by MAW Wicaksono et al at Dr. Kariadi General Hospital Semarang 2014-2016.[7] The same study by Ungky AS et al at dr. Saiful Anwar Hospital Malang 2018-2019 in cases of Wild Type lung adenocarcinoma were more in men and smokers with a survival rate of 5.01 months (153 days). [19]

The mean survival rate for the EGFR-TKI treatment group for women (11.53 months) was longer than that for men (8.13 months) but was not statistically significantly different. Overall, the survival rate for men and women was 10.50 months longer than the paclitaxel carboplatin chemotherapy group, which was 7.81 months, but was not statistically significantly different. These results are different from the studies of Tomasini et al. in 2017 (8.38 months vs. 4.99 months) and Kawaguchi et al. in 2014 in Japan which stated that the survival rate (survival rate) of chemotherapy in adenocarcinoma Wild type was 10.1 months compared to 9 months in EGFR- TKI (erlotinib). [20,21]

LIMITATIONS

This research was conducted during the Covid 19 pandemic where activity restrictions were imposed so that several research subjects were constrained in visiting the hospital. Comorbid factors in research subjects were not documented.

CONCLUSION

1. Gender, age, smoking status and staging showed no significant difference in the results of the survival rate analysis of the two groups. Status of the Exon 19 Del mutation had the longest survival rate and was statistically significantly different with p=0.046.
2. Overall the average survival rate in the EGFR-TKI group was 10.50 months.
3. Overall the average survival rate in the carboplatin – paclitaxel group was 7.84 months.
4. The median survival rate in the EGFR-TKI group for 7 months with a 95% confidence interval was between 3.81 and 10.20, while in the carboplatin-paclitaxel group for 5 months with a 95% confidence interval between 3.79 and 6 , 21. The overall median survival rate of the two groups was 6 months, with a p = 0.209 indicating that there was no significant difference between the two groups.

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TUBERCULOSIS MIMICKING LUNG CANCER IN EIGHT COUNTRIES WITH HIGHEST BURDEN OF TUBERCULOSIS: A SYSTEMATIC REVIEW A CHALLENGE FOR CLINICIANS TO DIFFERENTIATE IT

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ABSTRACT

Introduction: We face the challenge of eliminating tuberculosis by 2030, but the incidence was increasing in 2022. Pandemic COVID-19 is a challenge in itself that hinders us in eliminating tuberculosis. However, differentiating tuberculosis and lung cancer is another challenge but considered trivial yet have the potential to hinder tuberculosis elimination and threaten the patient's life.

Objective: Determine case of tuberculosis mimicking lung cancer in eight countries with high burden of tuberculosis.

Methods: This systematic review based on PRISMA statement. We used several search engines and keywords was "(Tuberculosis OR TB) AND (Mimicking OR Look a Like) AND (Lung Cancer)". Eligibility identified based on PICO framework.

Result: 11 of 7058 studies included in this study and 32 patients included. Most of the study are case report and only one observational study eligible in this study. Risk of bias was determined with JBI critical appraisal tools. Most of the study has score more than 78.3%.

Discussion: Only three from eight countries with high burden of tuberculosis has reported case of tuberculosis mimicking lung cancer. We predict that in fact this case is often found if the examiner is careful about the situation before the patient arrives cause potentially that's not the first time they check themselves to hospital.

Conclusion: At present, tuberculosis cases are increasing, so it is possible that TB cases that mimicking lung cancer will also be a challenge in the future for us to eliminate tuberculosis. Radiology and Histopathology skills play important role to differentiate between these two diagnoses.

Keywords: *Differentiating, Lung Cancer, Mimicking, Tuberculosis*

INTRODUCTION

We face the challenge of eliminating Tuberculosis (TB) by 2030 and it will not be easy. COVID-19 pandemic also a challenge in eliminating Tuberculosis all over the world. In Tuberculosis Global Report 2022, Tuberculosis incidence was increasing by 4% from 10.1M to 10.6M.[1] COVID-19 pandemic affecting Tuberculosis incidence all around the world. Study national population-based in Thailand showed that patient with history of COVID-19 will increase risk to develop tuberculosis by seven-fold.[2] Clinicians are currently not only faced with the COVID-19 pandemic but also challenged by its after effects, especially tuberculosis cases.

The challenge for us does not end there, differentiating between the diagnosis of tuberculosis and lung cancer is a problem that is considered trivial but potentially dangerous in the future, especially in countries with a high burden of tuberculosis. Recently our experience from Pekanbaru, we report case of tuberculoma mimicking lung cancer.[3] This patient suspected with mass-like lung cancer by CT-Scan and have negative AFB sputum, but during the course of time to diagnose the histopathological results showed a tuberculous mass.3 We tried to examined how likely this case would occur and lack of data that we found to answer that. Tuberculosis and lung cancer are two diagnoses that must be distinguished, especially if the patients lead to clinical tuberculosis. If a patient has positive AFB sputum, then we can be sure to establish the patient as tuberculosis. However, if we do not find the AFB in sputum but radiologically finds a mass resembling cancer, of course we are challenged to be careful in diagnosing this matter appropriately. Due to lack of data about this, this study aims to determine case of tuberculosis mimicking lung cancer in eight countries with high burden of tuberculosis. Eight countries with high burden of tuberculosis are based on Tuberculosis Global Report 2022, there are: India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and The Democratic Republic of The Congo.[1]

METHODS Search Strategy

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and synthesis without meta-analysis in systematic reviews for reporting. We searched articles from PubMed, Science Direct, Epistemonikos, Cochrane, and Google Scholar. Keywords for searching articles were: "(Tuberculosis OR TB) AND (Mimicking OR Look a Like) AND (Lung Cancer)". We include all studies: (1) last 10 years, (2) full text, (3) English or Indonesia Language, and (4) Population of the study coming from 8 countries with high burden of TB by Tuberculosis Global Report 2022. Figure 1 shows a detailed description of the search strategies. We excluded unpublished data, duplicate studies, and reviews.

Study Selection

Eligibility assessment by titles and abstracts was performed independently by 4 investigators (AMS, PMA, LV, and RSD) based on PICO framework (Population = Patients suspected with lung cancer with negative AFB in sputum; Intervention = Histopathological of the mass or Radiological Diagnosis; Compare = not specified; Outcome: Tuberculosis confirmed). Disagreements between investigators were resolved by consensus, or involving supervisors (SMM, and IY) when consensus was not reached.

Data Extraction and Quality Evaluation

Information was extracted from each included study on :(1) study design, (2) country, (3) population sample, (4) Age, (5) Gender, (6) History of smoking, (7) disease history, (8) Main Complaint, and (9) TB classification (Drug-Sensitive TB (DS-TB) or Drug-Resistant Tuberculosis (DR-TB)). The primary outcome is confirmation of tuberculosis by histopathological finding in the mass in patients suspected with lung cancer.

Full text articles were reviewed by AMS, PMA, LV and RSD with Joanna Briggs Institute Critical Appraisal tool

according to the type of articles received (jbi.global/critical-appraisal- tools). Disagreements were resolved by consensus, or involving supervisors (SMM, and IY) when consensus was not reached.

RESULT

Study Selection

A total of 11 studies were included in the review that the population of the study came from 8 countries with high burden of TB by Tuberculosis Global Report 2022. The search of PubMed, Science Direct, Epistemonikos, Cochrane and Google Scholar provided a total of 7058. Of these, 7058 studies were discarded because these papers did not meet the criteria. [11] studies were examined in more detail. We also assessed all references from included studies to find relevant papers and searched for studies that have cited these papers, no additional studies that met the criteria for inclusion were identified.

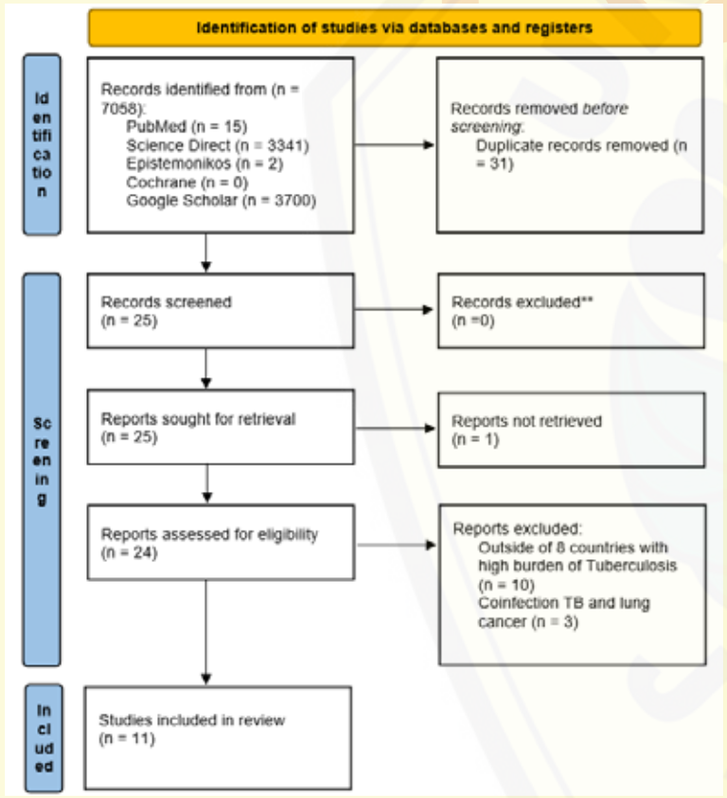

Figure 1. Flow Diagram of Included Studies

Characteristics of Included Studies

We extracted basic demographic of all included studies and compile it in Table 1. In total 32 patients included in this study. Most of the case dominated by male (68.37%) and history of smoking mostly not mentioned in included studies. Most of included studies are case report and only one observational study (cross-sectional) included. We suspect that the few articles obtained were due to the infrequency of reported cases or not tracking events before the disease was established at the hospital. Even if we looked for eight countries with high burden of tuberculosis, we only found three countries (China, India and Indonesia) out of eight.

Table 1. Characteristic of Included Studies

No	Author, Year	Design	Country	N	Age (year)	Sex	History of Smoking	Disease History
1	Fauzie et al, 2023[4]	Case Report	Indonesia	1	5 months	Male	Not Mentioned	Recurrent Pneumonia
2	Wulandari et al, 2022[5]	Case Report	Indonesia	1	24	Male	Not Mentioned	Not Mentioned
3	Hang et al, 2020[6]	Case Report	China	1	73	Male	Not Mentioned	Type 2 Diabetes
4	Nayanagari et al, 2015[7]	Case Report	India	1	30	Female	Not Mentioned	Not Mentioned
5	Lang et al, 2017[8]	Cross Sectional	China	22	18 (<60 years old) 4 (>60 years old)	17 Male and 5 Female	12 patients are smoker	12 patients have diabetes
6	Kaur et al, 2021[9]	Case Report	India	1	52	Female	Not Mentioned	Not Mentioned
7	Fauzi et al, 2022[3]	Case Report	Indonesia	1	55	Female	Not Mentioned	Type 2 Diabetes
8	Yadav et al, 2020[10]	Case Report	India	1	72	Female	Not Mentioned	Not Mentioned
9	Patel et al, 2015[11]	Case Report	India	1	45	Female	Not Mentioned	Not Mentioned
10	Lan et al, 2019[12]	Case Report	China	1	66	Male	Not Mentioned	Not Mentioned
11	Chen et al, 2018[13]	Case Report	China	1	7	Male	Not Mentioned	Not Mentioned

We extracted data about main complaint, classification of tuberculosis, diagnostic confirmation, finding and treatment after TB confirmation. Patients that suspected with lung cancer but actually has tuberculosis has various main complaint. Most of main complaint from all included studies are febrile[4,5], unintended weight loss,[3,4,6] chest pain[6,7,10–12], and cough.[4,7,9–13] . Most of studies confirm the diagnosis of tuberculosis using bronchoscopy (BronchoAlveolar Lavage) as well as by biopsy. Study by Yadav et al., confirm the diagnosis by AFB sputum. It's not like the others but we find out that this patient actually had radiological finding first (CT-Scan and PET scan), suspected with lung cancer then get confirmed by positive AFB in the sputum.[10] Most of the cases patient had clinical tuberculosis, only Yadav et al., find the patient with microbiological tuberculosis.

We tried to extract the duration of delay in diagnosis. However, we did not find any articles explaining how long the duration between this misdiagnosis of lung cancer and tuberculosis was. Study by Lang et al., showed chest CT evidence of TB lesion.[8] TB lesion affected the left upper lobe in seven cases (31.8%), left lower lobe in two cases (9.1%), right upper lobe in ten cases (45.5%) and right middle lobe in three cases (13.6%). The biggest sizes varied in diameter from 1 to 5cm, with a mean of 2,51 cm.[8]

Table 2. Extracted Data Regarding Main Complaint and Diagnostic Method to Confirmed Tuberculosis

No	Author, Year	Main complaint	DS-TB/DR-TB	Diagnostic Confirmation	Finding	Treatment After TB Confirmation
1	Fauzie et al, 2023[4]	Febrile in last 2 months, weight loss, cough, shortness of breath	DS-TB	Flexible Bronchoscopy (BAL)	Cheesy-like vegetation and M.Tb detected (sensitive to rifampicin) from BAL.	2RHZE+10H
2	Wulandari et al, 2022[5]	Febrile, frail condition	DS-TB	CT-guiding Fine Needle Aspiration Biopsy + Tumor resection	Granulomatic inflammation according to tuberculosis.	Anti Tuberculosis Drug (1st Category) + Streptomycin (2 months)
3	Hang et al, 2020[6]	Chest pain, asthenia, anorexia, weight loss	DS-TB	CT Scan-guided transthoracic needle biopsy	Coagulative necrosis with granulomatous inflammation. Positive AFB staining	3RHZE+9RH
4	Nayanagari et al, 2015[7]	Chest pain, cough, sputum	DS-TB	Thoracotomy and open biopsy	Lymphoid tissue replaced with caseation necrosis. Granulomas with epithelioid cells with Langerhans foreign body giant cells	Not Mentioned
5	Lang et al, 2017[8]	Not Mentioned	Not Mentioned	Pathological Examination	Pulmonary Tuberculosis	Not mentioned
6	Kaur et al, 2021[9]	Chest tightness, intermittent cough with hemoptysis	DS-TB	Bronchoscopy with biopsy	No atypical cell was found. Caseous granulomatous inflammation been found. GeneXpert detect *Mycobacterium tuberculosis*	RHZE
7	Fauzi et al, 2022[3]	Lump on back and Weight loss +/- 9 kgs in last 5 months	DS-TB	Transthoracic Needle Aspiration and Open Biopsy	Langerhans cell and epithelioid proliferation typical for tuberculosis	2RHZE+4RH
8	Yadav et al, 2020[10]	Persistent cough, chest pain.	Not Mentioned	Sputum AFB	M.Tb detected	R-cinex, pyzina, ethambutol, benadon, and pentocid for 3 months
9	Patel et al, 2015[11]	Dry cough, dull aching right chest pain	Not Mentioned	Bronchoscopy + Biopsy (AFB culture by cytology)	Positive for AFB	Category 1 AKT with steroids (1 mg/kg/day) tapered over 6 weeks.
10	Lan et al, 2019[12]	Hemoptysis, cough, chest pain, anorexia	DS-TB	Transbronchial lung biopsy	Granulomatous inflammation with Langhans giant cell, AFB identified in lung tissues	RHZE
11	Chen et al, 2018[13]	6 months history of cough	DS-TB	Pulmonary Needle Biopsy + H-E Staining	Inflammation (Possibly TB)	isoniazid, rifampicin, ethambutol and pyrazinamide

Risk of Bias

AMS, PMA, LV and RSD assessed risk of bias by critical appraisal tools by Joanna Briggs Institute (jbi.global/critical-appraisal-tools). All authors reviewed every included study independently. Disagreements were resolved by consensus, or involving supervisors (SMM, and IY) when consensus was not reached. All studies that already been reviewed showed score more than 78.3%. By all authors consensus, we agree that all included studies are low risk of bias.

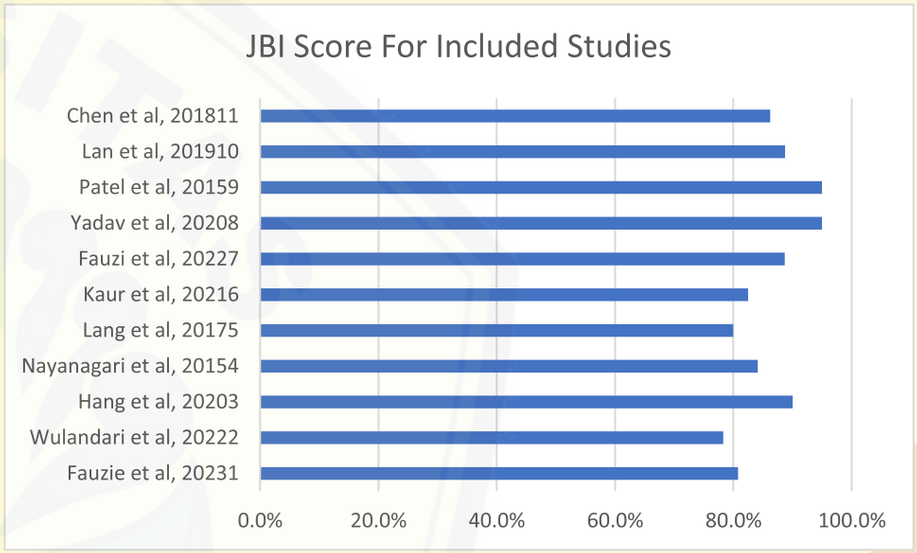

Figure 2. JBI Critical Appraisal Tools by All Authors for Included Studies.

DISCUSSION

Potential Mechanism Tuberculosis Look a Like Lung cancer

Tuberculosis infection can be divided into primary and secondary processes. Primary tuberculosis refers to the first infection of Mycobacterium tuberculosis in a previously unsensitized or unexposed person, while secondary tuberculosis refers to reactivation of Mycobacterium tuberculosis in a previously sensitized host. The infection will trigger an innate and adaptive immune response (Figure 3).[14] Macrophages and dendritic cell are the two main units in innate response because they play an important role as antigen-presenting cell.[15] This task is possible due to their ability to recognize mycobacterial structures and pathogen-membrane associated pattern recognition receptors such as TLR2, TLR4, and TLR9.[16] The interaction later on with TLRs will trigger the secretion of proinflammatory cytokines (e.g. TNF, IL-1B, IL-12, and NO) by macrophages. This interaction, although some of the bacteria may evade this process, will also help phagocytosis process, and the bacteria will be destroyed through acidification and phagosome-lysosome interaction.[17] Generally, the innate immune response will have three impacts: cell necrosis, apoptosis, and the survival of the infected macrophages.[17] Mycobacterium tuberculosis will be eliminated only through apoptosis; therefore, Mycobacterium tuberculosis may persist or even proliferate before a specific T-cell is activated, which occurs 2–3 weeks post- primary infection.[18]

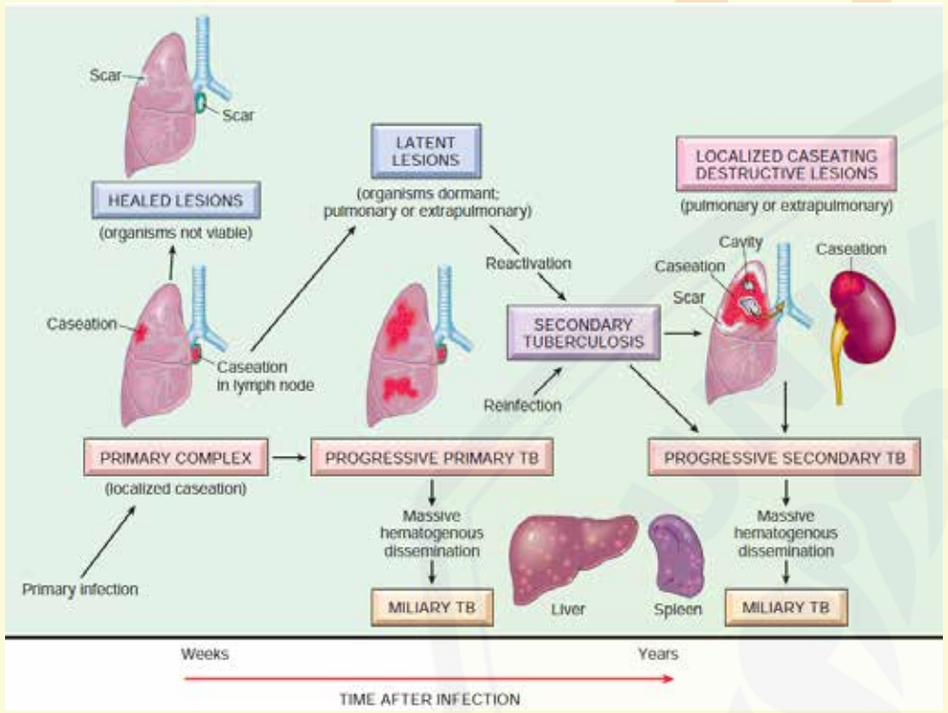

Figure 3. Timeline of tuberculosis infection including primary and secondary tuberculosis.14

T-cell activation marks the start of an adaptive immune response. T-cells will secrete IFN-γ, which is important for more macrophage activation and intracellular mycobacterial killing.19 Another cytokine secreted by macrophages, dendritic cells, and T cells is TNF-α.[14,20] TNF- is the key component in granuloma formation and might also cause unfavorable inflammatory responses in patients with progressive disease.[15,20] The tuberculoma or granuloma is the hallmark of mycobacterial infection.14,15,21 On a microscopic level, the granulomas, besides being marked with multinucleated giant cells, are also enclosed with lymphocytes punctuating the fibroblastic rim, which gives them a solid structure.14,19 The size of the granuloma will increase with the number of bacteria that it holds; therefore, in X-ray examination, it may show as nodules.[22] These nodules, if they are large, may be misdiagnosed as lung cancer; therefore, biopsy remains the gold standard for acquiring an accurate diagnosis.[23]

Secondary or post primary tuberculosis may occur shortly after primary tuberculosis and classically involves the apex of the upper lobes of one or both lungs.[14,24] The preexisting of type IV hypersensitivity in the patient, may cause a prompt and marked tissue response.[14] Tissue response may appear as destruction or structural remodeling of the lung parenchyma and its vascularization. The pulmonary and bronchial arteries are easily prone to bleeding because they are exposed and become hypertrophied and ecstatic, which diminish the architectural support.[25,26] This process is one of the mechanisms that cause hemoptysis in tuberculosis patient. Mycobacterium tuberculosis can induce necrotizing granulomatous vasculitis, which can directly damage the vascular system. The vascular remodeling brought on by the

granulomatous inflammation of the arterial wall weakens the lining of the blood vessels and promotes aneurysmal dilatation, which is prone to rupture.[26] Although the occurrence of this aneurysm is extremely unusual, it may potentially be the cause of the hemoptysis that happened in a patient with tuberculosis.[26,27]

Another systemic response caused by the macrophages is weight loss; therefore, weight gain will be one of the targets in tuberculosis treatment since it is considered to be a good indicator of patient response to treatment.[14,27] Leptin, mainly produced by the white adipose tissues, functions as hormone that suppressed appetite and stimulate energy metabolism by binding to specific receptors in hypothalamus.[28,29] Acute inflammation from Mycobacterium tuberculosis may cause an increase in serum leptin levels, which theoretically will cause a weight reduction.[29] Further fat loss from weight reduction due to chronic inflammation might decrease leptin levels and impairing the host cell-mediated immunity, which will worsen the prognosis.[29–31]

How to Differentiate Pulmonary Tuberculosis and Lung Cancer?

The diagnosis of tuberculosis and lung cancer can be difficult as symptoms of both diseases are similar. TB may be misdiagnosed as lung cancer both clinically and radiographically since both shares great similarities in symptoms, such as, weight loss, cough, haemoptysis, and shortness of breath and appear similar on chest imaging. A thorough history and detailed physical examination should be the first step in revealing features that are more suggestive of PTB than lung cancer.

Based on history examination, it is important to have questioned about the history of cough, bloody sputum, shortness of breath and emaciation are the symptom likely to appear in lung cancer. In this study, most of the cases (9/13) explained that most of the patient came with weight loss in time ranged between 2-5 month. The unexplained gradual weight loss and loss of appetite indicating either pulmonary tuberculosis rather than malignancy.[32] However, the studies do not much reveal about the detailed characteristic, only 5/9 cases about whether the chronic cough is productive, dry, or blood sputum contained. History of tobacco smoking is generally present in cases of lung cancer while it may be present or absent in tuberculosis. Lung cancer can be ruled out, if the patient marked with symptoms due to metastatic spread, specifically bone pain, fractures, cerebral metastasis, as well as neurological deprivement.[32] Nevertheless, only in 3/13 study with disseminated tuberculosis, same clinical features can be existed.

On lung examination, Wulandari et al., and Patel et al., revealed that mass like consolidation can be detected in tuberculosis with decreased fremitus and faint percussion.[5,11] This finding frequently confusing physician in diagnosis. Pulmonary tuberculosis manifesting as lesion, thus, mimicking a lung carcinoma is an unusual radiographic presentation of tuberculosis (TB). All of the patient in this study had both x-ray and CT scan with mass-nodules like lesion or irregular cysts. The case presented with lung cancer appear to. Thus, PTB and lung cancer difficult to distinguish clinically and radiologically

In the high TB burden country, the diagnosis of active tuberculosis should include smear and culture of sputum samples for acid-fast bacilli (AFB), as well as nucleic acid amplification testing.[33] In the present study, biopsy was performed to 11/13 cases in this study. Histopathological examination from biopsies revealed that caseous granulomatous inflammation was obtained. Invasive diagnostic techniques and histological examination of the mass usually clinches the diagnosis since traditional methods are usually disappointing amidst the diagnostic dilemma.[33]

How Tuberculosis Is Not Detected in Sputum but Detected in Mass?

Bacteriological examination to determine tuberculosis bacteria has an important role in making the diagnosis of tuberculosis. Materials for bacteriological examination can come from sputum, pleural fluid, cerebrospinal fluid, bronchial washings, gastric washings, urine or tissue. From all of the materials, sputum examination is commonly used in middle and low income countries due to easy to used and inexpensive.[3] The examination can be done by microscopy (Ziehl-Nielsen staining and rapid molecular test) and culture examination.[34] Previous study by Keflie et al. stated that the sensitivity and specificity of microscopic Ziehl-Nielsen staining were 48.9% and 95.56%, respectively.[35] Meanwhile, rapid molecular test with GeneXpert have sensitivity of 88% and specify of 99%. Despite of the wide application as primary diagnostic tool, the detection power of microscopic examination was found not consistent in some studies. It could be happened due to the paucibacillary nature of the disease, pre analytical error such as quality and quantity of sputum and smear preparation, analytical error such as skill of microscopist and lack of patience and exhaustion of lab technicians due to high load. The weakness of microscopic examination was found in diagnosing pediatric TB and in individual who is co-infected with HIV- TB. Moreover, Pulmonary tuberculosis (PTB) can misdiagnose with many diseases especially lung carcinoma which often aggravated by negative sputum smear in some cases.[3,36]

Acid Fast Bacilli (AFB) smear from sputum is hard to detect TB in children due to the poor bacteriologic specimen and hard to get the sputum.[37] The examination of sputum on children is also found challenging mainly because the sputum is directly swallowed and the amount of microorganisms in children is lacking.[38] Kumar et al. reported that the necessitates of bronchial aspirate (BAL) or gastric lavage to be carried out in the morning for three consecutive days have benefit in diagnosing PTB in children and patients who are unable to expectorate or whose spontaneous and induced sputum are negative despite high clinical suspicion.[10,38]

Overall, sputum microscopy in HV coinfection can reduce the sensitivity in TB detection. In the spot-spot approach the sensitivity in HIV coinfection decreased from 76.7% to 66.7% and from 68.4% to 50.0% for those screened with the 'spot-morning' approach. However, the decreased of sensitivity also found in three-specimen strategy (spot-spot-morning) for HIV coinfection which is 81.3% to 71,4%.39 HIV patient can get a negative result even got infected with TB germ due to the weakness of immune system. One of the hypothesis TB not detected in HIV patient is the role of CD4+ T cells and TNF in HIV patients made the granuloma formation fail.[40]

In some cases of PTB mimicking lung CA, mass biopsy was found to have ability in detected TB. As reported by Patel et al. A patient with endobronchial TB mimicking malignancy was found the negative result of sputum smear, while positive in mass. The sputum smear of AFB and gram stain were negative due to the proximal obstruction by the granulation tissue. Bronchoscopy biopsy is the most reliable method of endobronchial TB with the finding of mucosal ulceration and granulation tissue with epithelioid giant cell.[11]

Pragmatic Lesson: What We Need to Learn for This Case?

Tuberculosis cases are increasing, so we should be more sure of a definite diagnosis of tuberculosis (especially cases of clinical tuberculosis). Tuberculosis and lung cancer may present with similar manifestations in the history and radiology. From all the included studies we can learn that radiology and histopathological skills play a role in us knowing that a mass and lung cancer are not the only diagnoses. Tuberculosis can also be a diagnosis if the patient is known to have a mass in the lung. We suggest that patients who are examined by histopathology can be a good consideration if they have doubts between the two diagnoses.

Only three from eight countries with high burden of tuberculosis has reported case of tuberculosis mimicking lung cancer. We predict that in fact this case is often found if the examiner is careful about the situation before the patient arrives, because the patient may not have come to the health facility for the first time to check themselves. All studies also do not describe in detail how long it takes these patients to get a definite diagnosis. We argue that the longer the duration these patients take to get a definite diagnosis, prognosis will be worse. This certainly can increase the death rate from tuberculosis caused by patients getting late for treatment and hinder out common goal of eliminating tuberculosis.

CONCLUSION

Tuberculosis mimicking lung cancer cases were very few reported by the eight countries with a high burden TB. This could be due to a lack of careful examination in differentiating these two diagnoses and perhaps also due to the lack of generally reported data because these cases require good clinical skills to differentiate between them. At present, tuberculosis cases are increasing, so it is possible that TB cases that mimicking lung cancer will also be a challenge in the future for us to eliminate tuberculosis. Radiology and Histopathology skills play important role to differentiate between these two diagnoses.

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THE CORRELATION OF BASELINE HEMOGLOBIN WITH QUALITY OF LIFE IN LUNG CANCER PATIENTS RECEIVING PLATINUM-BASED CHEMOTHERAPY BASED ON EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE

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ABSTRACT

Lung cancer and its therapy can significantly affect a patient's quality of life, well-being, and daily social functions. Anemia is a condition that often occurs in lung cancer patients and could affect the quality of their life. This study aims to analyze the relationship between baseline hemoglobin (Hb) levels and the quality of life of lung cancer patients undergoing platinum-based chemotherapy. The cross-sectional study was conducted on 30 NSCLC patients who received platinum-based chemotherapy in January 2023 – February 2023 at Saiful Anwar General Hospital Malang. Baseline Hb level data were obtained through medical records while the patient's quality of life assessment was conducted through interviews using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13). There was a significant correlation between Hb baseline and the indicator of pain relief after medication ($r = 0.559$, $p < 0.05$), and between Hb baseline and difficulty of swallowing ($r = -0.386$, $p < 0.05$). There was no significant correlation between baseline Hb and overall quality of life ($r = -0.096$, $p > 0.05$). In this study, we found that decreased baseline Hb levels were correlated to decreased pain relief after medication and increased dysphagia, but the mechanisms are unknown and there is no significant correlation between baseline Hb levels and overall quality of life scores.

Introduction

Lung cancer is a complex disease affected both by internal and external factors. With increasing incidence globally, lung cancer is the main contributor to cancer-related deaths.[1,2] Early diagnosis and multidisciplinary treatment of lung cancer led to better prognosis and overall quality of life. Coexisting conditions such as anemia are known to contribute significantly to lung cancer patients' quality of life as well.[3]

Anemia is a common finding in cancer patients, especially in patients treated with chemotherapy, causing myelosuppressive effects. Anemia can affect various organs, depending on its severity, duration, and other aspects such as cancer-related medications. Symptoms such as dyspnea, palpitation, and lethargy can manifest in anemia patients, leading to a decrease in quality of life.[4,5]

The majority of lung cancer cases are lately diagnosed, with management mainly focused on supporting and improving patient's quality of life.[6,7] There is an increasing focus on studies on quality of life in cancer patients. Although various studies had analyzed the correlation between anemia and quality of life in cancer patients, there is currently no study investigating the correlation between baseline hemoglobin and the quality of life of lung cancer patients in Indonesia.[8] In this study, we analyzed the correlation between Hb levels and quality of life in lung cancer patients receiving platinum-based chemotherapy.

Method

This cross-sectional study involved non-small-cell lung cancer patients undergoing platinum- based chemotherapy in Saiful Anwar General Hospital from January 2023 to February 2023. Hb levels were analyzed from the venous blood sample. Quality of life was assessed using The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13).

The subject should have been diagnosed with non-small-cell lung cancer by histopathological analysis and have at least undergone 1 series of first-line platinum-based chemotherapy. Baseline hemoglobin data before chemotherapy were obtained from medical records. Lung cancer patients in severe condition, having certain blood-related diseases or nephropathy, and not a primary lung cancer were excluded.

Nominal data were shown as frequency (%), while numerical data were shown as mean + standard deviation. Baseline Hb data were categorized as normal (>13 g/dL), grade 1 (10-13 g/dL), and grade 2 (8-10 g/dL). The Kolmogorov-Smirnov test was used to determine data distribution normality. An independent T-test was used to determine the significance between the Hb category and quality of life.

Result

A total of 30 subjects participated in this study. The mean age was 58.97 ± 10.46 yearsand 63.3% of study subjects were male. 40% of study subjects have comorbidity, with the most common being hypertension (26.7%) and diabetes (10.0%). All study subjects underwent first- line platinum-based chemotherapy with various regimens, ranging from carboplatin-paclitaxel (63.3%), cisplatin-pemetrexed (30.0%), cisplatin-etoposide (3.3%), and cisplatin-paclitaxel (3.3%). Subjects clinical characteristics can be seen in Table 1.

Table 1. Clinical characteristics of study subjects

Variable	Freq (%) or Mean ± SD	P
Male gender	19 (63.3)	0.075
Age (years)	58.97 ± 10.46	0.566
Smoking history	19 (63.3)	0.097
Smoking history duration (years)	28.83 ± 11.56	0.210
Baseline Hb	11.90 ± 2.03	0.615
Baseline Hb Category		
Normal	8 (26.7)	0.949
Anemia Grade 1	17 (56.7)	
Anemia Grade 2	5 (16.7)	
Comorbidity		
Hypertension	8 (26.7)	0.911
Diabetes Mellitus	3 (10.0)	
Heart Disease	1 (3.3)	
Hepatitis B	1 (3.3)	
Lung Tuberculosis	1 (3.3)	
Chemotherapy Regimen	**Freq (%)**	
Carboplatin-paclitaxel	19 (63.3)	0.320
Cisplatin-permetrexet	9 (30.0)	

Cisplatin-etoposide	1 (3.3)
Cisplatin-paclitaxel	1 (3.3)
Chemotherapy Series	**Freq (%)**
Series 1	4 (13.3)
Series 2	7 (23.3)
Series 3	5 (16.7)
Series 4	4 (13.3)
Series 5	4 (13.3)
Series 6	6 (20.0)

The mean baseline Hb was 11.90 g/dL. Regarding EORTC QLQ LC-13 questionnaires, the mean LCCO was 31.97, the mean LCHA was 2.2, the mean LCD was 30.67, the mean LCSM was 3.3, the mean LCDS was 2.2, the mean LCPN was 15.4, the mean LCHR was 46.43, the mean LCPC was 28.63, the mean LCPA was 18.70, the mean LCPO was 18.70, and the mean score for pain relief after medication was 82.39. The mean total score for EORTC QLQ LC-13 was 261.37. No significant correlations and differences were found between demographic characteristics and total EORTC QLQ LC-13 scores.

Table 2. Baseline Hb and Quality of Life of Study Subjects

		EORTC QLQ LC-13 Score (Mean ± SD)	p
Baseline Hb (Anemia Grade)	Normal	236.75 ± 150.56	0.836
	Grade 1	268.18 ± 87.22	
	Grade 2	277.60 ± 244.50	

The total score of EORTC QLQ LC-13 was then plotted to the baseline Hb anemia grade. An increasing pattern of EORTC QLQ LC-13 score was found with more severe anemia grade, with gradual increases of EORTC QLQ LC-13 total score from normal, to anemia grade 1, and anemia grade 2. ANOVA test was conducted to determine the significance in EORTC QLQ LC-13 score differences between baseline Hb groups. ANOVA test showed an insignificant difference of EORTC QLQ LC-13 score between baseline Hb groups ($p = 0.836$).

Table 3. Correlation between Baseline Hb and EORTC QLQ LC-13

Variable Correlated with Hb Values	R	p
LCCO	-0.290	0.120
LCHA	-0.086	0.652
LCDY	-0.003	0.987
LCSM	-0.276	0.139
LCDS	-0.386	0.035
LCPN	-0.005	0.978
LCHR	0.202	0.284
LCPC	0.007	0.969
LCPA	-0.109	0.566
LCPO	0.117	0.539
Pain relief after medication	0.559	0.001
Total EORTC QLQ LC-13 Scores	-0.096	0.615

R: Correlation coefficient; p: significance ($p < 0.05$); LCCO: coughing; LCHA: haemoptysis; LCDY: dyspnea; LCSM: sore mouth; LCDS: dysphagia; LCPN: peripheral neuropathy; LCHR: alopecia; LCPC: pain in chest; LCPA: pain in arm or shoulder; LCPO: pain in other parts

Pearson correlation tests were done to determine the correlation between various EORTC QLQ LC-13 questions and baseline Hb. An insignificant correlation was found between EORTC QLQ LC-13 total score and baseline Hb ($p = 0.615$). A significant and negative correlation was found between LCDS and baseline Hb ($r = -0.386$, $p = 0.035$). This means that a higher LCDS score is correlated with a lower baseline Hb and vice versa. A significant and positive correlation was found between pain relief after medication and baseline Hb ($r = 0.559$, $p = 0.001$). This means that higher pain relief after medication score is correlated with higher baseline Hb and vice versa.

Discussion

In this study, although the EORTC QLQ LC13 total score was not found to be significantly correlated with Hb levels, specific questionnaire points including dysphagia and pain relief after medication were related to Hb levels. Dysphagia had a significant, negative correlation with Hb levels, showing that higher Hb is correlated with lower dysphagia symptoms. Anemia can be related to iron deficiency. Iron is an important element, taking part in various body homeostasis, including oxidative enzymes that are iron-dependent. Reduction in the activity of these iron- dependent enzymes can result in the degradation of pharyngeal mucosa and muscles, leading to dysphagia.[9]

A significant, positive correlation was found between pain relief after medication score and Hb levels. This finding indicated increased pain-relief drug efficacy with an increase in Hb levels. However, there is currently no previous study that specifically analyzed the relationship between cancer-related anemia and drug efficacy. A study by Joshi et al. showed no significant differences in the bioavailability of phenytoin in iron deficiency anemia subjects compared to normal subjects.[10] The relationship between anemia, pharmacokinetics, and pharmacodynamics of various drugs, especially pain relief medications should be studied further in future studies to provide a better understanding regarding the findings in our study.

Anemia is a complication often found in various types of cancer. In this study, a majority (73.4%) of study subjects were found with grade 1 and grade 2 anemia. A previous study showed that 30% of cancer cases were found with Hb of < 10.0 g/dL.11 Regarding lung cancer, a previous study showed that anemia prevalence in lung cancer with Hb of < 12.0 g/dL is 78.8%.[12] In lung cancer, anemia can lead to a decrease in quality of life and treatment option. Chemotherapy and radiotherapy require the patient to have a Hb of > 10 g/dL.[13]

Low levels of Hb can significantly affect body function and quality of life in relation to oxygen transport dysfunction. Impairment of oxygen transport from lung tissue to the entire body can lead to metabolic dysfunction, impairing energy production in the form of adenosine triphosphate (ATP). This can lead to various symptoms such as fatigue, decreasing quality of life.[14] Impairment of energy production can also lead to dysfunction of various body functions such as immunity, decreasing life expectancy, and quality of life.[15]

In cancer patients undergoing chemotherapy, a decreasing trend of Hb from baseline to chemotherapy progression is often found. This can be explained by cancer progression and chemotherapy. Regarding cancer progression, malignancy-related bleeding and poor nutrition can lead to the worsening of anemia.[5] In lung cancer, another cancer-related factor that can lead to anemia is hemoptysis, which is found in 7% to 35% of lung cancer patients.[16] Hematotoxic and myelosuppressive effect of chemotherapy can also lead to a decrease of Hb, which may lead to a worse quality of life.[17]

There is a decreasing trend in the quality of life in conjunction with decreasing levels of Hb. In this study, the level of Hb is classified by anemia grade. Compared to subjects without anemia, subjects with grade I anemia have a higher total EORTC QLQ LC-13 score (268.18 + 87.22 vs 236.75 + 150.56), hence lower quality of life. Subjects with grade II anemia were also found to have higher total EORTC QLQ LC-13 scores compared to subjects with grade I anemia (277.60 + 244.50 vs 268.18 + 87.22). However, this decreasing trend of quality of life was found to be insignificant ($p > 0.05$). Correlation analysis showed a negative correlation between Hb level and EORTC QLQ LC-13 total score ($R = -0.096$), although this finding was also found to be insignificant ($p > 0.05$).

This study's finding regarding the correlation between Hb level and quality of life was different compared to previous studies. A study by Barca-Hernando et al. analyzed the correlation between anemia and quality of life in cancer patients using EORTC QLQ-C30. In this study, anemia was found to have a negative impact on quality of life. Anemia was also found to be related to a higher number of symptoms including fatigue, pain, appetite loss, dyspnea, nausea, and vomiting.[8] This can be attributed to the difference in the quality of life assessment instrument used. This study used EORTC QLQ-C30, which is a core questionnaire for quality of life, covering more general aspects of quality of life. Our study used EORTC QLQ LC13, which is a disease and treatment- specific quality of life questionnaire.[18] Although simpler and easier to fill by the study subjects, the sole usage of this specific questionnaire may limit the study's ability to assess the whole quality of life aspects of the study subjects.

A previous study by Palasamudram et al. also showed different findings compared to our study. In this study, anemia was also found to be related to lower quality of life, assessed using the EORTC-QLQ–30 questionnaire.[19] A study by Buckstein et al. also showed similar findings. Both studies had similarly more severe anemia compared to our study. In Buckstein et al. study, the optimal Hb threshold to distinguish subjects' quality of life is 10 g/dL.[20] In our study, a Hb of < 10 g/dL is classified as grade II anemia, which is only 16.7% of the total subjects. Our study also has a lower number of subjects compared to previous studies mentioned above, which ranged from 204 to 689 subjects.

In this study, there was no significant correlation or difference found between demographic characteristics and total EORTC QLQ LC-13 score. Out of 30 subjects, there were 12 subjects with various comorbidities. There were 8 subjects with hypertension, 3 subjects with diabetes mellitus, and other comorbidities such as hepatitis B and lung TBC found in these subjects. Comorbidity is found to be related to quality of life and life expectancy in lung cancer. A previous study showed that comorbidity is related to treatment efficacy in lung cancer. Additionally, comorbidity is associated with age and smoking behavior, which are related to lung cancer[21]

However, neither comorbidity, age, nor smoking behavior were significantly related total EORTC QLQ LC-13 score, indicating that these factors do not directly affect the quality of life of lung cancer patients.

Conclusion

In this study, most lung cancer subjects suffered from anemia before chemotherapy. Chemotherapy resulted in more severe anemia. Previous studies have shown that anemia is correlated with quality of life in cancer patients. In this study, we found that baseline Hb levels were correlated to various quality of life problems such as dysphagia and pain relief after medication. However, we did not find a correlation between Hb levels and overall quality of life. Hence, we suggest that the usage of more disease-specific and shorter questionnaires was not able to assess the whole aspect of quality of life and the correlation between anemia and the quality of life itself. Hence, we recommend that to assess the quality of life in lung cancer patients, a more general quality of life questionnaire should be used.

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SENSITIVITY AND SPECIFICITY OF COVID 19 EWS IN DIAGNOSING COVID 19

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ABSTRACT

BACKGROUND

COVID-19 has caused health concerns around the world. Although most cases present with mild symptoms, a small proportion progress to acute respiratory illness and hypoxia requiring hospitalization, and some develop acute respiratory distress syndrome, multi-organ failure, or fatal.[2] As data of April 26, 2023, there were more than 1.2 billion confirmed cases of COVID-19 and more than 2.6 million deaths worldwide. In Indonesia, there were 6,765,727 confirmed cases of COVID-19 with 161,190 deaths.[3] The incidence of COVID-19 in Indonesia is estimated to be greater than the reported figures because in the early phase of the pandemic, COVID-19 testing capacity in Indonesia is still limited. This contributed to the diagnostic, preventive and curative measures of the COVID-19 pandemic in Indonesia.[4]

The COVID-19 pandemic has put tremendous pressure on healthcare systems around the world. There is a need for simple and effective evaluation tools to triage patients and allocate resources efficiently in the early phase of the pandemic.[5] The COVID-19 early warning score (EWS) has emerged as a valuable tool for predicting the prognosis of COVID-19 patients, monitoring patient's progress, and making clinical decisions. The COVID-19 EWS is one of EWS systems that has been extensively studied for its role in assessing COVID-19 cases. The COVID-19 EWS is useful for predicting of SARS- CoV-2 PCR results and estimating the risk of worsening as well as prognosis.[6] Hence we conducted a study to assess the sensitivity and specificity of Covid-19 EWS, in predicting the outcomes of pneumonia patients.

METHODE

A retrospective cohort study was conducted in all patients diagnosed with pneumonia admitted to Dr. Moewardi hospital, Surakarta from October to December 2022. We only included patients aged over 18 years old undergoing SARS CoV-2 PCR examination due to suspected Covid- 19 infection. Meanwhile pneumonia patients who did not undergo SARS CoV-2 PCR swab testing were excluded from the study. The patients were declared confirmed COVID-19 if the SARS-CoV-2 PCR examination gave a positive result and declared not COVID-19 if twice of the SARS-CoV-2 PCR examinations gave negative results. The outcomes were categorized as alive and dead. In this assessment, we used Covid-19 EWS based on the study b of Song CY et al., 2020. Nevertheless, in this study, we made adjustments, namely by not including signs of pneumonia on CT scans as an assessment. This is because in our hospital, CT Scan has not become a routine examination for suspected COVID-19 pneumonia. The EWS assessment is as follows: history of close contact with a confirmed COVID-19 patient (5 points); fever (3 points); age ≥ 44 years (1 point); male sex (1 point); maximum body temperature (defined as the highest body temperature from the onset of illness to the first hospital admission) ≥ 37 8º C (1 point); one or more significant respiratory symptoms, including cough, sputum, and shortness of breath (1 point); and neutrophil to lymphocyte ratio ≥ 5.8.6 The final score was calculated as the sum of the scores for each variable. In our study, patients were considered high risk if the score was ≥ 7.

Data on characteristics were presented in the form of frequency distribution tables. The statistical analysis was conducted using the SPSS version 22 program.Tests of differences between demographic and clinical characteristics were analyzed using the Chi-square test on categorical variables while numerical data that met the normality requirements of unpaired groups were subjected to the independent t test and numerical data that did not meet the normality requirements in unpaired groups were subjected to the Mann whitney test. Normality test was performed with Shapiro wilk test and the difference was declared significant if the test resulted in $p < 0.05$.

The diagnostic test of the EWS score as a predictor of SAR-CoV-2 PCR results was analyzed by determining the AUC value. The area under the curve (AUC) value was obtained by analyzing the receiver operating characteristic (ROC) curve followed by determining the cut-off point. The cut-off point of the EWS score was set at ≥ 7. Furthermore, sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

RESULTS

This study involved 199 subjects with clinical pneumonia. Based on the SARS-CoV-2 PCR results, 51 subjects (25.6%) had COVID-19 pneumonia and 148 subjects (74.7%) had non-COVID-19 pneumonia. There was no difference in mean age between the non-COVID-19 pneumonia and COVID-19 pneumonia groups (56.01±1.31 vs 57.49±1.98; p=0.661). The non-COVID-19 pneumonia group consisted of 77 males (52%) and 71 females (48%). The COVID-19 pneumonia group comprised 26 males (51%) and 8 females (49%). Statistical analysis obtained no difference in sex between the non- COVID-19 pneumonia and COVID-19 pneumonia groups (p=1.000).

The vital signs shown in Table 1 include systole, diastole, pulse, respiratory frequency and oxygen saturation. There were no significant differences between the non-COVID-19 pneumonia and COVID-19 pneumonia groups in systole blood pressure (132.37±2.25 vs 125.53±3.47; p=0.137), diastole blood pressure (80.31±1.46 vs 74.58±2.13; p=0.065), pulse frequency (95.88±1.64 vs 90.53±3.12; p=0.111), and oxygen saturation (97.01±0.18 vs 96.12±1.94; p=0.972). In term of respiratory frequency, there was a significant difference between the non-COVID-19 pneumonia group and the COVID-19 pneumonia group (22.79±0.35 vs 22.41±1.33; p=0.040).

Table 1 Characteristics of research subjects

Characteristics		Groups		Total	p- value
		Not COVID-19	COVID-19		
N		148 (74.7%)	51 (25.6%)	199 (100%)	-
Age (Mean±SD)		56.01±1.31	57.49±1.98	56.39±15.49	0.661
Sex					1.000
	Male	77 (52%)	26 (51%)	103 (51.8%)	-
	Female	71 (48%)	8 (49%)	96 (48.2%)	-
Vital Signs					
	Systole	132.37±2.25	125.53±3.47	130.61±26.80	0.137
	Diastole	80.31±1.46	74.58±2.13	78.84±17.32	0.065
	Pulse	95.88±1.64	90.53±3.12	94.51±20.65	0.111
	Breath frequency	22.79±0.35	22.41±1.33	22.70±6.03	0.040
	Saturation	97.01±0.18	96.12±1.94	97.45±7.25	0.972
Outcome					0.206
	Live	125 (84.5%)	39 (76.5%)	164 (82.4%)	-
	Died	23 (15.5%)	12 (23.5%)	35 (17.6%)	-

Description: Categorical data with a nominal scale is displayed using percentages, namely sex, smoking status, and outcome. Numerical data using mean and standard deviation were age, vital signs, and EWS score. Categorical data of unpaired groups were tested using Chi square test/Fisher exact test. Numerical data meeting the normality requirements of unpaired groups were subjected to the independent t test. Numerical data that did not meet the normality requirements in the unpaired groups were subjected to the Mann whitney test. Normality test was performed with Shapiro wilk test and the difference was declared significant if the test produced $p < 0.05$.

The outcome in non-COVID-19 pneumonia and COVID-19 pneumonia groups did not differ significantly. In the non-COVID-19 pneumonia group, 125 subjects (84.5%) lived and 23 subjects (15.5%) died. While in the COVID-19 pneumonia group, 39 subjects (76.5%) lived and 12 subjects (23.5%) died (Table 1).

Table 2 displays the mean COVID-19 EWS scores in COVID-19 and non-COVID-19 subjects. Subjects with positive SARS-CoV-2 had higher COVID-19 EWS score (8.45 ± 0.32) than that of those with negative SARS CoV-2 (4.61 ± 0.23) (p=0.000).

Table 2: The correlation between EWS score and swab PCR results

Variables	Total n = 199	SARS COV 2 PCR Result		p-value
		Negative COVID-19	COVID-19	
EWS score	5.59±3.12	4.61±0.23	8.45±0.32	0.000*

Description: *Numerical data that did not meet the normality requirements in unpaired groups were subjected to Mann whitney test.

Furthermore, we analysed the correlation of the Covid-19 outcomes with Covid-19 EWS score using cut off point of ≥ 10 in our subjects revealing that Covid-19 EWS score with the cut off point of ≥ 10 had significant correlation with SARS-CoV-2 PCR results and the outcomes (p=0.000 and p=0.011, respectively) (Table 3).

Table 3. Association of COVID 19 EWS at cut off ≥ 10 with outcome.

Characteristics		Score Covid-19 EWS		p- value
		≥ 10	< 10	
SARS-CoV-2 PCR				0.000
	Positive	18 (9%)	33 (16.6%)	
	Negative	9 (4.5%)	139 (69.8%)	
Outcome				0.011
	Not-survive	10 (5%)	25 (12.6%)	
	Survive	17 (8.5%)	147 (73.9%)	

Description: Categorical data of unpaired groups were tested using Chi square/Fisher exact test. It is declared significant if the test produces $p < 0.05$.

Figure 1 shows the receiver operating characteristic (ROC) curve analyzing the ability of EWS to predict SARS-CoV-2 PCR results. The area under curve (AUC) of EWS on SARS-CoV-2 PCR positive result was 0.895 (95% CI=0.811 - 0.919, p=0.000).

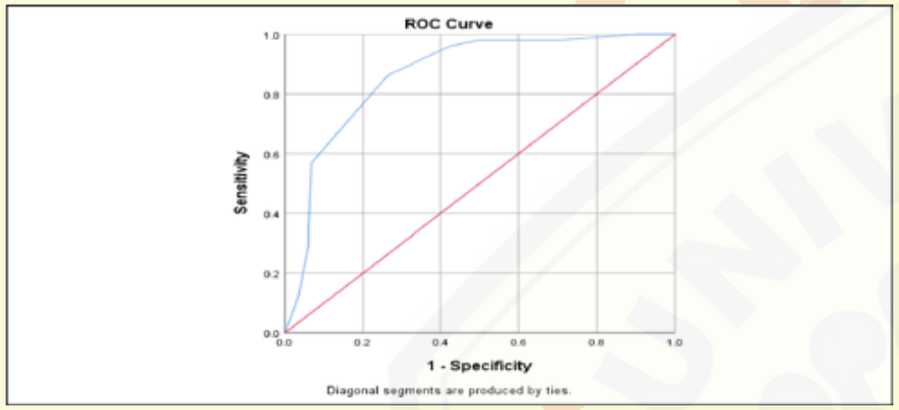

Figure 1. ROC curve of EWS score against SARS CoV 2 PCR result

We also compared our diagnostic value of EWS score with the cut off point ≥ 7 to the referenced cut off point of ≥ 10 in which the cut off point of ≥ 7 had a better diagnostic value than that of a cut off of ≥10. We obtained the sensitivity, specificity, PPV, and NPV of EWS score with the cut off point ≥ 7 and ≥ 10 of (86% vs 35%), (74% vs 94%), (53% vs 22%), and (94% vs 81%), respectively (Table 3).

Table 4. The diagnostic value of EWS over SARS-CoV 2 PCR

	Cut off	Sensitifitas	Spesifisitas	PPV	NPV
EWS COVID-19	≥ 7	86%	74%	53%	94%
	≥ 10	35%	94%	22%	81%

DISCUSSION

The COVID-19 Early Warning Score (EWS) is a clinical risk assessment system used to identify COVID-19 patients who are at high risk of complications and require intensive medical care. The system uses a score to assess the patient's condition based on several clinical parameters. In another context, the COVID-19 EWS can also be used as a predictor of SARS-CoV-2 PCR results. PCR swab testing is recognized as the most accurate method for diagnosing COVID-19 infection. However, there are limited resources for PCR testing, and there needs to be a strategy to prioritize patients to be tested wisely.[6]

COVID-19 EWS was initiated by Song CY et al., 2020. In the study by Song CY et al., 2020, EWS COVID-19 at a cut off ≥ 10 had a sensitivity of 0.932 and specificity of 0.874 as a predictor of SARS-CoV-2 PCR results.[6] In our study, the modified COVID-19 EWS without following CT scan assessment can be used as a predictor of SARS-CoV-2 PCR results at a cut off ≥ 7. COVID-19 EWS has a sensitivity of 86% and specificity of 74%. Another study using COVID-19 EWS was also conducted by Caldeira et al. in 2022 involving 924 patients, 19 of whom were SARS-CoV-2 positive. The mean EWS of non Covid-19 patients was 4.25 ± 3.44 while the EWS of COVID-19 positive individuals was 7.32 ± 4.69. Patients with EWS ≥ 10 were more likely to be infected than those with EWS < 10 (p = 0.021; 95% CI (1.35 - 10.95). The study reported that COVID-19 EWS had a sensitivity of 26.3% and a specificity of 91.5% as a predictor of PCR swab SARS-CoV-2.[7]

The use of the COVID-19 EWS helps identify patients detected as COVID-19 pneumonia and facilitates effective evaluation by medical personnel.[8] The implementation of a scoring system can promote proper allocation of health resources and improve patient safety.[9,10] The use of the COVID-19 EWS is easy, reliable, and quick to calculate, making it a valuable tool for triaging pneumonia patients with COVID- 19 upon hospital admission.[6]

CONCLUSIONS

Early warning score with the cut off point of ≥ 7 has good sensitivity and specificity in determining the diagnosis of COVID-19.

LITERATURE

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CORRELATION BETWEEN VOLATILE ORGANIC COMPOUNDS (VOC) WITH SERUM LEUKOTRIENEE B4 AND NEUTROPHIL IN COPD

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ABSTRACT

Background:

Chronic Obstructive Pulmonary Disease (COPD) is preventive and treatable disease with persistent respiratory symptoms caused by gas or toxic particle exposure.[1] Beside affecting lung, COPD also promote chronic systemic inflammation which contribute to extrapulmonar complications. Smoking is main risk factor of COPD.[2] According to WHO, 2.9 million people die due to COPD and it has been estimated that COPD become the third leading cause of death globally in 2030.[3]

Spirometry is still diagnostic standard for COPD, but it needs certain maneuvers and trained operator. In last few decades, the development of non invasive method for detecting lung disease has emerged, such as Volatile Organic Compounds (VOC) examination.[4] COPD is related to activation of macrophage, neutrophil, and CD8 T- lymphocyte in airway and lung parenchyma because of smoke and other toxic substances. This will stimulate production of cysteinyl leukotriene (LTB4, LTC4, LTD4, and LTE4) which can induce neutrophil recruitment, airway smooth muscle constriction, and mucus hypersecretion.[5]

This study aims to analyze the difference of VOC in exhaled breath of stable COPD and healthy subjects, furthermore the correlation of VOC between serum Leukotrienee B4 and neutrophil.

Material and Method:

A case-control study was conducted in Saiful Anwar Hospital recruiting 40 stable COPD patients and 40 healthy subjects that fulfill inclusion and exclusion criteria. Outpatient and inpatient were included in this study from period of March until October 2022. Exhaled breath sample was collected for VOC detection and venous blood sample for examining Leukotriene B4 and neutrophil. Breath sample was analyzed using an arrayed sensor breath analyzer to check the concentration of 13 VOC.

Inclusion criteria include: stable COPD patients, post ECOPD patients who were in stable condition, willing to join the study and sign informed consent form. Patients suffering from acute exacerbation symptoms of COPD were excluded. The criteria for control subjects include: subjects who were not diagnosed with COPD and spirometry test showed no obstructive pattern.

Result:

This study involved total of 80 subjects of which description can be seen at table 1.

Table 1. Sociodemographic characteristic of subjects

Characteristics		Control Subjects (n= 40)	COPD subjects (n= 40)
Gender	Male	22 (55%)	33 (82,5%)
	Female	18 (45%)	7 (17,5%)
Age	years old	31,35 (±3)	64,73 (±10,6)
Body Height	cm	164,9 (±9,0)	162,1 (±4,8)
Body Weight	kg	70,15 (±15,9)	52,4 (±8,7)
Body Mass Index (BMI)	kg/m^2	25,6 (±4,2)	19,9 (±2,9)
Smoking Status	No smoker	36 (90%)	0 (0%)
	Ex smoker	0	4 (10%)
	Passive smoker	2 (5%)	10 (25%)
	Active smoker	2 (5%)	26 (65%)
Symptoms	Dyspnea	0	27 (67,5%)
	Cough	0	23 (57,5%)
	Production of sputum	0	11 (27,5%)
	Chest pain	0	2 (5%)
Comorbid	Lung cancer	0	20 (50%)
	Lung TB	0	2 (5%)
	Asthma	6 (15%)	0

Some of blood and spirometry parameters were checked in this study. Blood parameters include leucocyte, neutrophil, and LTB4 level. Whereas, value of FEV1/FVC and FEV1 become parameters of spirometry included. Results of examination were shown in table 2.

Table 2. Laboratorium and spirometry result of subjects

Parameter		N	Mean	Std. Deviation	Minimum	Maximum	p value
Leucocyte	Control	40	7595,75	1876,9	3640	12570	0,002
	Case	40	9981,2	3800,3	4230	20630	
LTB4	Control	40	84,04	89,79	6,37	486,08	<0,001
	Case	40	244,1	186,9	28,79	546,78	
Neutrophil%	Control	40	63,03	9,099	43,1	78,9	<0,001
	Case	40	72,077	11,653	45,50	92,90	
Neutrophil Absolute	Control	40	4877,0	1730,5	2210	9920	0,001
	Case	40	7327,8	3576,1	2270	16630	
FEV1/FVC	Control	40	122,9	147,9	83,4	112,1	<0,001
	Case	40	62,06	8,08	41,1	69,8	
FEV1	Control	40	89,5	9,3	80,4	117,6	<0,001
	Case	40	46,08	9,9	20,9	66,1	

Note: significant if p value < 0,05; LTB4, Leukotriene B4; Neutrophil%, percentage of neutrophil; FEV1, *Forced Expiratory Volume 1 second*; FVC, *Forced Vital Capacity*

Breath analyzer was used to check the concentration of VOC. Thirteen VOC detected include CO2, C2H5OH, CH2O, C7H8, C3H6O, NH4, C6H14, NO2, CO, NH3, CH4, C6H6, and C3H8. Table 3 show the results of VOC.

Table 3. Level of VOC among subjects

Parameter		N	Mean	Std, Deviation	Minimum	Maximum	Nilai P
CO2	Control	40	2849,58	1076,51	400	4598	
	Case	40	1577,75	1052,70	400	4404	<0,001
C2H5OH	Control	40	1,4	0,32	0,8371	9,6526	
	Case	40	1,85	0,7	0,8798	9,2253	<0,001
CH2O	Control	40	0,08	0,02	0,0495	0,1350	
	Case	40	0,08	0,02	0,034	0,134	0,776
C7H8	Control	40	0,005	0,003	0,002	0,014	
	Case	40	0,005	0,003	0,001	0,013	0,776
C3H6O	Control	40	11,1	3,5	3,69	18,42	
	Case	40	4,8	2,4	0,351	14,647	<0,001
NH4	Control	40	1,41	1,46	0,0001	3,8486	
	Case	40	0,59	1,035	0,0001	3,5605	0,776
C6H14	Control	40	0,35	0,05	0,252	0,415	
	Case	40	0,29	0,09	0,006	0,405	0,776
NO2	Control	40	0,82	0,39	0,000	1,57	
	Case	40	0,06	0,15	0,0001	0,5725	<0,001
CO	Control	40	0,025	0,042	0,0001	0,1174	
	Case	40	0,60	0,24	0,0001	0,8368	<0,001
NH3	Control	40	0,0001	0,0000	0,0001	1,0000	
	Case	40	0,004	0,013	0,0001	0,0453	0,022
CH4	Control	40	0,08	0,02	0,0470	0,1088	
	Case	40	0,19	0,23	0,1029	0,9999	0,310
C6H6	Control	40	0,6	0,02	0,56	0,64	
	Case	40	0,6	0,05	0,53	0,72	<0,001
C3H8	Control	40	2,34	0,6	1,4770	3,6590	
	Case	40	3,2	1,2	1,6113	7,1166	0,001

Note: CO_2, Carbon dioxide; C_2H_5OH, Ethanol; CH_2O, Metanal; C_7H_8, Toluene; C_3H_6O, Acetone; NH_4, Ammonium; C_6H_{14}, Hexane; NO_2, Nitrogen dioxide; CO, Carbon monoxide; NH_3, Ammonia; CH_4, Methane; C_6H_6, Benzene; C_3H_8, Propane.

Among 8 VOC detected significant between COPD and healthy subjects, Spearman correlation test was done to determine the correlation with serum LTB4 and neutrophil. Analysis results were shown in table 4 and 5.

Table 4. Correlation between serum LTB4 and VOC

Correlation between variabel			P value	Correlation coefficient
Serum LTB4	with	CO2	0,155	0,229
	with	C2H5OH	0,009	0,410
	with	C3H6O	0,268	-0,180
	with	NO2	0,209	-0,203
	with	CO	0,353	-0,151
	with	NH3	0,227	-0,195
	with	C6H6	0,089	-0,273
	with	C3H8	0,137	0,239

Table 5. Correlation between serum neutrophil and VOC

Correlation between variabel			P value	Correlation coefficient
Serum Neutrophil	with	CO2	0,416	-0,132
	with	C2H5OH	0,882	0,024
	with	C3H6O	0,973	0,005
	with	NO2	0,343	-0,154
	with	CO	0,275	0,177
	with	NH3	0,129	0,244
	with	C6H6	0,438	0,126
	with	C3H8	0,686	-0,066

Discussion:

Patients with COPD are male in majority in this study (33 subjects). Prevalence of COPD in Indonesia is about 9.2 million people and more common in male.[6] Average age of COPD patients is 64.73 years old. Older age is related to decrease of mitochondrial function that stimulates oxidative stress. This is shown by increasing Reactive Oxygen Species (ROS) and lipid peroxidation.[7]

Subjects with COPD have lower average of IMT than control one. A retrospective study by Zhenchao et al., showed that IMT is positively correlated with lung function and negatively correlated with inflammation level and exacerbation degree. Overweight and obesity patients have better nutritional status and stronger respiratory muscles.[8] As many as 26 COPD subjects are active smoker and 10 others are passive smoker. This is related to pathogenesis of COPD where oxidative stress, protease imbalance, and inflammatory cells (macrophage and neutrophil) can cause lung inflammation, mucus hypersecretion, and airway remodeling.[9]

There is half of COPD subjects (50%) have lung cancer as comorbid. A review study demonstrate 40-70% of lung cancer patients show airway obstruction and indicative for COPD entity. While COPD increase 2 until 7 times fold risk of getting lung cancer. The same mechanism happen both in COPD and lung cancer is oxidative stress.[10]

Mean level of serum leucocyte is higher in case group. Neutrophil is involved in COPD pathogenesis and continuing infiltration in lung tissue is related to severity of COPD.[11] Also, serum LTB4 level is higher in COPD

in this study. Similar result was shown by Kazmierczak et al., that LTB4 level was higher in COPD subjects than in healthy subjects (1772,7 pg/mL vs 680,31 pg/mL).[2]

In this study, we can see that there is significant difference of 8 VOC (CO2, C2H5OH, C3H6O, NO2, CO, NH3, C6H6, and C3H8) between COPD and healthy group. Level of Carbon dioxide (CO2), acetone (C3H6O), and Nitrogen dioxide (NO2) are higher in control subjects. COPD patients have impairment of CO2 exhalation caused by increase of respiratory burden such as airway resistance and hyperinflation.[12] Aceto is common substance in exhaled breath from decarboxylation of lypolisis or amino acid degradation.[13] While sources of NO2 are from smoke, oven, and water heater. Besides, NO2 is surrounding air pollutant that can irritate human airway.[14]

The other 5 VOC are found higher in COPD group. Ethanol (C2H5OH) is product of carbohydrate and amino acid fermentation. It is found higher in active smoker than non smoker people.15 Benzene is also found higher in smoker's exhaled breath with specificity more than 90%. While propane (C3H8) is aldehyde contained in smoke.[13] Increase of exhaled Carbon monoxide (CO) is due to endogenously produced from the body and from lung inflammation process.[16] Ammonia (NH3) is resulted from urea hydrolysis in nitrogen cycle. Increasing level of ammonia also mean increasing of oxidative stress.[17] Ethanol is the only VOC correlated with serum LTB4 in this study ($p = 0.009$; $r = 0.41$), whereas there is no VOC correlated with neutrophil. Allers et al. show that exhaled level of ethanol is higher in smokers than in no smokers, though this result is not significant differs COPD with healthy subjects.[15] Theoretically, oxidative stress will cause accumulation of macrophage and neutrophil that increase ROS production. LTB4 is produced from arachidonic acid metabolism in lipid membrane. But exhaled breath VOC is produced from lipid peroxidation which is not related to arachinodic acid.[3]

Limitation in this study: environmental VOC surrounds location of sampling have not been checked first. Then, bias of this study can also be caused by absence of homogeneity between case and control group and lung cancer as comorbid.

Conclusion:

Level of several VOC in COPD patients differ from healthy subjects. Furthermore, VOC is also correlated with serum Leukotriene B4 in COPD, but there is no VOC detected correlated with serum neutrophil.

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CORRELATION OF PLATELET LYMPHOCYTE RATIO, ADVANCED LUNG CANCER INFLAMATION, AND SYSTEMIC IMMUNE INFLAMMATION INDEX WITH OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL IN LUNG ADENOCARCINOMA PATIENTS UNDERGOING PLATINUM-BASED FIRST LINE CHEMOTHERAPY

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ABSTRACT

Background: Lung cancer is the main cause of death from malignancy in both men and women. Adenocarcinoma is one of the most common types of lung cancer, accounting for half of lung cancer cases. Platelet-lymphocyte ratio (PLR), advanced lung cancer inflammation index (ALI), and systemic immune inflammation index (SII) are parameters that help evaluate lung cancer therapy through PFS and OS assessment. Until now, studies regarding PLR, ALI and SII to predict the prognosis of lung adenocarcinoma patients are still limited.

Methods: This cross-sectional study with retrospective approach aimed to determine the correlation of PLR, ALI and SII with PFS and OS in lung cancer patients. Subjects were lung adenocarcinoma patients with EGFR mutation who received platinum-based first-line therapy at Dr. Moewardi General Hospital between 1 July 2018 to 30 June 2021. Subjects were taken from medical record data with purposive sampling method.

Results: This study included 82 lung adenocarcinoma patients. PLR were correlated with PFS (HR=1.80; p=0.009), ALI with PFS (HR=2.32; P=<0.001) and SII with PFS (HR=2.41; p=<0.001). PLR were also correlated with OS (HR=1.78; p=0.011), ALI with OS (HR=2.23; p=0.025) and SII with OS (HR=2.81; p=<0.001).

Conclusion: Increased PLR, ALI and SII are associated with OS and PFS in lung adenocarcinoma lung patients. PLR, ALI and SII values can predict OS, while PLR and SII values can predict PFS.

Keywords: *PLR, ALI, SII, PFS, OS, lung adenocarcinoma*

BACKGROUND

Lung cancer is one of the highest morbidity and mortality cause worldwide, particularly in men. In United States, it was reported that approximately 2,2 million people suffered from lung cancer in 2020, with mortality rate reached 18%.[1] Incidence and mortality rate of lung cancer increased three to four times in developing country due to high number of smokers, such as Indonesia. Previous studies showed that middle- to low-income countries had higher pevalence of teenage smokers.[2] This also applies to Indonesia with 24,3% households were reported to have of at least one heavy smoker.[3]

Adenocarcinoma is one of the most common types of non-small cell lung cancer, accounting for half of all lung cancer cases. Adenocarcinoma had poor prognosis with average 5-year survival rate were 20.5%.[4] Early diagnosis may prevent progression of cancers to advanced stage. Inflammation and the immune system play a role in cancer development. Inflammatory parameters can predict survival and therapy outcome in cancer patients, such as platelet-lymphocyte ratio (PLR), advanced lung cancer inflammation

index (ALI), and systemic immune inflammation index (SII). C - reactive protein were found to be higher in advanced stage compared to early-stage lung cancer, while ALI <18 was an independent predictor for poor outcome in advanced lung cancer.[5,6] Other markers such as SII and PLR were also correlated with survival in lung cancers.[7,8] Studies regarding PLR, ALI and SII to predict the prognosis of lung adenocarcinoma patients are still limited. This study aimed to analyze inflammatory parameters PLR, ALI, and SII to evaluate lung cancer therapy through PFS and OS assessment.

METHOD

This cross-sectional study with retrospective approach aimed to determine the correlation of PLR, ALI and SII with PFS and OS in lung cancer patients. This study was conducted at Dr. Moewardi General Hospital, Surakarta, Indonesia during 1 July 2018 to 30 June 2021. Subjects were taken from medical record data with purposive sampling method. Clinical characteristics were obtained from medical records, whereas inflammatory parameters were obtained from laboratory results. Lung adenocarcinoma patients with EGFR mutation who received platinum-based first-line therapy were included in this study. Patients with incomplete medical record, had history of comorbidities such as autoimmune disorders, other malignancies, kidney disease, liver disease, and diabetes mellitus were excluded in this study. All statistical analysis was run in IBM Statistical Package for Social Sciences (SPSS) version 28. Comparison between groups was analyzed using T-test for normal distribution data and Mann-Whitney for abnormal distribution data. Receiver operating curve was done to determine the cut-off value for PLR, SII, and ALI, continued by survival analysis for OS and PFS using

Kaplan-Meier with log-rank test. Results were significant if p value is less than 0,05.

RESULT

This study included 82 lung adenocarcinoma patients who with positive EGFR mutations who received platinum-based first line chemotherapy. Basic characteristics of subjects can be seen in Table 1. Patients ranged from 18-78 years old with mean age 58.56 ±11.44 years old. Most of the subjects were male (73.2%). Mean BMI of subjects were still in normal range (19.35 ±3.11 kg/m2). According to tumor characteristics, most cancers were already in stage IV B (63.4%), followed by stage IV A (36.6%). The most common therapy given to the subjects was carboplatin-paclitaxel regimen (37.8%), while the least common was carboplatin-doxetacel (7.3%). Active smokers dominated subjects of this study (65.9%). Mean of PLR was 39.63±34.83 (4.62-168.26), SSI was 3135.40 ±3044.34 (179.20-13749.35), and ALI was 14.79±14.99 (2.61-120.65). Median for time-to- progression was 12 months, ranging from 2 to 39 months, whereas survival time was 19,5 months, ranging from 7 to 52 months.

Table 1. Characteristics of Lung Adenocarcinoma Patients

Variables	Frequency/mean ± SD	Percentage/min-max
Age (mean±SD)	58.56±11.44	18.00-78.00
Sex (n, %)		
Male	60	73.2%
Female	22	26.8%
BMI (kg/m^2)	19.35±3.11	14.30-30.14
Stage (n, %)		
IV A	30	36.6%
IV B	52	63.4%
Therapy (n, %)		
Carboplatin-Doxetacel	6	7.3%
Carboplatin-Paclitaxel	31	37.8%
Cisplatin-Docetaxel	20	24.4%
Cisplatin-Paclitaxel	25	30.5%
Smoking status (n, %)		
Non-smoker	23	28.0%
Smoker	54	65.9%
Passive smoker	5	6.1%
Laboratory value (mean±SD)		
PLR	39.63±34.83	4.62 - 168.26
SII	3135.40 ±3044.34	179.20 - 13749.35
ALI	14.79±14.99	2.61-120.65
Time to progression (median)	12.00	2.00-39.00
Survival time (median)	19.50	7.00 – 52.00

Subjects were divided into two groups according to PFS cut-off on 12 months and OS cut-off on 20 months, based on median value of PFS and OS (Table 2 and 3). Mann-Whitney test was used because data distribution was abnormal. Both PLR (54.10 ±42.71 vs 25.85 ±16.21; p<0.001) and SII (4512.60 ±3734.10 vs 1823.78 ±1197.46; p<0.001) were significantly higher in shorter PFS group compared to longer PFS group. ALI was significantly lower in shorter PFS compared to longer PFS (8.26±6.57 vs 21.02±17.93; p<0.001). Similar results were also observed in OS groups with cut-off of 20 months (Table 3). Platelet-to-lymphocyte ratio (56.09 ±41.69 vs 23.17 ±12.79; p<0.001) and SII (4732.05±3571.38 vs 1538.75±887.03; p<0.001) were significantly higher in shorter OS compared to longer OS. ALI was also significantly lower in shorter OS compared to longer PFS (7.72±3.98 vs 21.02±21.87±18.35; p<0.001)

Table 2. Comparison of PLR, SII, and ALI according to PFS

Variables	Time-to-progress <12 months	Time-to-progress >12 months	p-value
PLR	54.10 ±42.71	25.85 ±16.21	<0.001*
SII	4512.60 ±3734.10	1823.78 ±1197.46	<0.001*
ALI	8.26±6.57	21.02±17.93	<0.001*

***) p<0.05 significant value**

Table 3. Comparison of PLR, SII, and ALI according to OS

Variables	Survival time <20 months	Survival >20 months	p-value
PLR	56.09 ±41.69	23.17 ±12.79	<0.001*
SII	4732.05 ±3571.38	1538.75 ±887.03	<0.001*
ALI	7.72±3.98	21.87±18.35	<0.001*

***) p<0.05 significant value**

Cut-off for PLR, SII, and ALI based on survival time were analyzed using receiving operator characteristics (ROC) curve. We found that cut-off for PLR was 26.76 (AUC= 0.816) with sensitivity 78.0% and specificity 70.7%, cut-off for SII was 2163.34 (AUC=0.879) with sensitivity 85.4% and specificity 82.9%. For ALI, cut-off value was 10.60 (AUC= 0.898) with sensitivity 80.5% and specificity 82.9%.

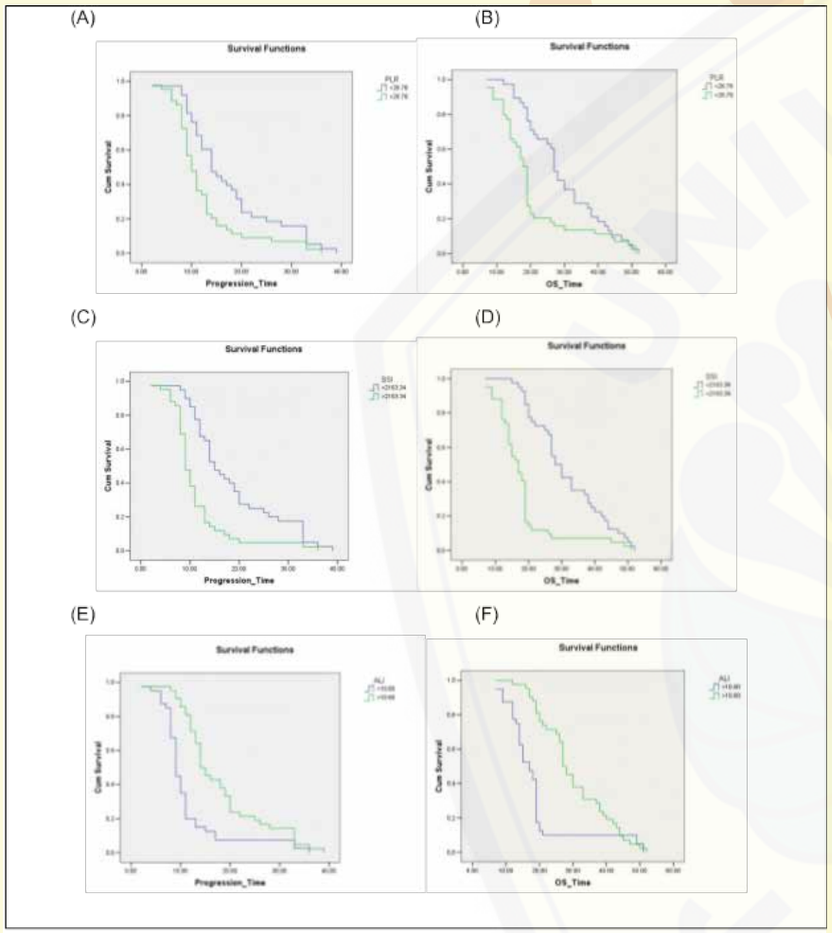

Figure 1. Kaplan-Meier curves. (A) PFS curve based on PLR, (B) OS curve based on PLR, (C) PFS curve based on SII, (D) OS curve based on SII, (E) PFS curve based on ALI, (F) OS curve based on ALI

After we determined the cut-off value for each parameter, we evaluated Kaplam-Meier curve for PFS and OS in lung adenocarcinoma patients receiving platinum-based first line chemotherapy (Figure 1). PLR >26.76 showed shorter time-to-progression and survival time compared to PLR <26.76 (PFS= 10 vs 14 months; OS= 18 vs 27 months) (Figure 1A and 1B). SII >2163.34 also showed shorter time-to-progression and survival time compared to SII<2163.34 (PFS= 9 vs 15 months; OS= 17 vs 28 months) (Figure 1C and 1D), while ALI <10.60 showed shorter time-to-progression and survival time compared to ALI>10.60 (PFS= 9 vs 14 months; OS= 17 vs 27 months).

Cox-regression analysis was done to find the correlation between PLR, SII, ALI, with PFS and OS. We found that PLR was significantly correlated with PFS (HR=1.80; p=0.009), ALI with PFS (HR=2.32; P=<0.001) and SII with PFS (HR=2.41; p=<0.001). In OS analysis, PLR were also correlated with OS (HR=1.78; p=0.011), ALI with OS (HR=2.23; p=0.025) and SII with OS (HR=2.81; p=<0.001) (Table 5).

Table 4. Correlation between PLR, SII, ALI, and PFS

Variables	Progression-Free Survival			
	Bivariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
PLR >26.76	1.80 (1.16- 2.81)	0.009*	0.70 (0.29-1.66)	0.415
SSI>2163.34	2.41 (1.53- 3.78)	<0.001*	3.28 (1.36-7.89)	0.008*
ALI <10.60	2.32 (1.48-3.64)	<0.001*	1.62 (0.94-2.77)	0.082

*) p<0.05 significant value

Table 5. Correlation between PLR, SII, ALI, and OS

Variables	Overall Survival			
	Bivariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
PLR >26.76	1.78 (1.14-2.79)	0.011*	0.53 (0.22-1.26)	0.151
SSI>2163.34	2.81 (1.78-4.44)	<0.001*	4.83 (1.99-11.74)	0.001*
ALI <10.60	2.20 (1.39-3.49)	0.001*	2.23 (1.11-4.52)	0.025*

*) p<0.05 significant value

DISCUSSION

This study utilized PLR, SII, and ALI obtained from routine blood test to predict PFS and OS in lung adenocarcinoma patients who received platinum-based first-line chemotherapy. Most subjects in this study were male with mean age 58,56 years old, ranged from 18 to 78 years old. The mean age in our study was relatively younger compared to the global peak incidence of lung cancer in 65-84 years old.1 Younger male in Indonesia showed greater smoking habit than other countries, which may contribute to increased risk of lung cancer.9 This theory is further supported by higher mortality and morbidity for lung cancer in men compared to women. Lung cancer in men was found to be twice at risk for incidence and death due to lung cancer than women.10

Mean body mass index of 19,35 kg/m2 was observed in our study, which is in normal category. However, range of BMI in our study were heterogenous from 14.30 to 30.14 kg/m2. Body mass index can be used as nutritional and prognostic assesment. Abnormal BMI, both malnutrition (<18 kg/m2) and obesity (>25 kg/m2), were associated with poor OS. Production of leptin decreased in obese patients which caused low-grade inflammation and decreased T-cell response. Cachexia is one of the frequent symptoms found in lung cancer. Cancer cells can expand energy for metabolism, resulting in malnutrition.11

This study consisted of 63.4% stage IV B patients and 36.6% stage IV A patients. Advanced lung adenocarcinoma patients were chosen for this study to minimize confounding factors. Most of the patients in this study received carboplatin-paclitaxel regimen for first-line chemotherapy (37.8%). Patients received first-line platinum and taxan chometherapy class in accordance to the national guidelines therapy for lung

cancer, which stated combination of cisplatin or carboplatin with new generation chemotherapy (etoposide, gemcitabine, paclitaxel, docetaxel, vinorelbine, or pemetrexed) for NSCLC stage IV.12

Most lung adenocarcinoma patients in this study were active smokers (65.9%). Tobacco smoke can induce alteration of gene expression in respiratory tract epithelium. Continous exposure can change cell structure and morphology from hyperplasia, squamous metaplasia, dysplasia, and carcinoma in situ (CIS). Carcinoma in situ is a precursor to tumor cells which can lead to lung malignancies with various molecular subtypes.13 Mean PLR value in this study was 39.63±34.83. Mean PLR levels in this study were lower

than previous research on lung adenocarcinoma which reported mean PLR value 324.30±166.80. However, that study analyzed adenocarcinoma from all stages, unlike this study which only analyzed advanced adenocarcinoma.14 Mean SII value was 3135.40±3044.34, higher than previous study of lung adenocarcinoma patients which reported mean SII 2162.55 ± 1555.69.15 Mean ALI value in our study was 14.79±14.99. ALI <18 were correlated with poor outcome in lung cancer.16 PFS median was 12 months (2-39 months) and OS median was 19.5 months (7-52 months). Average OS was longer than prior study which reported OS of 24.60±8.56 months in lung adenocarcinoma, whereas PFS value of 11.68±8.47 was comparable to our study. but that study included patients who received chemotherapy and radiation.15 Progression-free-survival <12 months and overall survival < 20 months were correlated significantly to higher PLR, SII, and lower ALI. Our findings were in line with previous study on stage IV NSCLC patients which stated that high PLR, high SII, and low ALI were associated with worse

PFS and OS.16,17 Parameters in this study represent inflammation status in patients. Blood tests in lung adenocarcinoma patients may show thrombocytosis, neutrophilia, and lymphocytopenia. Tumor cells produce proinflammatory cytokines and granulocyte-colony stimulating factor (G-CSF) which further stimulates neutrophil expression. This process caused increased neutrophil extracellular traps (NET), which in turn activate vascular endothelial growth factor (VEGF) to promote angiogenesis. Neutrophils together with macrophages and dendritic cells, can produce myeloid-derived suppressor cells (MDSC) that supress T-cells proliferation and activation, which resulted in lymphopenia. Increased platelet level is linked to hypercoagulability due to production of VEGF and platelet-derived growth factor (PDGF) that stimulate angiogenesis, therefore thrombocytosis is associated with poor outcome in lung cancers. Inflammatory parameters such as PLR, SII, and ALI integrated platelet, neutrophil, and lymphocyte activities, thus may benefit as prognostic evaluation in advanced lung adenocarcinoma.18

Using cut-off value from ROC analysis, PLR >26.76, SII >2163.34, and ALI <10.60 were also correlated significantly to PFS and OS. However, after multivariate analysis, only SII >2163.34 was an independent predictor for PFS, while SII >2163.34 and ALI <10.60 were an independent predictor for OS. Another study found different cut-off, for example SII ≥1767.0 associated with shorter OS (18 months vs 28 months, p= 0.014) and PFS (7 months vs 12 months, p=0.004) significantly. The same study also analyzed PLR with higher cut-off than our study and found PLR <356.94 had shorter survival time compared to PLR ≥356.94, yet it was also not found to be correlated significantly with OS and PFS. A study by Hu et al. used higher cut-off for ALI than our study and reported that ALI<48.2 displayed poorer survival rates in NSCLC patients.15,19 Our study showed that SII and ALI may be superior than PLR only in predicting OS and PFS, this may be due to various inflammation process in lung adenocarcinoma were more represented in SII (platelet, lymphocyte, and neutrophil) and ALI (BMI, albumin, and NLR). However, further research is still needed regarding inflammatory parameters as prognosis predictors for lung cancers.

This study had several limitations. First, this study was conducted only in single tertiary hospital, therefore sample size may be limited and causing bias in this study. Second, we did not account confounding factors that may affect relationship between inflammatory parameters and survival in this study, for example sociocultural characteristics and therapy compliance. Lastly, we only analyzed stage IV lung adenocarcinoma patients. Further research with bigger sample size, confounding factors, and other stages is needed in the future.

CONCLUSION

Increased PLR, ALI and SII are associated with OS and PFS in lung adenocarcinoma lung patients. PLR, ALI and SII values can predict OS, while PLR and SII values can predict PFS.

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EVALUATION OF ANTIBIOTIC USE BASED ON THE GYSSENS METHOD AND ITS RELATIONSHIP WITH PATIENT OUTCOMES IN COVID-19 INTENSIVE CARE UNIT

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ABSTRACT

BACKGROUND: COVID-19 with its Delta variant has shown increased incidence mostly for severe to critically-ill clinical severity. This condition leads to increasing antibiotic administration while bacterial infection is hard to prove. Excessive antibiotics could lead to antibiotic resistance. This study aims to find out the rationality of antibiotics used by the Gyssens method in COVID-19 and its association with outcomes.

MATERIAL AND METHOD: A cross-sectional study with a retrospective approach of 139 COVID-19 patients at the COVID-19 high-care and intensive-care unit of Dr. M Djamil Hospital from January 2021 to December 2021. Data were analyzed using Chi-Square, and outcomes were the relationship between the rationality of antibiotics use and outcome.

RESULT: We found a total of 139 patients. Most of the patients were male 58,99%), in a group of 60-69 years old group (36,69%) and high mortality rate (71,94%). Levofloxacin was the most used antibiotic and rational use was higher compared to irrational use (52,58% vs 47,41%). The irrationality mostly caused its toxicity to the kidney. The second most used was meropenem which had a rate of rational use lower than irrational use (48,10% vs 51,89%) The use of antibiotics in ICU was mostly rational (76,02%). The irrational use of antibiotics is mostly in category IV (8.76%). There was no association between the rationality of antibiotic use and mortality.

CONCLUSION: The majority of antibiotics used in the ICU of Dr. M Djamil Hospital during the variant delta pandemic were rational, however, there was no association between rationality and mortality of COVID-19 patients.

KEYWORD: *antibiotics, rationality, gyssens method, COVID-19, outcome*

Background

COVID-19 with its Delta variant shows an increased incidence mostly for severe to critically ill clinical severity.[1] This condition has led to increased administration of antibiotics while bacterial infection is difficult to prove. Antibiotic administration is carried out if there is a septic condition and it is stated that the appropriate empiric antibiotic administration is within 1 hour of identifying sepsis in COVID-19 patients.[2] Empiric antibiotics should be based on clinical diagnosis, local epidemiology, and data strongly suspected of being due to secondary bacterial infection.[2] Conditions in the field are often not in accordance with the guidelines that have been issued, and there is still irrational use of antibiotics, especially during COVID-19. Research by Lau and colleagues (et al) in 2022 stated that as many as 86.8% of COVID-19 patients treated in the ICU were prescribed carbapenems in empirical therapy.[3] Since early 2020, this situation has

expanded globally and may have supported the evolution of microorganisms. which are highly immune, which may play an important role in worsening the condition of some patients, particularly those in the ICU.[4] Excessive antibiotics can cause antibiotic

Material and Methods

A cross-sectional study with a retrospective approach of 139 COVID-19 patients in the COVID-19 intensive care and intensive care unit of Dr. M Djamil from January 2021 to December 2021. inclusion criteria All confirmed COVID-19 patients in the COVID- 19 intensive care unit at RSUP Dr. M. Djamil Padang from January 1 to December 31 2021 with complete medical record data including demographic data given antibiotics. Age ≥ 18 years. Exclusion Criteria. Patients hospitalized for less than < 72 hours. Data were analyzed using Chi- Square, the outcome is the relationship between the rationality of the use of antibiotics and the results

Result

This research was conducted in the COVID-19 Intensive Room at RSUP DR. M Djamil Padang. Data collection was carried out cross-sectionally with a retrospective approach and obtained the number of confirmed COVID-19 patients who met the study criteria as many as 139 subjects with a total of 342 antibiotic use.

Table 1. Characteristics of Study Subject Receiving Antibiotics in the Intensive Care Unit for COVID-19

Characteristic	f(%) n = 139
Age	
18-49	22 (15,82)
50-59	30 (21,58)
60-69	51 (36,70)
≥ 70	36 (25,90)
Gender	
Male	82 (58,90)
Clinical Severity	
Severe	38 (27,30)
Critical	101 (72,70)
Comorbidity	
No comorbidity	21 (15,10)
1 comorbidity	73 (52,50)
> 1 comorbidity	45 (32,40)
Secondary Infection	
Septic shock/ septis	69 (49,60)
Community Acquired Pneumonia (CAP)	54 (38,80)

Table 1. shows that of the 139 COVID-19 patients in this study, most had the characteristics of the age category 60-69 years (36.70%), male sex (58.90%), clinically critical (72.70%), had 1 comorbid (52.50%) septic shock/sepsis (49.60%) and end of hospitalization status died (71.90%).

Table 2. Frequency Distribution of Demographic Characteristic Based on the Gyssens Method

Characteristic	Irrational f(%)	Rational f(%)	p-value
Age			0,692
18-49	12 (54,55)	10 (45,45)	
50-59	16 (53,30)	14 (46,70)	
60-69	23 (45,10)	28 (54,90)	
≥ 70	15 (41,70)	21 (58,30)	
Gender			0,218
Man	43 (52,40)	39 (47,60)	
Clinical Severity			0,177
Severe	14 (36,80)	24 (63,20)	
Critical	52 (51,50)	49 (48,50)	
Comorbidity			0,895
No comorbidity	9 (42,90)	12 (57,10)	
1 comorbidity	31 (47,90)	42 (52,10)	
>1 comorbidity	22 (48,90)	23 (51,10)	

Table 2. shows that of the 139 COVID-19 patients in this study, the most irrational use of antibiotics based on the Gyssens method was at the age of 18 - 49 years (54.55%), male sex (52.40%), clinical degree critical (51.50%) and have more than one comorbid (48.90%). Based on the results of statistical tests, it was found that there was no relationship between age, sex, clinical degree, and co-morbidities with the rationality of using antibiotics according to the Gyssens method in the intensive care unit for COVID-19 (p> 0.05).

Table 3. Frequency Distribution of Rationality in Antibiotic Use based on the Gyssens Method in the Intensive Care Unit for COVID-19

Antibiotic	n = 342	Irrational f(%)	Rational f(%)
Levofloxacin	116	55 (47,40)	61 (52,60)
Meropenem	79	41 (51,90)	38 (48,10)
Azithromycin	30	21 (70)	9 (30)
Cefepime	18	8 (44,40)	10 (55,60)
Amikacin	32	16 (50)	16 (50)
Ampicillin - Sulbactam	14	6 (42,90)	8 (57,10)
Cefoperazone - Sulbactam	12	6 (50)	6 (50)
Ceftriaxone	14	10 (71,40)	4 (28,60)
Vancomycin	8	4 (50)	4 (50)
Metronidazole	3	2 (66,70)	1 (33,30)
Moxifloxacin	1	0	1 (100)
Piperecillin sulbcctam	9	5 (55,60)	4 (44,40)
Tigecyclin	6	4 (66,70)	2 (33,30)

Table 3. shows that there were 13 types of antibiotics with a total of 342 used in this study. Based on the rational (Category 0) and irrational (Cateogri I - VI) categories of antibiotics, the most widely used antibiotics were rational Levofloxacin 61 (52.60%) and 55 (47.40%) irrational, Meropenem rational 38 (48.10) %) and irrational 41(51.90%).

Table 4. Frequency Distribution Gyssens Categories	
Category	**f (%) n = 342**
Category Irrational	
Category VI	
Without a diagnosis	1 (0,30)
Category V	
No documented diagnosis of infection in medical records, clinical signs of infection and supportive infection evidence	8 (2,33)
Category IV	
Choosing les effective antibiotis (base don guidelines)	8 (2,33)
Choosing more toxic antibiotics when les toxic alternatives are available	21 (6,14)
Choosing more expensive antibiotic tihin the same class	1 (0,30)
Category III	
Allergy	2 (0,58)
Severe clinical condition	7 (2,04)
Death	12 (3,50)
Category II	
Incorrect antibiotic dosage	12 (3,50)
Incorrect adminis- tration Interval	4 (1,16)
Incorrect route of administration	1 (0,30)
Category I	
Inappropriate timing of antibiotic administration (prophylaxis)	5 (1,50)
Category Rational	
Category **0**	
Appropriate antibiotic administration	260 (76,02)

Table 4. shows that out of 139 patients in this study, a total of 342 categories (0 - VI) of antibiotic use were identified. Among the 342 instances of antibiotic use, the most frequent Gyssens category was category 0, classified as rational (76.02%), followed by the irrational categories of category IV (8.77%), category III (6.12%), and category V (2.33%). These findings indicate that the most common type of irrational antibiotic use was category IV, which involved the selection of more toxic antibiotics (6.14%).

Table 5. The Relationship between Rationality of Antibiotic Use Based on Gyssens Method and Treatment Outcome in COVID-19 Patinets in the Intensive Care Unit of RSUP Dr. M Djamil Padang

Use of Antibiotic	Survival status		Total f (%)	OR (95% CI)	p-value
	Survive f (%)	Death f (%)			
Rational	22 (30,1)	51 (69,90)	73 (100,0)	1,24 (0,59-2,62)	0,700
Irrational	17 (25,80)	49 (74,20)	66 (100,0)		
Total	39(28,05)	100(71,94)	139 (100,0)		

Table 5. shows that of the 139 COVID-19 patients who died more due to irrational use of antibiotics (74.20%) than rational (69.90%). Based on the results of the statistical test using Chi-square, it was found that there was no significant relationship between the rationality of using antibiotics based on the Gyssens method and the end- of-hospital status of COVID-19 patients in the intensive care unit at RSUP Dr. M Djamil Padang (p=0.700, p>0.05)

DISCUSSION

This study revealed that the majority of ICU patients were in the age range of 60- 69 years (36.70%) and were male (58.90%). T Bardi et al. in Spain reported similar findings, with an average age of ICU patients being 61 (57-67) years and a male phenomenon. Abnormal ciliary function and structural abnormalities can also impede the clearance of SARS-CoV-2 viral particles in elderly patients.[10]

This study found that the majority of COVID-19 ICU patients had a critical clinical status (72.70%). Gong J's study in Shanghai reported that the most common clinical statuses among COVID-19 patients were severe (34%) and critical (32%).[11] Goethem compared Delta and Omicron variant COVID-19 patients and reported higher proportions of severe and critical clinical statuses (31.8% vs. 15.7%), ICU admission rates (20.9% vs. 7.0%) mortality (17.6 vs.11.6%) in Delta variant patients.[12] Goethem suggested that these differences in outcomes were influenced by the uneven distribution of vaccination during the Delta variant period, leading to a higher number of COVID-19 patients with severe and critical clinical status.[12]

This study found that the majority of patients with COVID-19 had one comorbidity (52.50%), with hypertension being the most common type of comorbidity (46.80%). Similar findings were reported by Bordallo et al. in Brazil in 2020, where the majority of COVID-19 patients had one comorbidity (57%), with hypertension (46.7%) and diabetes mellitus (46.0%) being the most prevalent comorbidities.[13] Patients with hypertension have endothelial dysfunction and immunometabolism changes that contribute to increased serum inflammatory cytokines.[14] The mortality rate for COVID-19 patients without comorbidities is 3%, while it is 8% for patients with one comorbidity, and it increases to 27% for patients with more than one comorbidity.[14]

This study found that COVID-19 patients in the intensive care unit (ICU) experienced sepsis/septic shock in 49.60% of cases. A meta-analysis by Macintriye CR showed that only 7% of COVID-19 patients had secondary bacterial infections, which increased to 14% among patients treated in the ICU.9,15 Abumayyaleh et al. in Brazil reported an 11% incidence of sepsis in elderly COVID-19 patients with comorbidities, and sepsis in COVID-19 patients was associated with high mortality (55.5%).[16]

This study found that the majority of patients had a final treatment outcome of death (71.90%). A meta-analysis by Zhou et al. reported a mortality rate of 78% for COVID-19 patients in the ICU.[17]

This study found that the highest proportion of irrational antibiotic use based on the Gyssens method was observed in patients aged 18-49 years (54.55%) and 50-59 years (53.33%). Liu et al. in China reported that 53.5% of patients aged 50-69 years received antibiotic treatment without evidence of bacterial infection.[18] Liu et al. found that the mean age of COVID-19 patients with secondary bacterial infections was 65 years, while patients without evidence of secondary infection had a mean age of 58 years.[18] Taxifulati et al. conducted a study from 2015 to 2018 and found that antibiotics were most frequently prescribed in patients under 60 years old, indicating that the trend of younger age groups being more vulnerable to irrational antibiotic prescribing had already existed before the COVID-19 pandemic.[19]

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This study found that irrational antibiotic prescribing was more prevalent in males (52.40%). Kamara et al. in 2022 reported that male patients accounted for 50% of those receiving antibiotic prescriptions for COVID-19.20 In contrast, Martin et al. in 2023 reported different results, stating that females had the highest proportion of inappropriate antibiotic prescribing for COVID-19 patients (69%).[21]

These findings suggest that gender does not have a significant impact on irrational antibiotic prescribing. This study found that irrational antibiotic use was more common in patients with critical clinical conditions (51.50%). Lau et al. in 2022 reported that carbapenems were empirically prescribed in 86.8% of COVID-19 patients in the ICU with critical clinical conditions.[3] Liu et al. in 2021 stated that the administration of penicillin and meropenem in patients without evidence of bacterial infection increased the mortality rate and the occurrence of acute organ injury. Therefore, the study recommended that antibiotic therapy should only be used in patients with confirmed bacterial infection or supporting positive microbiological results.[18]

Calderon-Parra et al. in 2021 also highlighted the risks associated with inappropriate antibiotic use in COVID-19 patients, such as severe adverse effects like acute kidney injury, diarrhea, and candidiasis, which can worsen patient conditions. Furthermore, the improper use of antibiotics can lead to antibiotic resistance, making infection control more challenging during patient treatment, and contributing to critical conditions in COVID-19 patients.[22]

This study found that among patients with irrational antibiotic use, the majority had more than one comorbidity (48.90%). The administration of irrational antibiotics in patients with multiple comorbidities may aim to prevent secondary bacterial infections during treatment, as these patients are at higher risk due to compromised immunity. The inappropriate prescription of antibiotics contributes to the increasing rate of inappropriate antibiotic use.

This study showed that out of 342 antibiotic prescriptions, the most commonly used antibiotics were levofloxacin (33.91%) and meropenem (23.09%). Levofloxacin, a fluoroquinolone respiratory agent, was predominantly used in the rational group (52.60%) as it is one of the empirical therapy options for bacterial pneumonia based on the Hospital Antibiotic Policy. Similar findings were reported by Yusuf M in Kupang, where levofloxacin was the most frequently used antibiotic (48%).[23]

Masyirifah's study reported that levofloxacin (31.53%) was the most commonly used antibiotic due to its empirical therapy for respiratory bacterial infections. Masyirifah also reported that in the irrational group, levofloxacin was the most commonly used antibiotic (47.40%), primarily due to its administration in patients with comorbidities such as renal failure, where it was not replaced with another respiratory fluoroquinolone (moxifloxacin) (Category IV) or appropriate dose adjustment was not performed (Category II).[24]

The results of this study revealed that in the rational group, the most frequently used antibiotic was meropenem (48.10%) as it served as definitive therapy according to culture results. In contrast, meropenem use was also high in the irrational group (51.89%), which was attributed to its selection as an escalation antibiotic in patients who experienced clinical deterioration without supporting evidence of sensitivity to meropenem (Category IV).24 Masyirifah's study reported the use of meropenem in the rational group (12.44%) and irrational group (6.63%).[24]

The results of this study obtained a total of 342 Gyssens categories from 139 patients. The most common irrational category was Category IV, where clinicians chose more toxic antibiotics when less toxic alternatives were available (6.14%). This was observed in patients with comorbid kidney disease who have still been prescribed levofloxacin, while non- nephrotoxic antibiotics without the need for dose adjustment (such as moxifloxacin) were available. The study also found instances of levofloxacin being prescribed without dose adjustment in patients with kidney disease. Category IV was also identified in patients who did not receive definitive antibiotics according to culture results (2.33%). A similar study by Masyirifah at RSUP Fatmawati Jakarta reported Category IV (3.63%) where patients did not receive definitive therapy according to culture results.[24] Masyirifah concluded that the prescribing of antibiotics was not in line with culture results because most sepsis or septic shock patients had cultures that were resistant to all available antibiotics, leading doctors to choose antibiotics with the lowest resistance. The inappropriate use of antibiotics based on culture results could be attributed to the unavailability of specific antibiotics, which contributed to the high frequency of Category IV. Category III was identified due to the administration of antibiotics for a duration that was too short (<48 hours) (3.50%), primarily in patients who died. One limitation of the Gyssens method is its inability to assess the rationality of combined antibiotic therapy. Similar to the findings of Masyirifah, patients receiving irrational Category III antibiotics were those who received empirical antibiotics for one day or less (<48-72 hours) (20.0%), often due to the worsening condition of sepsis or septic shock, leading to patient mortality.[24]

Category III was also identified in cases where antibiotics were administered for an excessively long duration (>14 days) (2.04%), primarily due to the severity of the patient's conditions, which did not improve, and the delay in obtaining culture results from difficult-to-obtain sputum samples. Masyirifah's study also reported that the reasons for the inappropriate duration of antibiotic treatment were lack of improvement, mortality, and allergies (23.63%). Category II, involving inappropriate antibiotic dosing, was observed in 3.50% of cases. In this study, levofloxacin was prescribed empirically without dose adjustment in patients with chronic kidney disease. The study also identified Category II in cases where the interval of antibiotic use was inappropriate (1.16%). Four patients with kidney failure who received Levofloxacin had their dosing interval adjusted to 48 hours but continued to receive it every 24 hours. Masyirifah's study found a significant association between the interval and duration of antibiotic use and the quality of antibiotic use (p=0.012).24 Category II, involving an inappropriate route of administration, was observed in one patient (0.30%) due to the administration of meropenem as a bolus instead of a drip, as indicated for sepsis. Category II (4.95%). This study found that in Category I, inappropriate timing of prophylactic antibiotic administration was observed in 1.50% of cases, affecting five patients. Guidelines for prophylactic antibiotic administration, according to PPAB, recommend administering the antibiotics before surgery, 30-60 minutes before incision, ensuring effective antibiotic levels

in the target surgical tissue at the time of incision. The study's findings revealed Category 0, indicating rational antibiotic administration, accounted for 76.02% of cases. A similar study by Yusuf reported a rational antibiotic administration rate of 78.74%.23 Another study by Masyirifah showed that 54 patients (49.09%) received rational antibiotic therapy. A different study conducted by Adani S found that the proportion of rational antibiotic use was lower (35%) compared to irrational antibiotic use (65%).[24]

The results of this study found a relationship between rationality in antibiotic use based on the Gyssens method and treatment outcomes in COVID-19 patients in the intensive care unit of Dr. M Djamil Padang General Hospital. Subjects in the irrational group had a higher mortality rate (74.20%) compared to the rational group (69.90%). However, statistical analysis using the chi-square test did not find a significant

relationship between rationality in antibiotic use based on the Gyssens method and treatment outcomes in COVID-19 patients in the intensive care unit of Dr. M Djamil Padang General Hospital (p=0.700, p>0.05). A similar study by Masyirifah at Fatmawati General Hospital also reported no relationship between rational and irrational antibiotic use and mortality.[24]

A different study conducted by Dewi R at Dharmais Cancer Hospital showed that inappropriate antibiotic dosing, septic shock diagnosis, and the presence of two or more comorbidities could increase mortality in patients with sepsis.[25]

Zhang J's meta-analysis study also indicated that comorbidities such as hypertension, diabetes, and cardiovascular disease increased the risk of severe clinical COVID-19, ICU admission, and overall poor outcomes in patients of all age groups.[26] Two studies from Zhang J's meta-analysis reported that obesity, defined as a Body Mass Index (BMI) ≥ 30 kg/m2, was associated with higher mortality in COVID-19 patients.[26] Factors influencing mortality in COVID-19 patients in the severe and critical clinical stages included severe symptoms such as respiratory distress, sepsis, and Acute Respiratory Distress Syndrome (ARDS), which result from increased production of immune cells and inflammatory cytokines, especially IL-6. Excessive inflammatory mediators lead to lung damage and dysfunction due to inflammation.[11]

Based on the literature study, it can be concluded that there is no significant relationship between irrational antibiotic use and mortality outcomes in COVID-19 patients. This study has limitations, including the inability to assess combination antibiotic therapy and confounding factors influencing mortality in COVID-19 patients

CONCLUSION

This study focused on COVID-19 patients and found that the majority were males aged 60-69 with critical clinical severity and one comorbidity. Levofloxacin and meropenem were the most commonly used antibiotics in both the rational and irrational groups according to the Gyssens method. The study observed a homogeneity in the characteristics of the patients. However, there was no significant association between the rationality of antibiotic use based on the Gyssens method and treatment outcomes in the intensive care unit for COVID-19 patients, with the overall outcome being death.

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LENT SCORE AS A PROGNOSTIC FACTOR FOR OVERALL AND PROGRESSION- FREE SURVIVAL OF MALIGNANT PLEURAL EFFUSION PATIENTS IN TERTIARY HOSPITALS IN WEST SUMATRA

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ABSTRACT

Background: Malignant pleural effusion (MPE) had varying survival rates and prognoses. The LENT score is one of the methods to assess the survival rate in patients with MPE. This study aims to investigate the LENT score as a prognostic factor for overall survival (OS) and progression-free survival (PFS) of patients with malignant pleural effusion in a tertiary hospital in West Sumatra.

Material & Methods: This study is an observational analytical study involving several tertiary hospitals in West Sumatra. The observational period was 2 years minimally. Data were collected from medical records. We used Kaplan Meier analysis to assess OS and PFS.

Result: A total of 198 subjects met the inclusion criteria. Most of the MPE patients in this study were aged ≥60 years, male, smokers, pleural fluid LDH value <1500, ECOG 1, serum NLR value <9, and high-risk cancer namely lung cancer. The distribution of LENT scores for MPE patients was spread evenly among low, moderate, and high-risk groups. Kaplan Meier analysis showed that the median OS base on LENT score risk were 804 days, 275 days, and 161 days, respectively (log-rank test p=0.000). Median PFS based on LENT score were 715 days, 202 days, and 106 days, respectively (log-rank test p=0.000). These findings of OS and PFS were longer than the previous study.

Conclusion: Based on LENT score risk factors regarding OS and PFS, the West Sumatra Tertiary Hospital patients had better prognoses than those in the previous study.

Keywords: LENT score; malignant pleural effusion; overall survival; progression-free survival.

Background

The incidence of malignancy complicated by pleural effusion is currently increasing. As many as 76% of malignancies cause pleural effusion. Malignant pleural effusion (EPG) is proven by the presence of primary cancer and/or by finding malignant cells on anatomic pathology examination.[1,2] The incidence of EPG in the United States is reported to be 150,000 per year, while in China in 2021 it was found that 23% of EPG events.[3,4]

Data on EPG cases in Indonesia currently reaches 64.3% of cases.[5] Malignant pleural effusion causes high morbidity and mortality with varying patient survival rates and is related to prognosis.6 Patients with malignant pleural effusion generally have a poor prognosis with an average overall survival (OS) of 30 days to 1 year.[7,8] Overall Survival in patients after diagnosis of EPG averages 1-12 months.[9] A low survival rate will lead to a high mortality rate in patients with EPG. Shafiq et al. reported that the prevalence of death

from EPG was reported from 4.5 to 7.9% of cases in the United States.[10] Taghizadeh et al, the mortality rate of patients with EPG was reported in 11.6% of cases with an average hospitalization of 5.5 days.[11]

The study found methods that could be used to assess the survival rate of patients with EPG including the PROMISE Score and the LENT Score. The PROMISE score is used to predict the probability of survival of EPG patients within 3 months, this score is divided into 2, clinical and biological assessments with the TIMP-1 (Tissue inhibitor of metalloproteinase-1) examination.[12] This examination is not available in all hospitals, so this score is impractical to use.[13] It is different from the LENT score which is widely used in clinical practice and research because it is a simple indicator in predicting patient survival and guides the selection of management for patients.[14,15]

The LENT score consists of four values, namely lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG), neutrophil- lymphocyte ratio (NLR), and primary tumor type.[16] A study conducted by Verma et al. stated that in the EPG there was an increase in the LDH value of pleural fluid by 65%, besides that there was a relationship between pleural fluid LDH and prognosis in patients with EPG and showed the validity of pleural LDH as a predictor of long survival time in patients with EPG.[17,18] Zamboni et al. concluded that an ECOG level of 0 has a longer survival rate than patients with an ECOG score of 3-4.[13,19] Research by Popowiczl et al. found serum NLR increased by 80% in EPG patients.20 Study Lim et al. supported by the end of the patient's life.[14,21] Peng et al., the use of the LENT score can be used to determine the overall survival and progression-free survival of patients with malignant pleural effusion.[22]

This study aims to investigate the LENT score as a prognostic factor for overall survival (OS) and progression-free survival (PFS) of patients with malignant pleural effusion in a tertiary hospital in West Sumatra.

Material and Methods

This observational analytical study involves several tertiary hospitals in West Sumatra. The observational period was 2 years minimally. Data were collected from medical records. We used Kaplan Meier analysis to assess OS and PFS. The population of this study was all patients diagnosed with malignant pleural effusion who were treated at a tertiary hospital in West Sumatra, namely RSUP DR. M. Djamil Padang, Achmad Muchtar Hospital Bukittinggi and M. Natsir Solok Hospital for the period January 1, 2018, to December 31, 2020, observed for at least 2 years.

Result

Table 1. Characteristics Of Research Subjects

Variable		Frequency; (%) (n = 198)
Age		
	<60 year	97 (49)
	≥60 year	101 (51)
Gender		
	Male	104 (52,5)
	Female	94 (47,5)
Smoking status		
	Nonsmoker	68 (34,3)
	Smoker	77 (38,9)
	Former Smoker	53 (26,8)
LDH		
	<1500	100 (50,5)
	≥1500	98 (49,5)
ECOG		
	0	59 (29,8)
	1	89 (44,9)
	2	47 (23,7)
	3-4	3 (1,5)
NLR		
	<9	117 (59,1)
	≥9	81 (40,9)
Tumor Type		
Low Risk		3 (1,5)
	Mesothelioma	1 (0,5)
	Hematology	2 (1,0)
Moderate Risk		78 (39,4)
	Breast	23 (11,6)
	Gynecology	54 (27,3)
	Kidney	1 (0,5)
High Risk		117 (59,1)
	Lung	96 (48,5)
	Other	21 (10,6)

This research was conducted at a tertiary hospital in West Sumatra which included DR. M. Djamil Padang, Achmad Muchtar Hospital Bukittinggi, and M. Natsir Solok Hospital for the period January 1 2018 to December 31 2020 by examining patients diagnosed with malignant pleural effusion. Obtained a total sample of 198 subjects who met the inclusion criteria.

The characteristics of the study subjects can be seen in Table 1. Of the 198 study subjects, patients were aged ≥60 years (51%) and were male (52.5%). The prevalence of smoking patients (38.9%) and former smokers (26.8%). Pleural fluid LDH levels <1500 or ≥1500 have almost the same prevalence.

Most of the patients had an ECOG value of 1 (44.9%). Serum NLR levels of either <9 or ≥9 have almost the same prevalence. Tumor types were dominated by high-risk tumors (59.1%), with the highest proportion being lung tumors (48.5%).

Table 2. Frequency Distribution of LENT Score of MPE

Interpretation of LENT scores in MPE patients	Number of Patients (%) (n = 198)
- Low risk (0-1)	63 (31,8)
- Moderate risk (2-4)	66 (33,3)
- High risk (5-7)	69 (34,8)

Table 2 shows the distribution of LENT scores classified into low, medium, and high risk. The frequency distribution of LENT scores in EPG patients was almost the same whether high risk, moderate risk, or low risk.

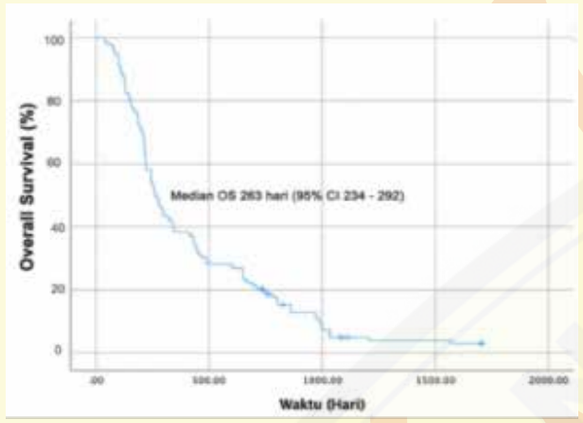

Figure 1. Kaplan Meier Curve Cumulative Overall Survival Probability of EPG Patients

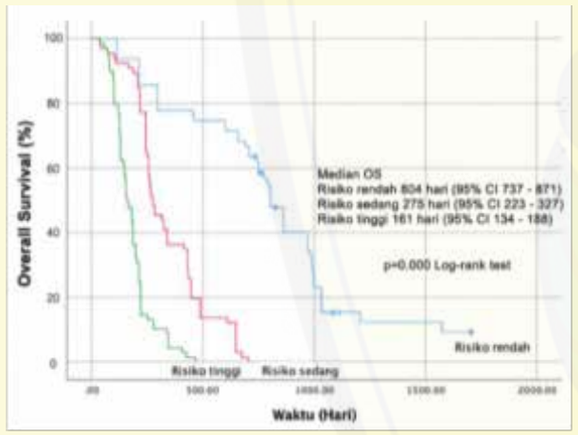

Figure 2. Kaplan Meier Curve Cumulative Overall Survival Probability Of EPG Patients Based On LENT Score.

It was found that the results of the Kaplan-Meier analysis were carried out to see the OS probability of patients with malignant pleural effusion in general. The patient's median OS was 263 days (95% CI 234-292). This means that 50% of patients survived after 263 days of observation (Figure 1).

Kaplan Meier's survival analysis found a median OS of 804 days (95% CI 737-871) for EPG patients with a low-risk LENT score, 275 days (95% CI 223 - 327) for EPG patients with a moderate-risk LENT score, and 161 days (95% CI 134–188) for EPG patients with high-risk LENT scores (figure 2). There were significant survival differences between risk groups using the log-rank test results, p=0.000 between low and medium risk, and p=0.000 between medium and high risk. It was concluded that the median OS of EPG patients

with low-risk LENT scores was significantly longer than the moderate-risk group and between medium and high risk.

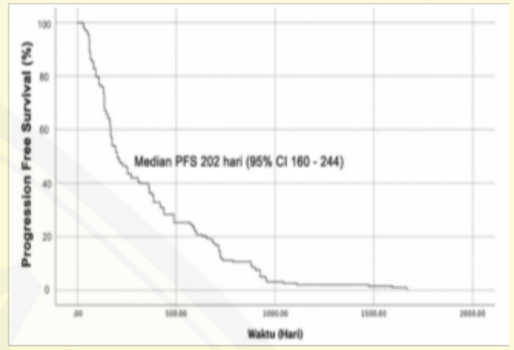

Figure 3. Kaplan Meier Curve Of The Cumulative Probability Of Progression-Free Survival In EPG Patients

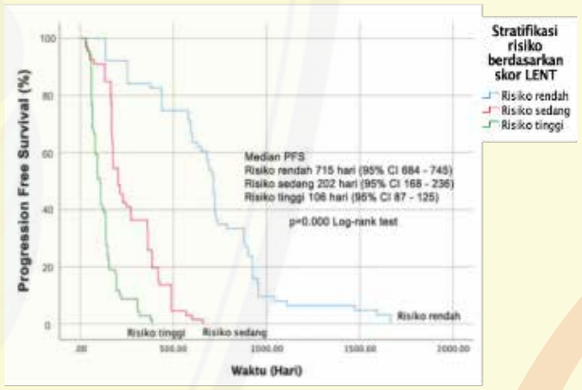

Figure 4. Kaplan Meier Curve Of The Cumulative Probability Of Progression-Free Survival In Patients With Malignant Pleural Effusion Based On The LENT Score.

The median PFS in EPG patients was 202 days (95% CI 160 - 244). This means that on the 202 days of observation, as many as 50% of patients with malignant pleural effusion were still alive. All subjects of this study experienced disease progression. Kaplan Meier analysis found a median PFS of 715 days (95% CI 684 - 745) for low-risk malignant pleural effusion patients, 202 days (95% CI 168 - 236) for moderate-risk patients, and 106 days (95% CI 87 - 125) for high-risk patients. There was a statistically significant difference in survival between risk groups with the log-rank test results, p=0.000 between low and medium risk, and p=0.000 between medium and high risk. It was concluded that the median PFS in the low-

risk group was significantly longer than the moderate-risk group, and also significantly different between moderate and high risk (Figure 4).

Discussion

The MPE patients who met the inclusion criteria in this study were 198 patients. The results of this study, for age characteristics, are almost the same. Most of the MPE patients were in the age group ≥60 years of 101 patients (51%) while the age group <60 years were 97 patients (49%). The results of this study are in line with that of Basso et al., the average age of EPG patients was 62.5 ± 24.8 years.[24]

Zamboni et al., EPG patients in the age group ≥60 years were more than patients in the age group <60 years, namely 86 patients and 79 patients.[19] The age factor is one of the prognostic risk factors in patients with MPE. Peng et al.'s study reported that old age increases the incidence of MPE 1.07 times.[22] Older age may have a higher risk for pleural effusion and MPE due to a higher chance of having any chronic disease that affects fluid balance in the body, such as malignancy. Older patients may also have a lowered immune system and a higher risk of malignancy which can result in increased inflammation and permeability of the pleural capillaries.[25]

The prevalence of men and women in this study was almost the same, there were 104 male patients, or 52.5% of cases. Wu et al. also reported a male prevalence of 58.9% of cases, or 514 patients out of 872 patients.[26] Zamboni et al., the prevalence of MPE was reported as 53% in males and 47% in females.[19] Old age and male sex Male has been reported as one of the prognostic risk factors for OS in patients with MPE. Peng et al., reported that the male gender increases the risk of MPE 1.11 times. The male has a higher risk of MPE because it is one of the risk factors for the primary malignancy underlying MPE.[22]

Based on smoking status, there were more smokers in this study, namely 77 patients (38.9%) followed by ex-smokers 53 patients (26.8%), and non-smokers 68 patients (34.3%). Smokers were also reported more in the Wu et al. study, namely 630 patients out of 872 patients or 72% of cases, while non-smokers were found in 240 patients or 28% of cases.26 Zhang et al., the prevalence of smokers was more reported, namely 60.9% of cases compared to non- smokers 39.1% of cases in MPE patients.[27]

The results of this study are in line with previous research that smoking status increases the risk of primary cancer incidence and is also increased in patients with MPE. Smoking status may be associated with an increased risk of MPE through several mechanisms, such as increasing the risk of lung cancer and malignant mesothelioma, lowering the immune system, increasing the risk of infection, and triggering inflammation and oxidative stress.[28,29]

This study showed that the pleural fluid LDH levels were <1500 and ≥1500, with almost the same prevalence of 50.5% and 49.5%, respectively. The study by Sousa et al. reported pleural fluid LDH levels in MPE patients in a cohort study, that is, with a median of 752 IU/L and a susceptibility between 522 to 1545 IU/L.[30] Research by Zhang et al., the average LDH level of patients was reported as <1500 or 54%.[27] LDH level is a parameter that can be used to determine the prognosis of MPE patients which is included in the LENT score indicator. High LDH levels found in the pleural fluid define local and acute inflammation and cell necrosis in the pleural space. A high LDH value is associated with a poor prognosis in MPE and can increase due to non-specific tissue injury response, including the presence of malignant cells in the pleural fluid, so it is recommended as a general marker of cell or tissue damage. Based on the ECOG values in this study, the majority of patients had ECOG 1, which was 44.9%, followed by ECOG 0, 29.8%, ECOG 2, 23.7%, and ECOG 3, 1.5%. In the study of Wu et al., more ECOG values were reported in the group with a value of 0-1, namely 725 patients (81%) followed by groups 2-4, namely 147 patients (19%).[26] The results of this study were in accordance with the study of Clive et al. al., who reported that ECOG was significantly significant as a prognostic factor in patients with MPE.[23]

Most NLR levels in this study had values <9 in 117 patients (59.1%) and NLR ≥9 in 81 patients (40.9%). Sousa et al. reported that the majority of patients with MPE had an NLR <9. The median NLR level was reported to be 4.6 with a range from 3.1 to 8.6.30 Gayaf et al., patients' NLR levels <9 were more than NLR levels >9, namely 76.96% of cases and 23.04% of cases.[14]

The NLR value is a parameter used to determine the prognosis of MPE patients. NLR is included in the LENT score indicator and is a marker of inflammation and immune response, due to increased neutrophils caused by angiogenesis of cancer cells. High serum NLR levels are associated with poor OS in various tumor types and stages.[14.23]

Based on the type of tumor in this study, patients with tumor types of lung cancer and other cancers were 59.1%, followed by breast cancer, gynecological cancer, and kidney cancer at 39.4%, and mesothelioma, hematological cancer at 1.5%.[27] Ramesh et al., conducted a study on 53 patients with MPE, and lung cancer was the most common cause of MPE with a prevalence of 86.79% of cases. patients with MPE which is 27.3% and greater than other cancers in this study.31 Lung cancer is cancer with a poor prognosis and is significant as a prognostic factor in patients with MPE.[23] This correlates with intrathoracic malignancy with a greater percentage of causing effusion massive pleural than extrathoracic malignancy. This is because the anatomic location is closer to the pleural space and can directly metastasize to the pleura or block lymphatic drainage. Extrathoracic malignancies can also cause pleural effusions but usually require hematogenous, lymphatic, or contiguous spread to reach the pleural space.[32]

The results of this study indicate that the frequency distribution of LENT scores of EPG patients between risk groups is almost the same, namely high risk of 34.8%, moderate risk of 33.3%, and low risk of 31.8%. Similar results were obtained from the Abisheganaden et al. study, which reported that 51.4% of EPG cases were in the high-risk category based on the LENT score. Patients with moderate risk category based on LENT scores in this study were reported in 48.5% of cases.33 Gayaf et al., the prevalence of EPG patients with high- risk LENT scores was more, namely, 52.88% of cases, followed by moderate risk at 36.65% of cases and low risk at 10.47% of cases.14 Ramesh et al., LENT score values on 53 patients with malignant pleural effusion of low, medium, and high risk, namely 5.7% of cases, 66% of cases, and 28.3% of cases. terms of the distribution of specific diseases in certain hospitals. Demographic differences may also have an influence, although there is no conclusive explanation for demographic differences in the incidence of EPG. This study used a much smaller number of samples (53 samples) so it is more likely that there will be visible differences in patterns. [31]

The results of this study indicate that the OS of EPG patients is longer on the low-risk LENT score of 804 days compared to the moderate risk of 275 days and the high risk of 161 days. The results of the analysis showed that there were significant survival differences between risk groups, with log-rank test results p =

0.000 in general, p = 0.000 between low and medium risk, and p = 0.000 between medium and high risk. Thus, it can be concluded that the median OS at low risk is significantly longer than the moderate risk group, as well as between medium and high risk, or in other words, EPG patients with low-risk LENT scores have longer OS than patients who have high-risk LENT scores. moderate or high, namely 804 (737 - 871) days. The results of this study, in general, on the analysis of the Kaplan Meier curve for the cumulative probability of OS on EPG, the patient's median OS was 263 days (95% CI 234 - 292). Gayaf et al., study found that the median OS in EPG patients based on LENT scores was 662 days, moderate risk 219 days, and high risk 103 days.[14] Clive et al.'s study, the median OS in EPG patients based on LENT scores was 319 days, moderate risk 130 days, and high risk 44 days.[23]

This research can be a complement as well as a comparison of Clive et al.'s data, by providing an overview of the Indonesian population. The population in Clive et al.'s study in Western countries which are classified as developed countries (high- income countries/HIC) when compared to Indonesia as a developing country (low- middle income countries/LMIC) have several differences in health systems and services, including the ease of and the affordability of access to health services to the quality of health services.[26]

Differences in the quality and access to health services can affect the quality of health services received by EPG patients so which can affect their outcomes. Clive's research population is dominated by the Caucasian race when viewed from where the data was taken, while this research was conducted on the Indonesian population, especially West Sumatra, which is generally dominated by the Malay race, which can influence the difference, although there is no more direct explanation regarding racial differences in the EPG. [23]

When compared with the findings of Clive et al., which is the basis for compiling the LENT score, this study found a different median OS. The median OS of this study is different from that of Clive et al., but both have the same pattern, namely the higher the risk based on the LENT score, the lower the OS of the EPG patients. The study of Clive et al., which is the basis for the LENT score study, involved three international cohort studies with a follow-up of at least 12 months in the UK, Australian, and Dutch populations, with a total of 789 patients included. The three populations in the study showed different cumulative OS, where the United Kingdom population showed an OS of 168 days (95% CI 106 – 228); Australia 205 days (95% CI 167 – 238); and the Netherlands 84 days (95% CI 72 – 115).[23]

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Differences between the three populations, including the OS observed in this study in the West Sumatran population, can be influenced by various things. Clive et al.'s study used the Cox regression method to find OS, while this study used the Kaplan- Meier method. The difference between the two lies in the Kaplan-Meier which is a non- parametric method, while the Cox regression is a parametric method. Kaplan Meier could not use multiple predictors, whereas the Cox regression method could use multiple predictors.[23,24] Another difference could be due to the study design, where Clive et al. used a prospective cohort design with direct follow-up for at least 12 months, while this study used a cross- sectional approach. The characteristics of each population can also influence the findings in this study which indicate OS in EPG patients from Indonesia, especially West Sumatra.[23]

Differences can also be influenced by the incidence of underlying disease causing malignant pleural effusion. According to the global cancer database GLOBOCAN 2020, the age-standardized incidence rates (ASR) of lung cancer is 38.8/100,000 in the UK population; 40.9/100,000 in the Netherlands; 32.6/100,000 in Australia; and 16.1/100,000 in Indonesia. Meanwhile, the age- standardized mortality rate (ASR) for lung cancer is 29.8/100,000 population in the United Kingdom; 32.7/100,000 in the Netherlands; 23.4/100,000 in Australia; and 13.9/100,000 in Indonesia.[28] These data show a difference in the incidence and death rates associated with lung cancer, with Indonesia showing lower rates. The difference in incidence and death rate could be the cause of the difference in OS in this study with that of Clive et al., although further research is needed to determine the relationship between differences in the incidence/death rate of lung cancer and the incidence and survival of malignant pleural effusion.[23]

The results of this study indicate that the progression-free survival of patients with malignant pleural effusion is longer at a low-risk LENT score of 715 days compared to a moderate risk of 202 days and a high risk of 106 days. The results of the analysis showed that there were statistically significant survival differences between risk groups, with log-rank test results p=0.000 in general, p=0.000 between low and medium risk, and p=0.002 between medium and high risk. Thus, it can be concluded that the median PFS in the low-risk group was significantly longer than the medium-risk group and significantly different between medium and high-risk.

Taniguchi et al., one of the indicators of the LENT score, namely LDH, is significantly related to PFS, especially in patients with LDH >240 IU/L with poor PFS (p<0.05).34 Tang et al., NLR is one of the indicators of PFS-related LENT score. The results of this study showed a significant relationship between NLR and PFS (p<0.001). Patients with NLR ≥5.0 had an average PFS of 6.17±1.23 months and patients with NLR <5.0 had an average PFS of 13.27±2.11 months.[35]

In various studies that have been conducted, analysis of PFS and LENT scores is rarely performed, so this study can provide a new study on the performance of LENT scores to predict progression in EPG patients. In this study, the median cumulative PFS in patients with EPG was 202 days (95% CI 160 - 244). Follow-up analysis using the Kaplan Meier method found a median PFS of 715 days (95% CI 684 - 745) for EPG patients with low-risk LENT scores, 202 days (95% CI 168 - 236) for patients with moderate-risk LENT scores, and 106 days. (95% CI 87 - 125) for patients with a high-risk LENT score, with significant differences between risk groups. These findings indicate that the higher the LENT score so that the patient belongs to the higher risk group, the lower the PFS, and vice versa.

A retrospective study measuring PFS was conducted by Lim et al., in several centers in Korea. Lim et al. specifically used the serum NLR parameter to measure PFS. Lim et al. found that the low NLR group showed a longer PFS of 8.7-21 months than the high NLR group (4.5 (2.8-6.2 months)). Lim et al. found a median PFS of 6.8 (4.5–9.0) months. Follow-up multivariate analysis showed a high serum NLR (p=0.004) to be an independent predictor of shorter PFS with a hazard ratio of 1.036 (1.011–1.061).[21]

The results obtained in this study are an indication that the LENT score can also be used to estimate the progression of EPG patients, especially in the population of Indonesia and West Sumatra. Further research needs to be conducted on a larger and more representative population scale to assess the prognostic ability of the LENT score in relation to disease progression.

Conclusion

Characteristics of EPG patients in this study were age ≥60 years, male sex, smoker, pleural fluid LDH value <1500, ECOG 1, NLR value <9, and high-risk cancer with the highest proportion of lung cancer. The distribution of LENT scores in this study was almost the same in the three groups, with the highest proportion being in the high-risk group, followed by moderate risk and low-risk. Median low-risk OS is significantly longer than medium risk, and high-risk. The median low-risk PFS was significantly longer than the moderate-risk and high-risk groups.

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DIAGNOSTIC ACCURACY OF CANCER RATIO FOR DETECTION MALIGNANT PLEURAL EFFUSION IN EXUDATIVE PLEURAL EFFUSION PATIENTS AT M DJAMIL HOSPITAL PADANG

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ABSTRACT

Background: Pleural effusion is one of leading caused for hospitalization. In Indonesia there are two major cause of pleural effusion namely malignancy and infection. Rapid diagnostic tool is needed to differentiate the causative agent both of them to prevent delay of patient management. Cancer ratio is a ratio between serum lactate dehydrogenase (LDH) and pleural fluid adenosine deaminase (ADA) of >20 were predictive to detect malignant pleural effusion (MPE). This study was aimed to find the accuracy of diagnostic value and find the cut-off point of cancer ratio at RSUP Dr. M. Djamil Padang.

Material & Methods: This study is an observational analytic retrospective study with a cross- sectional approach to detect MPE in patients treated at RSUP Dr. M. Djamil Padang in the period from May 2022 to December, 2022. The data in this study were obtained from patient medical records.

Result: A total of 89 subjects who met the inclusion criteria were obtained. The cancer ratio >20 showed a sensitivity of 80,4%, a specificity of 86,8%, positive predictive value (PPV) of 89,1%, and negative predictive value (NPV) of 76,7%.The cut-off cancer ratio set at >20,01 in DR M Djamil Hospital Padang. The area under the curve (AUC) showed 0,895 (95% CI =0,819-0,972).

Conclusion: The cancer ratio >20 cut-off was specific and highly predictive for MPE in patients with exudative pleural effusion

Keywords: *Lactate dehydrogenase, adenosine deaminase, cancer ratio, MPE*

Background

Pleural effusion is an abnormal accumulation of fluid in the pleural space which occurs as a result of an imbalance in the production and excretion of pleural fluid in the pleural space. Pleural effusion cases are quite high in several countries. In industrialized nations, it affects 320 instances per 100,000 people and affects 1.5 million individuals annually in the United States, while it affects 200,000– 250,000 people annually in Europe.[1] Although the most recent national data are not yet available, a study conducted in Lampung discovered that the majority of pleural effusion cases are caused by cancer, followed by infection and heart failure.[2]

A malignant tumor that originates in the pleura or a malignant tumor that has spread to the pleura from another site are the two main causes of malignant pleural effusion (MPE). The average patient survival is only 3-12 months after diagnosis with MPE. Pleural fluid cytology or pleural pathology examination is very helpful in diagnosing MPE but the positive rate of MPE is around 60%.[3] Although pleural biopsy from thoracoscopic examination has a high degree of diagnostic sensitivity, this method is quite invasive with

risk of complications, requires high cost, requires complex technical, as well as the availability of tools. Finding affordable and practicable parameters for pursuing the differential diagnosis of MPE has significant clinical application value because new diagnostic approaches must take into account issues like diagnostic efficiency, technical constraints, and cost.[4]

Research by Feng et al in 2018 showed that the ratio of serum lactate dehydrogenase (LDH)/adenosine deaminase (ADA) of pleural fluid has high sensitivity and specificity for diagnosing MPE and is referred to as the cancer ratio (CR).[5] Increased LDH levels can occur due to anemia, shock, cancer, sepsis, and tumor metastases. Increased plasma LDH can be used as a diagnostic and prognostic marker to detect sepsis and cancer, but its diagnostic potential as a biomarker for MPE has not been evaluated in detail.[5] As of yet, the biomarker for TB pleural effusion has been identified as adenosine deaminase. Mononuclear cells, lymphocytes, neutrophils, and red blood cells all release this enzyme, which is crucial for the metabolism of purine nucleosides. Pleural fluid adenosine deaminase can be used as a biomarker of malignancy when combined with serum LDH. Both of these indicators can indicate if a pleural effusion is cancerous.[6]

Due to the high prevalence of TB in Indonesia, patients with pleural effusion who are thought to be infected with the disease are frequently tested for pleural fluid ADA.[7] Malignancy can also be the source of pleural effusions, which are not always caused by TB infection. ADA pleural fluid combined with serum LDH which is known as the cancer ratio can be a predictor for a malignancy,[5] therefore it is advisable for all patients with pleural effusion to be routinely examined for ADA pleural fluid to reduce the missed diagnosis of malignancy in patients.

Patients with MPE usually show low levels of point >26 was highly predictive of exudative pleural effusion with a sensitivity and specificity of 61% and 80%. This study is a reference for deciding the diagnostic modality that will be used going forward in patients with pleural effusion who are treated in the pulmonary ward of DR M Djamil Hospital, Padang, so that there is no delay in treatment for the patient. Both of these studies demonstrate that this ratio can be used as a diagnostic marker for MPE.[9]

Material and Methods

This study is an observational analytic retrospective study with a cross-sectional approach to detect MPE in patients treated at RSUP Dr. M. Djamil Padang in the period from May 2022 to December, 2022. The data in this study were obtained from patient medical records.

Patient with analysis of pleural fluid transudate and exudate in acute process is excluded. Patients with TB pleural effusion concomitant with malignancy is also excluded. The independent variable in this study was data on the characteristics of patients with pleural effusion consisting of (age, sex, smoking status, occupation, comorbid diseases, color of pleural fluid, serum LDH, ADA of pleural fluid). The dependent variable in this study was the cancer ratio value and the results of anatomic pathology examination All statistical analyzes were performed using the SPSS program. Categorical variables are shown in frequency and tables. Data analysis was performed using a 2x2 table and then a diagnostic test was performed to assess the sensitivity and specificity of the cancer ratio compared to the results of anatomic pathology as the gold standard.

Table 1. Patient Characteristics.

		Sample (total n = 89)
		n (%)
Age (years)	≤ 60 th	58 (65.2%)
	> 60 th	31 (34.8%)
Sex	Men	55 (61.8%)
	Women	34 (38.2%)
Smoking status	Smoker	20 (22.4)
	Former smoker	33 (37.0)
	Not a smoker	36 (40.4)
Brinkman Index	Mild (≤ 200)	4 (7.5)
	Moderate (201-600)	19 (21.3)
	Severe (>600)	30 (33.7)
Occupation Status	Risk	27 (30.3)
	No risk	62 (69.7)
Comorbid	DM Type II	13 (14.6)
	Hypertension	11 (12.4)
	Malnutrition	21 (23.6)
Pleural fluid color	Serous	38 (42.7)
	Serohemorrhagic	31 (34.8)
	Hemorrhagic	20 (22.5)
Serum LDH values	≤ 300 U/L	35 (39.3)
	> 300 U/L	54 (60.7)
Pleural fluid ADA values	< 40 U/L	62 (69.7)
	≥ 40 U/L	27 (30.3)
Cancer ratio	< 20	43 (48.3)
	> 20	46 (51.7)
Pathology of pleural fluid	Positive	51 (57.3)
	Negative	38 (42.7)
	Total	10 (38.5%)

Figure 1 is a curve that explains that there are several intersection points for the cancer ratio in patients with pleural effusion who are being treated at M Djamil Hospital, Padang. The optimal cut point is at point number 40. Point number 40 has a cancer ratio value of more than 20.01 with a sensitivity value of 80.4% and a specificity of 86.8%. The cancer ratio cutoff point of more than 20.01 gives a sensitivity and specificity value according to the output from the Table 2 calculation results for the diagnostic test in this study. The curve in Figure 2 explains that in this study it shows that the cancer ratio has an area under the curve (AUC) obtained a value of 0.895 which is statistically significant (95% CI 0.819-0.972).

Table 2. Cancer Ratio Value Against Anatomical Pathology To Detect MPE.

		Pathology		Total
		Positive	Negative	
Cancer ratio	> 20	41	5	46
	≤ 20	10	33	43
Total		51	38	89 (100%)

The sensitivity, specificity, negative predictive value (NPV) and positive predictive (PPV) value of the cancer ratio to anatomical pathology for the detection of MPE in patients with pleural effusion treated at M Djamil Hospital can be seen in the Table 2. The value of sensitivity, specificity, NPV and PPV is 80.4%; 86.8%; 89.1%; and 76.7% respectively.

Figure 1. Cancer Ratio Cut Point Value of Pleura Effusion Patients To Detect MEP.

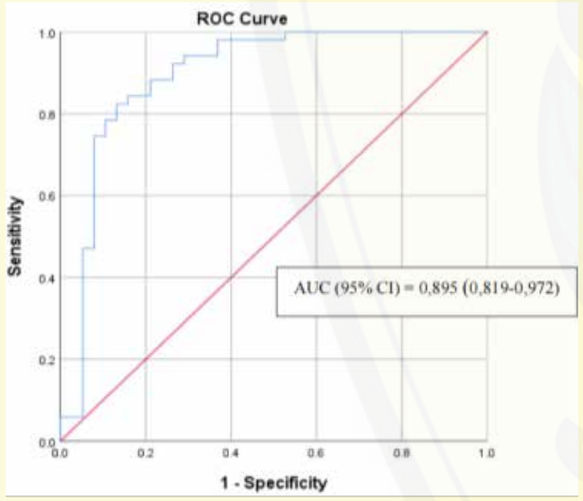

Figure 2. ROC Cancer Ratio Curve for Pleura Effusion Patients To Detect MPE.

Discussion

Most age group experiencing pleural effusion is the age group ≤ 60 years (65.2%). The findings of this study are consistent with earlier studies conducted in Jambi from 2017 to 2018, which also revealed that the age group 60 years was the most prevalent to develop pleural effusion.10 The findings in Palembang 2019 also revealed that the age group 60 years had the highest frequency of pleural effusion (76%).[11]

Another study conducted in Bali indicated that the age group 60 years had the highest percentage of pleural effusion (76.6%), with the age group 40-59 years having the lowest (53/107).[12] Adeoye's study in Nigeria found that the age group 40 years has a higher frequency of pleural effusion than other age groups due to differences in genetics.

MPE was detected in smokers (22.4%) and former smokers (37.0%) with a severe Brinkman index (33.7%) in this investigation. The results of this study are in accordance with research conducted by Mangkouta et al in 2015 which found that nicotine as the main ingredient in cigarettes can affect mutagenesis, initiation and proliferation of lung cancer and cause MPE as a manifestation of metastasis. Cigarettes stimulate cell inflammation which affects the occurrence of pleural effusion.[14] Research conducted by Tian et al also explained that smoking patients are a risk factor for MPE compared to non-smoker patients with a percentage of smokers 33.1% and non-smokers 28.3% obtained a value (p value < .001).[15]

Risky jobs, namely drivers, cooks and farmers was found in 30.3%. This data is in accordance with research conducted by Marcelino et al in 2020 found that work exposed to chemicals such as farmers can be a risk factor for breast cancer, one of the manifestations of metastasis is pleural effusion.[16] Research conducted by Spyratos et al in 2013 also explained that farming as one of the occupations is a risk factor for lung cancer. Pesticides exposure experienced by farmers can increase the risk factor for lung cancer.[17] Occupation of drivers and cooks is also a risk factor for cancer, especially lung cancer in patients.

The most common comorbidity of malnutrition was found in patients with pleural effusion (23.6%). Research conducted by Ferigollo et al in 2018 also explained that malnutrition was the most common comorbid in patients with pleural effusion, namely 77%, especially found in patients with MPE.[18] The most color of pleural fluid found in this study was serous (42.7%).

The majority of patients had a serum LDH value greater than or equal to 300 U/L (60.7%). Serum LDH values in MPE tend to be higher when compared to non-MPEs. Serum LDH is a cellular enzyme that can increase in the event of tissue injury. This enzyme will increase in response to the tissue injury.19 Increased serum LDH in malignancy occurs due to the use of glycolysis by tumor cells as an energy producer, oxidative phosphorylation and a role in LDH-mediated ATP pathways. A high rate of glycolysis is necessary for cell growth because it is capable of producing ATP much more rapidly than oxidative phosphorylation. Tumor cells grow rapidly so there is a great demand for ATP to drive their growth and the process of glycolysis to meet the demand for ATAP. This process causes an increase in LDH in the serum of patients with malignancy.[20]

The results of pleural fluid ADA in this studyshowed the majority were less than 40 U/L (69.7%). Research conducted by Terra in 2016 also explained that patients with malignancy have lower ADA values and can be a poor survival prognostic in patients with MPE.[21] Adenosine deaminase is an enzyme that catalyzes the conversion of adenosine and deoxynosine to inosisn and deoxynoisn in the pathway purine degradation. ADA activity is ten times greater in lymphocytes than in B lymphocytes and varies during T cell differentiation with significantly increasing levels. The increase in ADA in TB cases is explained because there is a gradual increase in CD4 blastogenesis after mybacterial antigenic stimulus.[22] Increased ADA activity in TB peluritis is associated with an increase in CD4 lymphocytes while a decrease in MPE will correlate with a higher percentage of CD11 lymphocytes and a decrease in CD4 T cells.[9]

The cancer ratio is the ratio of serum LDH/ADA pleural fluid which has a high sensitivity and specificity value for diagnosing MPE.5 The cancer ratio can diagnose an MPE if a value of more than 20 is obtained. The majority of pleural effusion patients in this study had a cancer ratio of more than 20. This study showed that the number of patients with pleural effusion who had a cancer ratio of more than 20 was found in 51.7%. This study's findings are consistent with those of Verma et al., who reported in 2016 that patients with MPE had a cancer ratio more than 20, with a sensitivity of 98% and a specificity of 94% in identifying MPE.8 In 2019, Prasenohadi et al. discovered that a cancer ratio greater than 26 was highly predictive of exudative pleural effusion, with sensitivity and specificity of 61% and 80%, respectively.[9]

The accumulation of significant amounts of pleural fluid in the pleural space associated with malignancy is vast and productive, as evidenced by the discovery of malignant cells on anatomic pathology examination based on the results of pleural fluid cytology or histopathology, known as MPE.[23] Pleural effusion was identified in 57.3% of patients, along with the presence of malignant cells on anatomic pathological investigation (cytology and histology). Research conducted by Parman in 2022 also explained that cytological examination of pleural fluid has a sensitivity of 95% and a specificity of 75% in diagnosing MPE.62 Dewi's research in 2020 explained that the probability of the difference is at a good level.24 The area under the curve obtained a value of 0.895 in this study showed statistically significant results (95% CI 0.819-0.972) and showed that the cancer ratio parameter can be a good parameter for detecting MPE.[25]

The primary evaluation of a diagnostic instrument is its sensitivity and specificity. A gold standard diagnostic standard compares both of these.[24] In this study, the results of anatomical pathology are used as a gold standard in comparison to the cancer ratio. This study showed the results of the sensitivity and specificity of cancer ratio to pathological anatomical features of 80.4% and 86.8%, respectively. A sensitivity value of 80.4% indicates that a cancer ratio of more than 20.01 can detect effusion patients who are correctly suspected of having an MPE of 80.4%. The specificity value of 86.8% indicates a cancer ratio of more than 20.01 which can confirm a pleural effusion that is not an MPE of 86.8%.

This research is in line with a meta- analysis conducted in 2019. This study showed a cancer sensitivity ratio greater than 94% and various sensitivities with a value range of 60-100%. The meta-analysis revealed that the cancer ratio has a sensitivity of 97% and a specificity of 89%, implying that it can confirm 97% of MPE cases and remove 89% of non-MPE cases.[25]

A positive predictive value indicates how probable the patient is to have an illness, whereas a negative number suggests that the patient does not have a condition.[26] The negative predictive value in this study was 76.7%, which could suggest that patients with effusion pleura and a cancer ratio of less than 20.01 have a 76.7% chance of not having MPE. The positive predictive value obtained in this study was 89.1% which could mean that patients with pleural effusion who had a cancer ratio of more than 20.01 had a percentage of 89.1% having MPE.

The negative predictive value for a cancer ratio of more than 20 in this study was found to be higher than the negative predictive value of 27.59% established in Prasenohadi's research. This study's positive predictive value for a cancer ratio of more than 20 was found to be lower than Prasenohadi's research, which reported a positive predictive value of 94.44%.[9]

Verma's 2016 study also found a positive predictive value and a negative predictive value for a cancer ratio more than 20, which was higher than this study. The obtained positive predictive value is 97%, while the obtained negative predictive value is 96%.[8]

Conclusion

The demographic features of patients with pleural effusion treated at RSUP DR M Djamil padang revealed that 65.2% of MPEs were experienced by patients aged less than 60 years, with 61.8% being male. MPE was found in many smoking patients with a smoker status of 22.4% and 37.0% of former smokers with a severe Brinkman index of 33.7%. Risky jobs, namely drivers, cooks and farmers was 30.3%. Malnutrition is the most common comorbidity found in patients with MPE as much as 23.6%. Pleural fluid color was obtained the most, namely serous as much as 42.7%. The majority of patients had a serum LDH value of more than 300 U/L of 60.7% and pleural fluid ADA of less than 40 U/L of 69.7%.

The distribution of the frequency of patients with pleural effusion based on a cancer ratio of more than 20 is 51.7%. The distribution of the frequency of patients with pleural effusion based on the findings of cell types from anatomical pathology results was 57.3%. The cut point value of the cancer ratio of pleural effusion patients to detect MPE in this study was 20.01. The sensitivity and specificity values of cancer ratio >20 to anatomical pathology for detecting MPE in this study were 80.4% and 86.8%. The positive predictive value of cancer ratio for pathological anatomical features for detecting MPE was 89.1% and the negative predictive value of cancer ratio for anatomic pathological features for detecting MPE was 76.7%.

We suggest that the cancer ratio value consisting of the results of pleural fluid ADA and serum LDH is recommended as a routine examination in patients with pleural effusion because it can be an effective and efficient predictor of MPE.

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FACTORS ASSOCIATED WITH BLEEDING EVENTS AND DESATURATION IN BRONCHOSCOPY AT M. DJAMIL GENERAL HOSPITAL, PADANG

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ABSTRACT

Background: Bronchoscopy is a diagnostic and therapeutic procedure with a low rate of complications and mortality. The most common complications are oxygen desaturation and bleeding. Early screening of factors associated with the increased incidence of complications in patients undergoing bronchoscopy is needed to ensure safety during the procedure and minimize complications. This study aimed to discover the factors associated with bleeding and complication during a bronchoscopy procedure.

Material & Methods: This is an observational analytic study with a cross-sectional approach by evaluating the video of the bronchoscopy procedure and collecting data from medical reports.

Result: We got 142 eligible videos of patients whose complete data. Most of the patient was males (73%), in the group < 60 years old (57,7%) had a smoking history (62,6%). More than half (56.3%) had comorbidity, which is the majority of COPD (35,9%). The complication of moderate bleeding was 4,9% and severe bleeding 2,8%. Meanwhile, desaturation was found in 36,6%. The factors associated with bleeding were specimen collection technique, cell type, and visual bronchoscopic appearance (p=0,001; p=0.006; p=0,006, respectively). The factors associated with desaturation were specimen collection technique and comorbidity (p=0,019 and p=0.007; respectively) The independent factors associated with bleeding were comorbidity (COPD, OR 3,099 CI95% (1,482-64.79); p=0,027 and cardiovascular diseases OR 1,497 CI 95% (1,791-12,518) p=0,013). The independent factor associated with desaturation was the presence of comorbidity (OR 2,378 CI 95% (1,052-5,376); p=0,037).

Conclusion: The presence of comorbidity is independently associated with the risk of bleeding and desaturation during a bronchoscopy procedure.

Keywords: *bronchoscopy, desaturation, bleeding*

Background

Bronchoscopy is a procedure used for direct visualization of the airways through a bronchoscope. Advances in technology have facilitated the development of bronchoscopy as a diagnostic and therapeutic tool in lung and airway diseases. Bronchoscopy is a procedure with complications and the mortality rate ranges from 0.56.8% depending on the type of procedure performed. [1,4] Reported bronchoscopy complication rates vary widely. A retrospective study found serious complications in 1.08% of cases with a mortality rate of 0.02%. Hen's study reported that there were 4.3% cases of complications due to bronchoscopy from 1358 procedures, 2.8% complications not related to breathing, and a mortality rate of 0.1%. Leiten et al conducted a systematic fraud of 45 scientific publications about complications due to bronchoscopy. They found severe complications due to bronchoscopy which are rare. The most common complications are oxygen desaturation in 0.7-7.3% of patients and bleeding in 2.5-8.9% of patients.[6]

Intraoperative bleeding is the most common complication after hypoxemia. The occurrence of bleeding in several studies is often associated with thrombocytopenia, increased pulmonary artery pressure, and previous use of antiplatelet and anticoagulants. The incidence of heavy bleeding often occurs in procedures such as TBLB with a prevalence rate of 0.83-1.9%. This number will increase to 8% if this action is combined with several other actions such as a Bronchial Brush and Trans Bronchial Needle Aspiration (TBNA). The severity of bleeding is indicated by the volume of blood and fluid aspirated or according to the intervention needed to control bleeding. The degree of severity is also influenced by measurement variability and dilution of blood with bronchial secretions, and the measures performed. The most significant increase in bleeding after transbronchial lung biopsy (TBLB). [3,5,6]

Prevention and early screening of factors associated with the incidence of complications in patients undergoing bronchoscopy are needed to ensure safety during the procedure and minimize complications that occur. In addition, adequate patient preparation is required, assessment of the risks and benefits of action, and adherence to patient safety protocols during the procedure. [3,6] Based on the reasons above, the authors are interested in examining the risk factors that most contribute to intraoperative bleeding and hypoxemia in patients who underwent bronchoscopy at Dr. M. Djamil Padang.

Material and Methods

This study was cross-sectional with a retrospective approach to determine factors associated with intraoperative bleeding and desaturation in patients undergoing bronchoscopy at RSUP Dr. M. Djamil Padang. The implementation of this research was carried out from December 2022 to May 2023.

Data was collected based on medical record data and videos of patient bronchoscopy procedures. There were a total of 158 bronchoscopy procedures performed at Mdjamil Padang General Hospital, both under general anesthesia and local anesthesia. [158]

samples will then be sorted according to inclusion and exclusion criteria. Bronchoscopy was performed using an Olympus ESG-100 series connected to the Evis Exera III video system. Scope used with a diameter of 10 mm. The video will be analyzed and supervised by an expert in the intervention and respiratory department of M. Djamil Hospital, Padang. Every week, a maximum of 70 video bronchoscopy analyses are carried out to see the degree of bleeding, bronchoscopy findings, and the length of the procedure. These results will then be combined with data obtained from anesthesia reports, bronchoscopy reports, and action reports contained in medical record data.

Result

Of a total of 154 patients aged >18 years who underwent bronchoscopy at Dr. M. Djamil Padang from January 1 to December 31, 2022, 142 patients were found who met the sample criteria. A total of 12 patients were excluded, 10 of whom did not provide complete video data, and 2 of them did not provide complete data. The frequency of intraoperative desaturation and bleeding events from the patients or study sample is shown in Table 3. The data in the table above shows that intraoperative desaturation occurred in almost half of the patients (36.6%), and some patients (48.2%) experienced bleeding. dominated by light bleeding (40.8%).

Based on Table 1, it was found that the majority (57.7%) of the patients who underwent bronchoscopy were aged <60 years and were female (73.2%). Nearly half of the patients (49.3%) had normal BMI and were smokers (40.8%). Most of the patients (56.3%) had comorbidities with the most types of comorbidities namely cardiovascular disease as much as 35.9% of which 18.3% were hypertension. Based on the type of anesthesia, most of the patients (73.9%) received general anesthesia. The most common type of action, in almost half of the patients (33.8%), was bronchial washing and brushing. Most of the patients (74.6%) underwent the procedure for 10-30 minutes, and most (54.9%) had the procedure in 1 location.

Table 1. Characteristics in the study

Characteristics	N	%
Age		
< 60 years	82	57,7
≥ 60 Years	60	42,3
Gender		
Man	104	73,2
Women	38	26,8
BMI		
Overweight	3	2,1
Normal	70	49,3
Underweight	69	48,6
Smoking status		
Smoker	58	40,8
Former smoker	31	21,8
Non smoker	53	37,3
Comorbidities		
Yes	80	56,3
No	62	43,7
Type of comorbids		
COPD	10	35,9
Cardiovascular desease	51	7,0
Type 2 Diabetic	10	0,7
Renal failure	1	0,7
Others		
Jenis Anestesi		
Local	37	36,2
General	105	73,9
Procedure		
Bronchial wash	24	16,9
Bronchial wash + Bronchial brush	48	33,8
Bronchial wash + forceps biopsy	14	9,9
Bronchial wash + Cryobiopsi	16	11,3
2 procedure	40	28,2
Duration		
10-30 menit	36	25,4
30 minute	106	74,6
Location of procedure		
1 location	78	54,9
1 location	64	45,1
Patologic finding		
Squamous cell carsinoma	34	23,9
Adenocarsinoma	44	31,0
Adenoskuamosa paru	1	0,1
Small cell carsinoma	1	0,1
Thymoma	1	0,1
Others	61	43,8
Drugs history		
Yes	7	4,9
No	135	95,1
Bronchoscopy finding		
Direct tumor	76	53,5
Indirect tumor	17	12,0
Chronic bronchial changes	8	5,6
Mucosal injury	41	28,9
Desaturtion event		
Yes	52	36,6
No	90	63,4
Bleeding event		
No bleeding	73	51,4
Mild	58	40,8
Moderate	7	4,9
Severe	4	2,8

Table 2 shows that in patients aged <60 years, the majority (56.1%) did not experience bleeding. Whereas in patients aged ≥ 60 years most (55.0) experienced bleeding (46.7% of them were light bleeding). However, the results of the Fisher's exact test obtained a value of p = 0.072 (p> 0.05) indicating that age was not associated with intraoperative bleeding. Based on gender, it was found that half (50.0%) of the male patients did not experience bleeding, in most female patients (55.3%) also did not experience bleeding. The results of the Fisher's exact test obtained a value of p = 0.493 (p> 0.05) indicating that gender was not associated with intraoperative bleeding. Based on BMI, most patients (66.7%) who were overweight (66.7%) did not experience bleeding, patients with normal weight patients without bleeding also the most (47.1%), as well as in patients with underweight most of them Most (55.1%) also did not experience bleeding. The results of the Fisher's exact test obtained a value of p = 0.865 (p> 0.05) indicating that BMI was not associated with intraoperative bleeding.

Smoking status was also not associated with intraoperative bleeding (p=0.406). The distribution of intraoperative bleeding according to the patient's smoking status showed that half (50.0%) of smoking patients did not experience bleeding, whereas most (54.8%) of former smokers had mild bleeding, and most (60.4%) of non-smoker patients had no bleeding. According to the presence of co- morbidities, nearly half of the patients (43.8% and 46.3%) were non-bleeding and had mild bleeding, respectively. However, the majority of patients without comorbidities (61.3%) did not experience bleeding. The results of the Fisher's exact test obtained a value of p = 0.110 (p> 0.05) indicating that the presence of comorbidities was not associated with intraoperative bleeding. Types of comorbidities were also not related to intraoperative bleeding (p=0.088) because both patients with comorbid COPD, cardiovascular, and CKD tended to experience mild bleeding (50.0%; 49.0% and 100.0%, respectively) whereas for the majority of patients with other comorbidities (75.0%) did not experience bleeding.

Table 2. Association of characteristic with bleeding events

Characteristics	Bleeding events, n (%)				p-value#
	No bleeding	Mild	Moderate	Severe	
Age					
< 60 years	46 (56,1)	30 (36,6)	2 (2,4)	4 (4,9)	0,072
≥ 60 Years	27 (45,0)	28 (46,7)	5 (8,3)	0 (0,0)	
Gender					
Man	52 (50,0)	44 (42,3)	4 (3,8)	4 (3,8)	0,493
Women	21 (55,3)	14 (36,8)	3 (7,9)	0 (0,0)	
BMI					
Overweight	2 (66,7)	1 (33,3)	0 (0,0)	0 (0,0)	0,865
Normal	33 (47,1)	32 (45,7)	3 (4,3)	2 (2,9)	
Underweight	38 (55,1)	25 (36,2)	4 (5,8)	2 (2,9)	
Smoking status					
Smoker	29 (50,0)	23 (39,7)	3 (5,2)	3 (5,2)	0,406
Former smoker	12 (38,7)	17 (54,8)	2 (6,5)	0 (0,0)	
Non smoker	32 (60,4)	18 (34,0)	2 (3,8)	1 (1,9)	
Comorbidities					
Yes	35 (43,8)	37 (46,3)	6 (7,5)	2 (2,5)	0,110
No	38 (61,3)	21 (33,9)	1 (1,6)	2 (3,2)	
Type of comorbids					
COPD	3 (30,0)	5 (50,0)	1 (10,0)	1 (10,0)	0,088
Cardiovascular desease	22 (43,1)	25 (49,0)	3 (5,9)	1 (2,0)	
Type 2 Diabetic	4 (40,0)	4 (40,0)	2 (20,0)	0 (0,0)	
Renal failure	0 (0,0)	1 (100,0)	0 (0,0)	0 (0,0)	
Others	6 (75,0)	2 (25,0)	0 (0,0)	0 (0,0)	
Jenis Anestesi					
Local	26 (70,3)	10 (27,0)	0 (0,0)	1 (2,7)	0,034
General	47 (44,8)	48 (45,7)	7 (6,7)	3 (2,9)	
Procedure					
Bronchial wash	22 (91,7)	2 (8,3)	0 (0,0)	0 (0,0)	<0,001
Bronchial wash + Bronchial brush	32 (66,7)	14 (29,2)	0 (0,0)	2 (4,2)	
Bronchial wash + forceps biopsy	4 (28,6)	9 (64,3)	0 (0,0)	1 (7,1)	
Bronchial wash + Cryobiopsi	5 (31,3)	11 (68,8)	0 (0,0)	0 (0,0)	
2 procedure	10 (25,0)	22 (55,0)	7 (17,5)	1 (2,5)	
Duration					
10-30 menit	63 (59,4)	35 (33,0)	5 (4,7)	3 (2,8)	
≥ 30 minute	10 (27,8)	23 (63,9)	2 (5,6)	1 (2,8)	0,005
Location of procedure					
1 location	43 (55,1)	31 (39,7)	2 (2,6)	2 (2,6)	0,457
≥ 1 location	30 (46,9)	27 (42,2)	5 (7,8)	2 (3,1)	
Patologic finding					
Squamous cell carsinoma	11 (32,4)	19 (55,9)	3 (8,8)	1 (2,9)	0,006
Adenocarsinoma	19 (43,2)	22 (50,0)	3 (6,8)	0 (0,0)	
Adenoskuamosa paru	0 (0,0)	1 (100,0)	0 (0,0)	0 (0,0)	
Small cell carsinoma	0 (0,0)	1 (100,0)	0 (0,0)	0 (0,0)	
Thymoma	1 (100,0)	0 (0,0)	0 (0,0)	0 (0,0)	
Others	42 (67,7)	16 (25,8)	1 (1,6)	3 (4,8)	
Drugs history					
Yes	3 (42,9)	4 (57,1)	0 (0,0)	0 (0,0)	0,831
No	70 (51,9)	54 (40,0)	7 (5,2)	4 (3,0)	
Bronchoscopy finding					
Direct tumor	21 (27,6)	48 (63,2)	6 (7,9)	1 (1,3)	0,006
Indirect tumor	15 (88,2)	0 (0,0)	1 (5,9)	1 (5,9)	
Chronic bronchial changes	8 (100,0)	0 (0,0)	0 (0,0)	0 (0,0)	
Mucosal injury	29 (70,7)	10 (24,4)	0 (0,0)	2 (4,9)	

: *fisher exact test*

Table 3. Association between characteristics with desaturation event

Characteristics	Desaturation event				p-value
	Yes		No		
	n	%	N	%	
Age					
< 60 years	31	37,8	51	62,2	0,732*
≥ 60 Years	21	35,0	39	65,0	
Gender					
Man	39	37,5	65	62,5	0,719*
Women	13	34,2	25	65,8	
BMI					
Overweight	0	0,0	3	100,0	0,420#
Normal	28	40,0	42	60,0	
Underweight	24	34,8	45	65,2	
Smoking status					
Smoker	20	34,5	38	65,5	0,777*
Former smoker	13	41,9	18	58,1	
Non smoker	19	35,8	34	64,2	
Comorbidities					
Yes	37	46,3	43	53,8	0,007*
No	15	24,2	47	75,8	
Type of comorbids					
COPD	5	50,0	5	50,0	0,674#
Cardiovascular desease	25	49,0	26	51,0	
Type 2 Diabetic	3	30,0	7	70,0	
Renal failure	1	100,0	0	0,0	
Others	3	37,5	5	62,5	
Jenis Anestesi					
Local	10	27,0	27	73,0	0,159*
General	42	40,0	63	60,0	
Procedure					
Bronchial wash	8	33,3	16	66,7	0,019*
Bronchial wash + Bronchial brush	11	22,9	37	77,1	
Bronchial wash + forceps biopsy	8	57,1	6	42,9	
Bronchial wash + Cryobiopsi	4	25,0	12	75,0	
≥ 2 procedure	21	52,5	19	47,5	
Duration					
10-30 menit	36	34,0	70	66,0	
≥ 30 minute	16	44,4	20	55,6	0,259*
Location of procedure					
1 location	27	34,6	51	65,4	0,584*
≥ 1 location	25	39,1	39	60,9	
Patologic finding					
Squamous cell carsinoma					
Adenocarsinoma	11	32,4	23	67,6	0,072#
Adenoskuamosa paru	21	47,7	23	52,3	
Small cell carsinoma	1	100,0	0	0,0	
Thymoma	1	100,0	0	0,0	
Others	18	29,0	44	71,0	
Drugs history					
Yes	3	42,9	4	57,1	0,707#
No	49	36,3	86	63,7	
Bronchoscopy finding					
Direct tumor	33	43,4	43	56,6	0,128#
Indirect tumor	7	41,2	10	58,8	
Chronic bronchial changes	3	37,5	5	62,5	
Mucosal injury	9	22,0	32	78,0	

: uji *fisher exact, * = chi square*

Most of the patients who received general anesthesia showed no bleeding, while almost half of the patients who received local anesthesia (45.7%) experienced light bleeding, and a small proportion (6.7%) and 2.9% experienced moderate and severe bleeding. The Fisher exact test results obtained p = 0.034 (p <0.05) indicating that the type of anesthesia is associated with intraoperative bleeding. According to the type of action, there was a significant relationship with intraoperative bleeding (p<0.001). Patients with bronchial washings generally (91.7%) did not experience bleeding, patients with bronchial rinses + brushing mostly (66.7%) also did not experience bleeding, but in patients with bronchial washings and forceps biopsies, bronchial washings and cryobiopsi, and patients with > 2 procedures mostly experienced light bleeding (64.3%, 68.8%, and 55.0%, respectively).

The length of action was also associated with intraoperative bleeding (p=0.005). The majority of patients with an active duration of >30 minutes (63.9%) experienced light bleeding while patients with an operating duration of 10-30 minutes (59.4%) did not experience bleeding. Based on the location of the action, the majority of patients with small action sites or at least 1 location (55.1%) did not experience bleeding, while in patients with > 1 action site, almost half (46.9%) did not experience bleeding and 42.2% experiencing light bleeding. The results of the Fisher's exact test obtained a value of p = 0.457 (p> 0.05) indicating that the location of the procedure was not related to intraoperative bleeding.

Based on the findings of anatomical pathology, both patients diagnosed with lung squamous cell carcinoma, lung adenocarcinoma, and small cell carcinoma lung cancer tended to experience mild bleeding (in 55.9%; 50.0%; and 100.0% of patients, respectively). whereas patients diagnosed with thymoma or other diseases tend not to experience bleeding (respectively shown by 100.0% and 67.7% of patients). The results of the Fisher's exact test obtained a value of p = 0.006 (p <0.05) indicating that anatomic pathology findings were associated with intraoperative bleeding.

Table 4. Independent factors that play a role in bleeding event

Karakteristik	Koefisien	SE	p	OR (IK95%)
Age				
< 60 years	-0,085	0,479	0,859	0,918 (0,359 – 2,349)
≥ 60 Years	Ref			
Comorbidities				
Yes	-1,987	1,072	0,064	0,137 (0,017 – 1,121)
No	Ref			
Type of comorbids				
COPD	3,434	1,551	0,027	3,099(1,482 – 64,7921)
Cardiovascular desease	2,706	1,083	0,013	1,497 (1,791 – 12,5187)
Type 2 Diabetic	2,200	1,274	0,084	9,022 (0,743 – 109,568)
Renal failure	20,142	0,000	-	$5,59 \times 10^8$
Others	Ref			
Type of Anestesi				
Local	-0,541	0,644	0,401	0,582 (0,165 – 2,056)
General	Ref			
Procedure				
Bronchial wash	-2,021	1,118	0,071	0,133 (0,015 – 1,187)
Bronchial wash + Bronchial brush	-1,033	0,766	0,178	0,356 (0,079 – 1,598)
Bronchial wash + forceps biopsy	-0,533	0,871	0,541	0,587 (0,106 – 3,239)
Bronchial wash + Cryobiopsi	-0,582	0,812	0,474	0,559 (0,114 – 2,746)
2 procedure	Ref			
Duration				
10-30 menit	0,837	0,659	0,204	2,309 (0,634 – 8,408)
>30 minute	Ref			
Patologic finding				
Squamous cell carsinoma	0,158	0,609	0,795	1,171 (0,355 – 3,862)
Adenocarsinoma	0,245	0,550	0,656	1,277 (0,435 – 3,756)
Adenoskuamosa paru	18,391	0,000	-	$9,71 \times 10^7$
Small cell carsinoma	-0,469	0,000	-	0,625
Thymoma	Ref			
Bronchoscopy finding				
Direct tumor	1,106	0,633	0,081	3,023 (0,874 – 10,456
Indirect tumor	-1,803	1,004	0,073	0,165 (0,023 – 1,179)
Chronic bronchial changes	-18,104	4920,775	0,997	$1,37 \times 10^8$
Mukosal injury	Ref			

Ref = pembanding

Table 3 shows that both patients aged <60 years and aged ≥ 60 years (62.2% and 65.0%) did not experience intraoperative desaturation as indicated by no hypoxemia. The results of the chi- square test obtained a value of p = 0.732 (p> 0.05) indicating that age was not associated with intraoperative desaturation events. Based on gender, it was found that in both male and female patients, the majority (62.5% and 65.8%) also did not experience hypoxemia. The results of the chi-square test obtained a value of p = 0.719 (p> 0.05) indicating that gender was not associated with the incidence of intraoperative desaturation. Based on BMI, both patients with overweight, normal, and under normal weight also tend not to be hypoxemic (100.0%; 60.0%, and 65.2% of patients respectively). The results of the Fisher's exact test obtained a value of p = 0.420 (p> 0.05) indicating that BMI was not associated with intraoperative desaturation.

Smoking status was also not related to intraoperative desaturation (p-value from the chi- square test obtained was 0.777 or p>0.05), because both smoking patients, ex-smokers, and non- smokers were mostly (65.5% each; 58.1% and 64.2%) also did not show hypoxemia. According to the presence of comorbidities, it was found that the presence of comorbidities was associated with intraoperative desaturation (p-value from the chi-square test of 0.007 or p<0.05).

Table 5. Independent factors in the incidence of desaturation experience hypoxemia.

Karakteristik	Koefisien	SE	p	OR (IK95%)
Comorbidities				
Yes	0,866	0,416	0,037	2,378 (1,052 – 5,376)
No	Ref			
Type of Anestesi				
Local	-0,702	0,563	0,212	0,496 (0,164 – 1,493)
General	Ref			
Procedure				
Bronchial wash	-0,121	0,841	0,885	0,886 (0,171 – 4,603)
Bronchial wash + Bronchial brush	-1,027	0,601	0,087	0,358 (0,110 – 1,162)
Bronchial wash + forceps biopsy	0,087	0,698	0,900	1,091 (0,278 – 4,283)
Bronchial wash + Cryobiopsi	-1,220	0,703	0,083	0,295 (0,074 – 1,171)
>2 Procedure	Ref			
Temuan patologi anatomi				
Karsinoma sel skuamosa paru	-0,442	0,563	0,433	0,643 (0,213 – 1,940)
Adenokarsinoma paru	0,484	0,478	0,311	1,622 (0,636 – 4,137)
Kanker paru karsinoma sel kecil	20,324	0,000		$6,71 \times 10^8$
Timoma	19,442	0,000		$2,78 \times 10^8$
Lainnya	Ref			
Bronchoscopy finding				
Direct tumor	0,741	0,612	0,226	2,098 (0,632 – 6,965)
Indirect tumor	1,076	0,675	0,111	2,932 (0,781 – 10,999)
Chronic bronchial changes	0,264	0,979	0,788	1,302 (0,191 – 8,868)
Mucosal injury	Ref			

Ref = pembanding

According to the type of action, there was a significant relationship with intraoperative desaturation (p=0.019). Patients with bronchial washings mostly (66.7%) did not experience desaturation, patients with bronchial washings + bronchial washings and bronchial washings + cryobiopsi most (77.1% and 75.0%) also did not experience desaturation, whereas in patients with bronchial washings and forceps biopsies and most of the patients with > 2 actions (57.1% and 52.5%) experienced desaturation. The duration of action was not related to intraoperative desaturation (p=0.259) because neither the patients with a duration of action > 30 minutes nor 10-30 minutes (55.6% and 66.0%) did not experience hypoxemia. The location of the action was also not related to the incidence of intraoperative desaturation (p = 0.484), both patients with small action sites or at least 1 location or patients with > 1 action site mostly (65.4% and 60.9%) did not

Based on the findings of anatomic pathology, both patients diagnosed with lung squamous cell carcinoma, lung adenocarcinoma, or other diseases tend not to experience hypoxemia (67.6%; 52.3%; and 71.0% of patients respectively), whereas in Patients diagnosed with lung cancer, small cell carcinoma or thymoma, all (100.0%) experienced desaturation. The results of the Fisher's exact test obtained a value of p = 0.072 (p> 0.05) indicating that the findings of anatomic pathology were not associated with intraoperative desaturation. According to the history of drug use, it was found that in both patients with a history of drug use or not, the majority (57.1% and 63.7%) did not experience desaturation. Fisher's exact test obtained p = 0.707 (p> 0.05) indicating that a history of drug use was not associated with intraoperative desaturation.

Based on the results of the analysis of the relationship between the characteristics of patients undergoing bronchoscopy with intraoperative bleeding and desaturation events, a multivariate analysis was performed using multinomial logistic regression on several characteristic factors that had a p-value <0.25 to determine which characteristics had the most dominant relationship with intraoperative bleeding and desaturation

events. Characteristic factors that met the requirements for multivariate analysis for intraoperative bleeding included age, comorbidities, type of comorbidity, type of anesthesia, type of procedure, duration of action, anatomical pathology findings, and bronchoscopy findings. The results of the multivariate analysis are shown in Table 4.

Patient characteristic factors associated with intraoperative bleeding Based on Table 4 are types of comorbidities which include COPD and cardiovascular disease, indicated by the acquisition. Furthermore, patient characteristic factors that meet the requirements of multivariate analysis for intraoperative desaturation events include comorbidities, type of anesthesia, type of procedure, anatomical pathology findings, and bronchoscopy findings. The results of the multivariate analysis are shown in Table 5.The presence of comorbidities is consistently associated with intraoperative desaturation events. This is indicated by the acquisition of a p-value of 0.037 ($p < 0.05$). The OR value obtained was 2.378 (95% CI: 1.052 – 5.376), OR > 1 with a 95% CI not including the number 1 indicating that the presence of comorbidities is a risk factor for intraoperative desaturation events. The OR value of 2.378 indicates that patients with comorbidities are 2.378 times more likely to experience intraoperative desaturation than patients without comorbidities.

Discussion

The prevalence of intraoperative desaturation events in patients undergoing bronchoscopy in this study was 36.6%. The results of this study are similar to a study conducted by Zhang W et al in 2022 which stated that hypoxemia can occur in 28.8 to 56% of patients undergoing bronchoscopy. Other literature states that the reported incidence of oxygen desaturation during bronchoscopy is in the range of 1 % to 97%.[13]

This desaturation event occurs due to the partial pressure of arterial oxygen decreasing by more than 10-20 mmHg during bronchoscopy, which in turn increases the risk of respiratory failure. [39] The results of this study are different from the study conducted by Carlens J et al. This study found that intraprocedural bronchoscopy complications occurred in 7.2% with 4.8% of them being hypoxemia.40 The different results of this study could be due to the many risk factors associated with desaturation during bronchoscopy. Some of these include lung function, comorbidities, use of sedation, and procedure-related factors. [14]

Another complication that can occur during a bronchoscopy procedure is bleeding. In this study, it was found that 48.5% of patients experienced bleeding, with 40.8% of them experiencing mild bleeding, 4.9% moderate bleeding, and 2.8% severe bleeding. Research conducted by Bo L et al in 2021 found an overall incidence of bleeding in patients undergoing bronchoscopy of 61.8%. Based on the type of bronchoscopy procedure, the overall incidence of bleeding in patients undergoing bronchoscopy biopsy was found to be 37%. Nearly half of the patients (41.37%) who underwent the procedure experienced light bleeding, and only a small proportion of patients experienced heavy bleeding (1.47%). Whereas in patients who underwent therapeutic bronchoscopy procedures, the overall incidence of bleeding was 37.76% with 1.63% of them having severe bleeding.[16]

The risk of bleeding depends on the procedure performed and the vascularity of the tissue sampled. The procedure that is considered to be very traumatic and causes bleeding is bronchoalveolar lavage. Bleeding may also result from accidental perforation of a pulmonary vessel during TBNA, but this complication is very rare. Significant bleeding may occur after sampling a highly vascularized tumor (eg, carcinoid tumor) or after an endobronchial biopsy of an endobronchial tumor (bleeding from a central lesion).[2,8]

From the results of the study, it was found that the majority (57.7%) of the patients who underwent bronchoscopy were aged <60 years and were female (73.2%). Nearly half of the patients (49.3%) had normal BMI. Faiz et al in his research found that the median age of patients undergoing bronchoscopy was around 59.9 years with an age range of 17.4 to 90 years with an average age of 57.[6]

± 14.7 years, with the most sex being male, namely 56.6% and a median BMI of 26.3 kg/kg m2 with a range of 14.3-54.9 kg/m2 and an average of 26.9±5.8 kg/m2.42 Kobayashi et al in their study had patient characteristics with an average age of 67.83±13.44 years, with a higher proportion of males than females (68%: 32%), with an average BMI of patients ranging from 22.1 ± 3.35 kg/m2.18 Dixon et al in their research found the median age of carcinoid tumor patients undergoing bronchoscopy was 60.7 years with an age range of 33 years to 79 years, with a proportion of women as much as 75.5% and male 24.5%. [19]

Characteristics of the sample as a smoker were obtained at 40.8%. Characteristics of patients in the study of Dixon et al smokers were found as many as 53.1%. Most of the patients (56.3%) had comorbidities with the most types of comorbidities namely cardiovascular disease as much as 35.9% of which 18.3% of them were hypertension. Putra et al in their study Most did not have comorbidities. Based on the type of anesthesia, most of the patients (73.9%) received local anesthesia. Most of the patients in Putra et al's study only underwent local anesthesia and conscious sedation.[19]

In almost half of the patients (33.8%), the most common type of action was bronchial washing and brushing. Most of the patients in Faiz et al's study had 1 procedure as much as 71.9%, 2 procedures as much as 19.7%, and 3 or more procedures as much as 8.4%. 17 Kobayashi et al in their study got the most procedures in the form of endobronchial ultrasonography with a guide sheath transbronchial biopsy (EBUS-GS) -TBB) as much as 43.6%, followed by endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) 32%, bronchoalveolar lavage (BAL / bronchial washings) 20.3%, transbronchial lung biopsy (TBLB) 16.3%, endobronchial biopsy (EBB) 7 %, observation 5.8%, bronchial sweep 5.2%, and management 2.3% and transbronchial biopsy (TBB) 1.7%. Therapeutic bronchoscopy has a significantly higher risk of bleeding compared to diagnostic bronchoscopy. [30]

The majority of patients (74.6%) underwent the procedure for 10-30 minutes, and most (54.9%) of the action locations were small (≤ 1 location). In the study of Kobayashi et al, it was found that the average examination time was around 38.48 ± 17.20 minutes. [18]

The most common anatomic pathology findings in patients were others (43.7%) followed by lung adenocarcinoma (31.0%). Vivekanand et al in their study found adenocarcinoma to be the most common lung cancer disorder, namely at 34.82%, followed by squamous cell carcinoma at 31.02%. 21%. Most bronchoscopy findings were direct tumors, namely in 53.5% of patients. Rabahi et al in their study found that bronchoscopy findings were associated with mucosal injury either with or without secretions.[12]

Most of the patients (51.4%) did not experience bleeding, 20.8% had light bleeding, followed by 4.9% moderate bleeding, and 2.8% severe bleeding. A review of the literature shows the overall bleeding incidence varies from 0.5-1.3%. Mild bleeding occurs in approximately 0.19% and major bleeding occurs in approximately 0.26% of patients undergoing bronchoscopy. In the study of Takashima et al, it was found that 11.1% of patients experienced bleeding. Bronchoscopy intraoperative bleeding is one of the iatrogenic bleeding that is rarely reported, although this complication is potentially life- threatening. Iatrogenic bleeding ranges from 0.26 to 5% of cases depending on the definition, patient population, and procedure performed.

Bleeding at bronchoscopy was clinically significant in 0.83%, increasing to 1.9% with biopsy including TBLB. TBLB causes light to heavy bleeding around 0.8%, while RBB bleeding occurs only in 0.45%. TBLB causes a 2-fold increased risk of mild- moderate bleeding and a 3-fold increased risk of severe bleeding compared to EBB. [9] Most of the patients aged ≥ 60 years (55.0) experienced bleeding (46.7% of them were light bleeding) but no association was found. significant. Research by Faiz et al found the same thing with p=0.934. In this study, it was found that gender was not associated with intraoperative bleeding. The analysis carried out by Faiz et al found something similar with a value of p = 0.323.[17]

The type of action found a significant relationship with intraoperative bleeding (p<0.001). The incidence of bleeding is almost the same in both transbronchial and endobronchial biopsies with a variability of 1-2.8%. 46 Transbronchial lung biopsies will significantly increase the risk of bleeding. Massive bleeding was predominately induced by therapeutic bronchoscopy compared to diagnostic (incidence 0.059% vs 0.031% and 0.012% vs 0.003%). The risk of bleeding based on the type of procedure starts with procedures that are atraumatic and reported as safe via transnasal inspection and BAL, followed by EBB, EBUS-TBNA, TBNA, EBB in tumor lesions, TBLB, and cryobiopsi.[8]

The highest reported bleeding risk was lung parenchymal cryobiopsi which is considered the highest diagnostic procedure in pulmonary interstitial disease. This technique can take more tissue from the biopsy than conventional transbronchial lung biopsies, which will result in a significantly higher bleeding frequency. Significant bleeding may occur after sampling a tumor that has increased vascularity such as a carcinoid tumor or after an endobronchial tumor biopsy.[8] Anatomical pathological findings are associated with intraoperative bleeding. Lung malignancy is the most common indication for fiber bronchoscopy and is reported to affect risk. [16] Carr in his study found that in the primary lung carcinoma group bleeding occurred from undetected to 23.5 mL with an average blood loss volume of 1.6 mL in patients with a primary diagnosis. malignancy compared to bronchogenic carcinoma which has a bleeding rate of about 1.5 mL.[20]

Age, sex, BMI, smoking status, comorbidities, location of action, history of drug use, not related to intraoperative bleeding. Type of anesthesia, duration of action, type of action, anatomical pathology findings associated with intraoperative bleeding. In multivariate analysis, the most related characteristics were the type of comorbid COPD (p=0.027 OR = 3.0991, 95% CI) and cardiovascular disease (p=0.041 OR = 1.497, 95% CI). Patients with COPD comorbidities have 3.099 times more intraoperative bleeding than patients with other comorbidities and patients with cardiovascular disease comorbidities experience 1.497 times more intraoperative bleeding than patients with other comorbidities.

Analysis conducted by Takashima et al found that age, sex, BMI, smoking status, use of antiplatelet and anticoagulant agents, lesion location, bronchoscopy diagnosis, and anatomical pathology findings, did not have a significant relationship with the incidence of intraoperative bronchoscopy bleeding. The location of the lesion, especially the central part, bronchoscopy diagnosis, additional biopsy, and tricuspid regurgitation velocity (TRV) assessment have a significant relationship with bleeding events. Takashima et al concluded that pulmonary hypertension is one of the risks that will increase the occurrence of moderate bleeding during bronchoscopy. [47] Wang et al in their study found no relationship between age, gender, or comorbidities such as diabetes, hypertension, COPD, and heart disease with the incidence of bleeding during bronchoscopy.[21]

Location, histological type, and lung cancer stage associated with bleeding during bronchoscopy were found in the study of Wang et al. The risk of bleeding is increased if the lesion is located in the central part of the airway compared to the peripheral bronchi with an OR of 2.211; 95% CI 1.276-3.830; p=0.005. In histological type, squamous cell carcinoma and small-cell carcinoma are more at risk of bleeding than adenocarcinoma OR 3.107 and 2.389; 95% CI 1.832-5.271 and 1.271-4.489; p=0.000 and p=0.007. Furthermore, patients with advanced lung cancer are more at risk of bleeding than those with early stages OR 1.583; 95% CI 1.065-2.354; p=0.023.[21]

Accurately measuring the amount of bleeding during bronchoscopy is difficult for several reasons, such as bleeding that is not visible in the bronchial tree and inaccurate estimation of the volume of aspirated blood. Bleeding during bronchoscopy is usually estimated only from direct observation. Carr et al in their study by measuring bleeding in 234 patients undergoing bronchoscopy, found that 89.7% of patients experienced minimal bleeding, 8.1% of patients with mild bleeding, and 2.1 patients with bleeding. was moderate with a bleeding volume range of 21.39-32 mL, and none of the cases experienced heavy bleeding. [20] The cohort conducted by Dixon et al found 5.7% of patients experienced moderate to severe bleeding. The incidence of bleeding complications in the Dixon et al cohort was lower than in the previously published series and there were no events of severe bleeding requiring transfusion, immediate thoracotomy, or death. [44] The cohort conducted by Faiz et al found that the risk of bleeding was minimal with an overall rate of 1.1% and only a 0.2% risk of major bleeding. The need for transfusion or death after bleeding secondary to clopidogrel is rare. [17]

Patients with comorbid cardiovascular disease experience a higher rate of intraoperative bleeding than other comorbid patients. The British Thoracic Society guidelines suggest that COPD patients should be managed optimally if possible before bronchoscopy is performed. Caution should also be exercised when sedating patients with COPD. 17 The study conducted by Solis et al found that intraoperative bronchoscopy bleeding, whether minor or major, was not related to the patient's previous COPD experience. Bleeding in COPD patients was as much as 7.4% with p=0.372.[22]

Desaturation occurred in almost half of the patients (36.6%). Research conducted by Putra et al found that patients who experienced hypoxemia during bronchoscopy were around 20.5%. with patient desaturation. Whether there are comorbidities or not, bronchoscopy findings are not related to patient desaturation. In the multivariate analysis, it was found that there were consistent comorbidities associated with intraoperative desaturation events, indicated by the acquisition of a p-value of 0.037 (p <0.05). The OR value obtained was 2.378 (95% CI: 1.052 – 5.376). The analysis conducted by Kim et al concluded that

high-risk factors for respiratory failure during bronchoscopy were old age, female sex, active smokers, and patients with a history of COPD or previous decompensated heart failure. statistically on the incidence of hypoxemia during bronchoscopy with a value of p = 0.738 while gender found a significant relationship with the incidence of hypoxemia with p = 0.041.[7]

In this study smoking status was also not associated with intraoperative desaturation. This study investigated the smoking status of patients undergoing bronchoscopy by looking at the smoking history and the patient's Brinkmann index. The patient's smoking history was found to be significantly associated with the incidence of hypoxemia with p=0.005, but the Brinkmann index did not have a significant relationship p=0.999.7 The type of anesthesia was not associated with intraoperative desaturation. This is in line with Putra et al's research which obtained an analysis of p =0.431. The bronchoconstrictive effect of lidocaine accompanied by the respiratory depressant effect of midazolam, fentanyl, and propofol is supported by inadequate airway patency so that hypoxemia occurs more frequently in the local anesthetic group accompanied by conscious sedation.

According to the type of action, a significant relationship was found with intraoperative desaturation. Fang et al in their research stated that the type of bronchoscopy procedure had a significant relationship with the incidence of hypoxemia (p<0.001). Putra et al's study found that the type of bronchoscopy procedure did not have a significant relationship with the incidence of hypoxemia (p =0.741), with the type of procedure that experienced hypoxemia the most, namely bronchial washings + TBLB as much as 28.1%, followed by bronchial washings + TBNA 27, 3%, actions that are the same or more than 3 actions 23%, bronchial washings + biopsy forceps 18.4%, and bronchial washings + bronchial brushing 18.2%, and bronchial washings only about 15%.[7]

The length of time of action in Putra et al's study found a significant relationship p = 0.038. The duration of time for patients who experienced hypoxemia was longer with an average of 26 minutes compared to patients without hypoxemia with an average length of action of about 20 minutes. 8 The multivariate analysis conducted in this study showed that patients who had comorbidities had a 2.378 risk of experiencing intraoperative desaturation compared to patients without comorbidities. On the other hand, Putra's study did not find a significant association between the presence of comorbidities and the incidence of hypoxemia during bronchoscopy with p=0.351.[7]

The British Thoracic Society's guidelines for flexible diagnostic bronchoscopy in adults state that patients should be monitored closely using a continuous oximeter during bronchoscopy. Oxygen supplementation can be used when there is desaturation, i.e. when SpO2 is <90% and prolonged for more than 1 minute to reduce the risk of hypoxemia associated with bronchoscopy complications.9 The risk of complications of hypoxemia is related to baseline arterial oxygen saturation (SaO2) and pulmonary function, comorbidities, sedation, and sampling procedures. , changes in acidosis, and increased cardiac output thereby effectively increasing oxygenation to the tissues.[14] A significant decrease in oxygen saturation is usually seen during bronchoscopy beginning with sedation and worsening as it passes through the vocal cords. Desaturation saw in BAL at 89%, bronchial washings at as much as 44%, and bronchial brushing at around 15%.[9]

Most desaturations are transient and do not require specific intervention. Supplemental oxygen administered via nasal or pharyngeal catheter may reduce the incidence, degree, or duration of desaturation. Desaturation

can be prevented by administering oxygen supplementation compared to breathing room air alone, however, the proportion of patients requiring supplemental oxygen varies between 5-32% and depends on forced expiratory volume at 1 second (FEV1) or peak expiratory flow rate (PEFR). [9]

When hypoxemia appears, it occurs as soon as the bronchoscope passes through the larynx because the bronchoscope will fill almost the entire bronchial area resulting in airflow obstruction which results in an imbalance of pulmonary ventilation- perfusion. (V/Q mismatch). In addition, there is a decrease in arterial oxygen tension resulting in hypoxemia. Stimulation by forceps and suction biopsies can stimulate bronchial subepithelial receptors which trigger bronchoconstriction which triggers V/Q mismatch which also leads to hypoxemia and can decrease tidal volume by 40-75%.[8] The hypoxemia hat occurs during bronchoscopy is associated with increased cardiovascular stress and overwork. In addition, there are also changes in lung compliance, both static and dynamic. There are also hemodynamic changes with increase15pulmonary vascular resistance during hypoxia.[15]

Patient characteristic factors associated with intraoperative bleeding are co-morbid types which include COPD and cardiovascular disease. Patients with comorbid COPD and cardiovascular disease have a risk of 3,099 and 1,497 times higher for intraoperative bleeding, respectively than patients with other comorbidities. Research conducted by Leiten EO et al found that 13.1% of COPD patients who underwent bronchoscopy experienced bleeding (9% did not require intervention, 3.3% required intervention, 0.8% required discontinuation of the procedure). Another study conducted by Grendelmeier P et al found that 4.1% of COPD patients had minor bleeding and 0.2% had major bleeding.[6,23]

There are several reasons why COPD increases the risk of bleeding. COPD is characterized not only by chronic local inflammation but also by systemic inflammation. Thus, COPD patients are exposed to oxidative stress secondary to chronic hypoxia and produce reactive oxygen species (ROS) which can damage the mucosa. Second, COPD patients share other smoking-related chronic diseases, such as hypertension, coronary artery disease, or heart failure, and have more cases of using anti-platelet agents, which protect against cardiovascular events but increase the risk of bleeding. However, the exact pathogenesis is still unknown.[24,25]

Research by Nafiu et al found COPD is one of the predictor factors for bleeding events in heart patients. Meanwhile, Huang's study stated that COPD is an independent risk factor for gastrointestinal bleeding. The association of COPD with bleeding events has not been widely studied, so it should be explored further in future studies.[26] Comorbid cardiovascular disease is an independent factor associated with bleeding events. The incidence of hypertension occurs in the majority of patients. Several studies have shown that there may be a strong association between blood pressure and bleeding events during bronchoscopy. Increased pulse pressure may be the cause of the high bleeding rate on percutaneous biopsy. In addition, in several retrospective studies, indices of systolic and diastolic pressure have resulted in a valid detection method demonstrating good sensitivity and specificity for predicting bleeding. Although blood pressure may play a role in some hemorrhagic diseases, the exact theory is still unknown.

Wang and Qian Ye's study found no significant correlation between systolic pressure, diastolic pressure, MAP, pulse pressure, and the risk of bleeding during bronchoscopy. However, a low ratio of pulse and diastolic pressure was associated with an increased risk of bleeding due to biopsy. this ratio has the potential to be

used for risk assessment and risk modification before bronchoscopy. Pulmonary hypertension (HP) can also theoretically cause excessive bleeding after TBLB, and current recommendations suggest that TBLB should be performed with caution in patients with elevated pulmonary artery pressure. Another study also reported that most pulmonologists considered an average pulmonary artery pressure greater than 40 mm Hg to be unsafe for TBLB. A prospective controlled trial in patients with HP of various etiologies with 24 patients who had an average mPAP of 45 mm Hg and underwent transbronchial biopsies demonstrated that patients with severe HP did not experience significant bleeding or worsening hypoxemia.[5,10,11]

The risk of bleeding in patients with cardiovascular disease may also be related to the therapy the patient receives to treat these comorbidities. Research conducted by Ernst et al found that the use of clopidogrel increases the risk of bleeding. Therefore, consumption of clopidogrel must be stopped before the bronchoscopy procedure is carried out. Aspirin is also known to exacerbate the bleeding effects of clopidogrel. Clopidogrel is a thienopyridine compound that inhibits adenosine diphosphate-induced platelet aggregation. This drug can prevent thrombosis in patients with acute coronary syndrome, coronary artery stenting, and cerebrovascular disease. A study conducted by Ernst et al found that the incidence of bleeding in patients taking clopidogrel compared to controls was very high (89% vs 3.4%). Likewise with patients taking clopidogrel and aspirin when compared to controls (100% vs 3.4%). Bleeding rates were also significantly higher in the clopidogrel group, with 27% light, 34% moderate, and 27% severe bleeding. Based on these findings, the study recommends discontinuing clopidogrel use for 5 to 7 days before patients undergo bronchoscopy procedures. In addition, the indication for the procedure must be clear because the clinical decision has consequences in the form of stopping treatment which is considered beneficial for patients with cardiovascular disease.[23]

In this study, the presence of comorbidities was found to be associated with intraoperative desaturation events, as indicated by the acquisition of a p-value of 0.037 ($p < 0.05$). The OR value obtained was 2.378 (95% CI: 1.052 – 5.376), OR > 1 with a 95% CI not including the number 1 indicating that the presence of comorbidities is a risk factor for intraoperative desaturation events. The OR value of 2.378 indicates that patients with comorbidities are 2.378 times more likely to experience intraoperative desaturation than patients without comorbidities. The British thoracic society states that comorbidities, basal arterial oxygen saturation (SaO2), pulmonary function, and sedation are associated with the risk of complications in the form of hypoxemia during bronchoscopy procedures. Comorbidities as risk factors can be associated because they tend to occur in older patients who have an increased risk of bronchoscopy.[25]

Increased respiratory complications in patients who are included in the comorbid group with low oxygen saturation, one of which is COPD can be caused by the impact of bronchoscopy on cardiopulmonary disorders. Bronchoscopy alters the mechanism of breathing by increasing airflow resistance and the work of breathing. These changes can disrupt exchanges and may take several minutes to several hours to return to normal.[25]

Oxygen desaturation during bronchoscopy may also indicate an impaired cardiopulmonary reservoir that is not capable of adequate hemodynamic adaptation. In healthy individuals with good cardiopulmonary function, the acute hypoxemia that can occur during the procedure will elicit compensatory responses, such as regional pulmonary vasoconstriction, hyperventilation, a rightward shift of the oxyhemoglobin dissociation curve associated with acidosis, and increased cardiac output, which effectively increases oxygenation to the tissues. However, patients with compromised cardiopulmonary reservoirs have inadequate compensatory mechanisms and are therefore vulnerable to hypoxic stress, which in turn activates a vicious cycle of inflammation and infection.[1]

LIMITATION

This study did not include other variables such as blood gas analysis, pulmonary function examination, and the type of anesthetic drug use. This can be used as further research in the future

CONCLUSION

Desaturation occurs in nearly half of patients and most patients do not bleed. Most of the patients undergoing bronchoscopy are aged less than 60 years and are female. Nearly half of the patients had normal BMI and were smokers. Most of the patients had comorbidities with the most types of comorbidities namely cardiovascular disease where half of them were hypertension. Based on the type of anesthesia, most patients receive local anesthesia. In almost half of the patients, the most common type of action is bronchial rinsing and brushing. Most patients undergo surgery for 10-30 minutes, and most of the action locations are in 1 location. The most common anatomic pathology findings in these patients were followed by lung adenocarcinoma. Patients generally do not have a history of drug use, and the most common bronchoscopic findings are direct tumors.

There is a relationship between several characteristics of the incidence of bleeding. These characteristics include the type of action, duration of action, anatomical pathology findings, and bronchoscopy findings. There is a relationship between several characteristics of intraoperative desaturation events. These characteristics include comorbidities and types of action. COPD and cardiovascular disease are independent factors associated with bleeding on bronchoscopy. Co- morbidities are independent factors associated with intraoperative desaturation events

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Conflict of Interest

There is no conflict of interest

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PROGNOSTIC NUTRITIONAL INDEX AND INSTANT NUTRITIONAL ASSESMENT IN CORRELATION WITH OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL OF LUNG ADENOCARCINOMA PATIENTS RECEIVING PLATINUM-BASE FIRST LINE CHEMOTHERAPY

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ABSTRACT

INTRODUCTION

Lung cancer or known as bronchogenic carcinoma is a tumour originating from lung parenchyma or bronchus. It is the leading cause of death due to cancer around the globe. World Health Organization (WHO) reports that the most common cause of cancer death in 2020 was lung which reached up to 1.80 million deaths. In Indonesia the incidence of lung cancer has risen over time. In 2018, WHO reported 30,023 new cases of this kind of cancer in Indonesia and 2.6% of Indonesia's total deaths is due to lung cancer.

Malnutrition is one of complications in lung cancer. Previous studies have reported that malnutrition occurs in 31-97% of lung cancer patients. Anti-cancer regimen is the most cause of malnutrition. Chemotherapy can result in nausea, vomiting, abdominal cramps and distension, mucositis, and paralytic ileus. Several antineoplastic agents, including fluoracil, adriamycin, methotrexate, and cisplatin have been known to induce severe gastro intestinal complication.

Prognostic Nutritional Index (PNI) is an indicator as nutritional and immune status of cancer patients. It is calculated based on the serum albumin concentration and peripheral blood lymphocyte count. This parameter is one of nutritional status parameters which have been widely used. Instant Nutritional Assessment (INA) is an assessment of nutritional status based on serum albumin level and total lymphocyte count (TLC). Both PNI and INA can be used for assessing nutritional status of patients.

It has been known that Progression Free Survival (PFS) and Overall Survival (OS) can assess the progression as well as the success of therapy in lung cancer. Progression Free Survival is the length of time from therapy initiation to disease progression or worsening, while OS is the duration of patient survival between therapy initiation and death. Therefore, we analyzed the correlation of PNI and INA with PFS and OS in patients with lung adenocarcinoma.

METHODS

We conducted a retrospective cross-sectional cohort study in lung adenocarcinoma patients with EGFR mutation who received platinum based first line chemotherapy in Dr. Moewardi Hospital, Surakarta, Indonesia between 1st July 2018 and 30th June 2021. The sample collection used total purposive sampling technique. We included adult patients aged over 18 years old who were diagnosed with lung adenocarcinoma based on anatomic pathology features receiving platinum-based chemotherapy and having laboratory data of routine blood, lymphocyte, and serum albumin examinations. Patients who had incomplete medical records, autoimmune, malignancy other than lung cancer, lung infection, infection beyond the lungs, stroke, kidney function disorder, liver function disorder, diabetes mellitus, and received immunosuppression therapy were excluded from study.

The variables that we analyzed were PNI and INA which were calculated based on serum albumin and total lymphocyte count. Meanwhile the outcomes measured were PFS and OS.

All the data obtained were statistically analyzed with IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 28. The distribution data were analyzed with Shapiro-Whilk test if the samples were less than 50 or Kolmogorov-Smirnov test if the samples were over 50. Univariate analysis was performed for determining the subjects' characteristics. The comparison test used t-test for normal distribution data or Mann-Whitney test for differences in total lymphocyte count, serum albumin level, PNI, and INA.

Subsequently, the optimal cut off point, sensitivity, and specificity of PFS and OS were measured with a receiver operating characteristic (ROC) curve. The median values of OS and PFS based on the scores of PNI and INA were visualized on Kaplan-Meier curve. The difference in significance of Kaplan-Meier curve was determined with log-rank test, and $p< 0.005$ was considered significant. Cox regression test was applied to find out hazard ratios of PNI and INA on PFS and OS of these lung adenocarcinoma patients.

RESULTS

This study involved 82 patients with lung adenocarcinoma who met the inclusion and exclusion criteria. The mean age of subjects was 58.5 ± 11.44 years old, ranging from 18 to 78 years old. The subjects were dominated by male (73.2%) and smokers (65.9%). The mean BMI was 19.35 ± 3.11 kg/m2 ranging from 14.30 to 30.14 kg/m2. Paclitaxel-Carboplatin was the most common therapy used (37.8%), followed by Paclitaxel-Cisplatin (30.5%), Docetaxel-Cisplatin (24.4%), and Docetaxel-Carboplatin (7.3%). The mean PNI score was 40.72 ± 6.79. based on PNI score 65 subjects (79.3%) were categorized as B and 17 subjects (20,7%) were in category A. instant Nutritional Assessment obtained 40 subjects (48.8%) with serum albumin of ≥ 3.5 and lymphocyte of ≥ 1.5 and 42 subjects (51.2%) having serum albumin of < 3.5 and lymphocyte of ≥ 1,5 (Table 1)

Characteristic	N/Mean±Sd	%/Min-max
Age	58.56 ±11.44	18.00-78.00
Sex		
Male	60	73.2%
Female	22	26.8%
BMI kg/m^2	19.35 ±3.11	14.30-30.14
Stadium		
IVA	30	36.6%
IVB	52	63.4%
Therapy		
Docetaxel-Carboplatin	6	7.3%
Paclitaxel-Carboplatin	31	37.8%
Docetaxel-Cisplatin	20	24.4%
Paclitaxel-Cisplatin	25	30.5%
Smoking Status		
Non-Smoker	23	28.0%
Smoker	54	65.9%
Passive smoker	5	6.1%

Laboratory Test		
Monocyte	7.20 ±3.05	1.80 - 15.82
Lymphocyte	15.60 ±8.21	3.20 - 46.50
Neutrophil	76.40 ±10.87	38.80 - 99.40
Albumin	3.30 ±0.51	2.20 - 4.30
Leukocyte	99.20 ±6.86	78.80 - 123.20
Total Lymphocyte	1551.82 ±825.29	293.44 - 4767.55
PNI (Prognostic Nutritional Index)	40.72 ±6.79	29.70 -61.94
A	17	20.7%
B	65	79.3%
INA (Instant Nutritional Assessment)		
Albumin ≥ 3.5 & lymphocyte ≥ 1.5	40	48.8%
Albumin < 3.5 & lymphocyte ≥ 1.5	42	51.2%

Table 1. The Demographic Characteristics of The Study Subjects

The Kaplan-Meier curves of PFS and OS in Figures 1.A and 1.B demonstrate the value of PFS and OS of the total samples. Using these curves, we obtained the median progressive time was 48 weeks, ranging from 8 weeks to 156 weeks, while the median survival time was 76 weeks, ranging from 28 weeks to 208 weeks. (Tables 2)

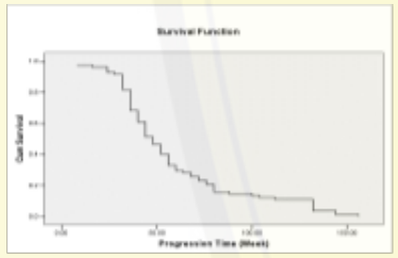
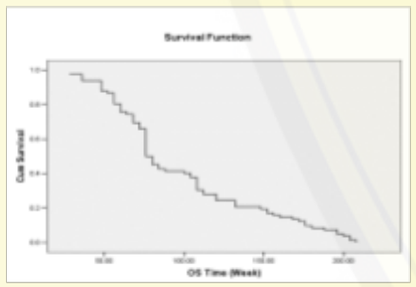


Figure 1.A. The Kaplan-Meier curve of PFS of The Study Subjects



	Median	Min-Max
Progression Time (Weeks)	48	8 -156
Survival Time (Weeks)	76	28-208

Using the cut-off point of 48 weeks for time progress, we found no significant differences between time progress of < 48 weeks and > 48 weeks in terms of age, sex, stadium, therapy received, and smoking status (p>0.05). These findings indicated that age, sex, stadium, therapy given, and smoking status were not factors influencing the time progress. (Table 3)

Characteristics	Time Progress		p-value
	<48 weeks	>48 weeks	
Age[a]	56.23 ±12.73	58.68 ±10.20	0.981
Sex[b]			0.258
Male	27 (67.5%)	33 (78.6%)	
Female	13 (32.5%)	9 (21.4%)	
Stadium[b]			0.531
IVA	16 (40.0%)	14 (33.3%)	
IVB	24 (60.0%)	28 (66.7%)	
Therapy[b]			0.799
Docetaxel-Carboplatin	4 (10.0%)	2 (4.8%)	
Paclitaxel-Carboplatin	15 (37.5%)	16 (38.1%)	
Docetaxel-Cisplatin	10 (25.0%)	10 (23.8%)	
Paclitaxel-Cisplatin	11 (27.5%)	14 (33.3%)	
Smoking Status[b]			0.292
No smoker	12 (30.0%)	11 (26.2%)	
Smoker	24 (60.0%)	30 (26.2%)	
Passive Smoker	4 (10.0%)	1 (2.4%)	

Note: [a]Mann whitney test (numerical data which did not meet the normality assumption), [b]chi-square test (nominal categorical data)

Table 3. The Subjects characteristics Based on Time Progress

Similar outcomes were obtained in Time Survival using the cut off point 76 weeks. We found that age, sex, stadium, therapy, and smoking status did not differ significantly between subjects who had time survival < 76 weeks and those with time survival > 76 weeks (p<0.05) Table 4)

Characteristic	Time Survival		p-value
	<76 weeks	>76 weeks	
Age[a]	58.10 ±11.91	59.02 ±11.07	0.816
Sex[b]			0.618
Male	31 (75.6%)	29 (70.7%)	
Female	10 (24.4%)	12 (29.3%)	
Stadium[b]			0.169
IVA	12 (29.3%)	18 (43.9%)	
IVB	29 (70.7%)	23 (56.1%)	
Therapy[b]			0.091
Docetaxel-Carboplatin	3 (7.3%)	3 (7.3%)	
Paclitaxel-Carboplatin	16 (39.0%)	15 (36.6%)	
Docetaxel-Cisplatin	14 (34.1%)	6 (14.6%)	
Paclitaxel-Cisplatin	8 (19.5%)	17 (41.5%)	
Smoking Status[b]			0.717
No Smoker	13 (31.7%)	10 (24.4%)	
Smoker	26 (63.4%)	28 (68.3%)	
Passive Smoker	2 (4.9%)	3 (7.3%)	

Note: [a]Mann whitney test (numerical data which did not meet the normality assumption), [b]chi-square test (nominal categorical data)

Table 4. The Subjects' Characteristics Based on Time survival

The Kaplan Meier curve of PFS based on PNI demonstrated that patients with lung adenocarcinoma who had PNI category B tended to have faster progression than those with PNI category A. The median values

of PFS of patients with category A and B were 76 weeks and 44 weeks, respectively. Log rank analysis obtained p=0.02 suggesting a significant difference between them. (Figure 2)

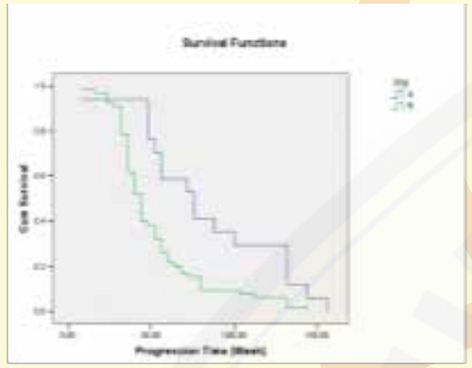


Figure 2. The Kaplan Meier Curve of PFS based on PNI

Figure 3 delineates that lung adenocarcinoma patients with poor INA (albumin <3.5 and lymphocyte ≥15) were likely to progress faster than those with good INA. The medians of PFS for poor and good INA were 44 weeks and 56 weeks. Log rank test revealed no significant difference between those two curves (p=0.067)

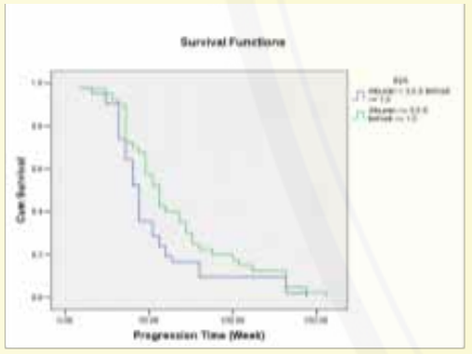


Figure 3. The Kaplan Meier Curve of PFS based on INA

The OS Kaplan Meier curve shows that patients with lung adenocarcinoma who had PNI category B tended to die more quickly than those with PNI category A. The medians OS for PNI categories A and B were 120 weeks and 76 weeks, respectively and log rank test had p=0.006. (Figure 4)

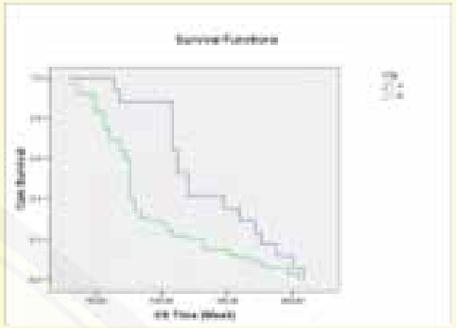


Figure 4. The Kaplan Meier Curve of OS based on PNI

Figure 5 describes those subjects with poor INA (albumin < 3.5 and lymphocyte ≥ 15) seemed to die faster than those with good INA (albumin ≥ 3.5 and lymphocyte ≥ 15). The median OS for poor INA was 76 weeks, while the median PFS with good INA was 104 weeks. The log rank test obtained p=0.050.

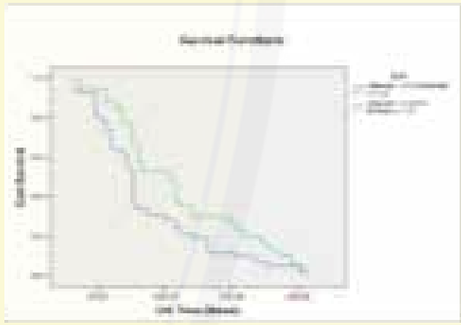


Figure 5. The Kaplan Meier Curve of OS based on INA

The correlation analyses are presented in tables 5 and 6 below. Bivariate analysis found that PNI had a significant correlation with PFS (HR=2.25; 95% CI: 1.29-3.94; p=0.05). Subjects with PNI category B had higher risk of progression by 2.25 folds per week as compared to those with PNI category A.
Meanwhile INA did not correlate significantly with PFS.

Variable	Progresion Free Survival			
	Bivariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
PNI	2.25 (1.29-3.94)	0.005*	2.25 (1.18-4.30)	0.014*
INA	1.46 (0.94-2.26)	0.093	1.00 (0.60-1.65)	0.994

Note: Cox Regression Test *) Significant at a=5

In multivariate analysis, PNI was a dominant variable which had significant correlation with PFS (HR=2.25; 95% CI: 1.18-4.30; p=0.014) and INA remained not correlated with PFS (HR=1.00; 95% CI:

0.60-1.65; p=0.994).

Subsequently, the bivariate and multivariate analyses on the correlations of PNI as well as INA with OS showed that PNI correlated significantly with OS (HR=2.05; 95% CI: 1.18-3.57; p=0.011 and HR=1.89; 95% CI: 1.01-3.54; p=0.046; respectively), while INA did not correlate with OS (p=0.589). (Table 6)

Variable	Overall Survival			
	Bivariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
PNI	2.05 (1.18-3.57)	0.011*	1.89 (1.01- 3.54)	0.046*
INA	1.52 (0.98-2.36)	0.064	1.15 (0 .70- 1.89)	0.589

Note: Cox Regression Test *) Significant at a=5

Table 5. The Correlation of Prognostic Nutritional Index and Instant Nutritional Assessment with Overall Survival

DISCUSSION

One of complications in lung adenocarcinoma is malnutrition. Malnutrition can lead to decreased immune function, high risk of infection, low response as well as tolerance to therapy, and decreased quality of life and survival rate. A study by Xara et al reported that malnutrition occurred in 35.7% of patients with non-small cell lung carcinoma. 5-8

The relative risk of mortality due to malnutrition was reported to be 1.8 times higher in cancer patients with malnutrition than those without malnutrition. Hence, nutritional status monitoring is necessary in the management of cancer. Ge et al study in 2019 revealed that 25.1% lung cancer patients required management related to nutrition and/ or immediate nutritional support. In addition, only 11.1% lung cancer patients with advanced stadium did not require nutritional intervention. This indicate that malnutrition is common among patients with advanced stadium of lung cancer. Many of these patients confirmed inadequate food, as it has been reported that 58.8% lung cancer patients experienced feeding difficulty.5-9

Prognostic Nutritional Index is one of nutritional status parameter which has been widely used to evaluate nutritional conditional of chronic patients. A meta-analysis by Liv et al (2021) demonstrated that low PNI score is associated with survival rate of lung cancer patients. Another parameter to assess nutritional status is INA. Both parameters use similar indicators, namely serum albumin and total lymphocyte count. 5-12

In order to evaluate the success of lung cancer therapy, there are two parameters which can be used, they are PFS and OS. However, the use OS has been criticized as it is difficult to determine the beginning and end of OS. The primary limitation of this study is it was done in one hospital only, so that the outcomes may not be generalized. Therefore, further study involving multicenters are required.

CONCLUSION

In conclusion, increased PNI correlates with increases of PFS and OS. Thus, PNI score can predict the PFS and OS of patients with non-small cell lung cancer.

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POSTER

SURVIVAL RATE OF LUNG CANCER PATIENTS CONCOMITANT PULMONARY TUBERCULOSIS INFECTION AND INFLUENCING FACTORS

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ABSTRACT

Background

Lung cancer is one of the diseases with a poor prognosis in Indonesia that tends to increase, but Indonesia is also an endemic area of pulmonary tuberculosis and it is not uncommon for a patient to suffer from both diseases. Pulmonary tuberculosis is a risk factor for lung cancer so the purpose of this study was to determine the prognosis of lung cancer when detected along with tuberculosis infection.

Method

This study is a retrospective cohort study and data was collected by consecutive sampling of 72 patients diagnosed with lung cancer concomitant pulmonary tuberculosis infection at RSUP Prof. R. D. Kandou, Manado in 2022-2023. Data comes from the patient's medical record.

Result

The sociodemographic characteristics of lung cancer patients committed to pulmonary TB infection were 60% male, average age 58.5 years, and 57% with a history of smoking. The most common type of cancer was adenocarcinoma (29%), stage 4 (75%), with the most bacteriological status of TB is acid fast bacteria Negative (56%).

The 1-year survival rate of lung cancer patients with pulmonary TB infection was 46% with the average survival rate of lung cancer patients with pulmonary TB infection was 9 months. The characteristic that showed a significant association with the survival rate of lung cancer patients concomitant with pulmonary TB infection was TB treatment status. In patients with cured TB treatment status, survival rate of more than 9 months was 39% and in complete TB treatment status of 58%. Other factors that affect the survival rate of lung cancer patients concomitant with pulmonary TB infection such as sex, age, smoking history, type of cancer cells, cancer cell degree, lung cancer therapy, and bacteriological status of TB were found not to be related to the survival rate of lung cancer patients concomitant with pulmonary TB infection.

Conclusion

Factors that can affect the survival period of lung cancer patients at RSUP Prof. R. D. Kandou, Manado are TB treatment status of cured (39%) and complete (58%) patients.

Keywords

Lung cancer, concomitant pulmonary TB infection, survival rate.

SERUM ALBUMIN AS A PREDICTOR FACTOR IN DECREASING PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL IN ADVANCED STAGE ADENOCARCINOMA WITH EGFR COMMON MUTATION TREATED WITH AFATINIB AT DR MOEWARDI HOSPITAL

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ABSTRACT

Background: Albumin is a predictor of decreased PFS and OS in adenocarcinoma patients receiving afatinib therapy.[1,2]

Methods: Retrospective cohort study. There were 57 subjects who met the inclusion and exclusion criteria. Serum albumin data was taken from medical records.

Result: There were 26 (45.6%) patients with hypoalbumin (<3.5 g/dl) and 31 (54.4%) patients who had normal albumin levels (< 3.5 g/dl). The median PFS in patients with hypoalbumin was 13 months while those with normal serum albumin levels was 19 months (p = 0.029). The median OS in patients with hypoalbumin was 15 months while patients with normal serum albumin levels was 22 months (p = 0.027). Multivariate analysis showed albumin levels (HR=1.09; CI: 1.35-7.09; p=0.008), ECOG PS (HR=14.05; CI: 4.84-40.82; p<0.001) and EGFR mutation (HR=2.51; CI: 1.03-6.12; p=0.043) were independent predictors of PFS. The results of the multivariate analysis also showed albumin levels (HR=2.47; CI: 1.27-4.81; p=0.008), age (HR=0.53; CI: 0.28-1.00; p=0.049), body mass index (HR=3.67; CI: 1.01-13.36; p=0.049), ECOG PS (HR=7.92; CI: 3.10-20.22; p<0.001) and mutation EGFR (HR=2.29; CI: 1.11-4.72; p=0.024) was an independent predictor factor for OS.

Discussion: Serum albumin is the simplest and most effective variable indicating the function of visceral proteins. Albumin is used in assessment of malnutrition and inflammation. Malnutrition is also associated with lower quality of life, decline response to treatment, increased risk of chemotherapy toxicity and decrease survival rates.[3,4,5]

Conclusion: The results of this study show that hypoalbumin before treatment is associated with decreased PFS and OS in lung adenocarcinoma.

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EMPYEMA THORACALIS MIXING WITH MALIGNANT PLEURAL EFFUSION IN METASTASE ENDOMETRIAL CARCINOMA: CASE REPORT

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ABSTRACT

Background: Empyema is a condition of pus collection in the pleural cavity. Nevertheless, there have been few reports of empyema from metastatic pleural effusion, especially in patients with endometrial carcinoma.

Case: A 45 years old female patient with a history of endometrial carcinoma stage III came to the polyclinic with chief complaints of dyspnea and cough three days before admission. The CXR revealed a right pleural effusion. Thoracocentesis was performed with the production of cloudy yellow fluid. Two days later the patient came back with the same complaint. Thoracocentesis was performed with the production of seroxanthochrome fluid. The CXR was performed and showed an increase in bilateral pleural effusion. A pigtail was placed on the right hemithorax with an initial production of 1000 ml of milky white fluid. The Cytopathological examination from pleural fluid suspected metastatic adenocarcinoma.

Discussion: Pleural fluid production in empyema patients is characterized by thick and purulent fluid. In our patient, there was the transformation of the pleural fluid characteristic of the pleural fluid during repeated thoracocentesis. This can be caused by the presence of underlying adenocarcinoma metastases in a patient that had been identified after the cytological examination. Thus, the cytological examination must be performed on all pleural effusion fluids.

Conclusion: Pleural effusion is a rare clinical manifestation found in endometrial carcinoma. Infected pleural effusion may cause empyema. Empyema as a clinical finding can also occur in endometrial carcinoma patients. Therefore, the cytopathological examination is essential in all pleural fluids.

Keyword: *empyema, pleural effusion, metastatic*

CLINICAL OUTCOME OF YOUNG AGE GROUP LUNG CANCER PATIENTS AND INFLUENCING FACTORS

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ABSTRACT

Background

Lung cancer is the deadliest malignancy of all cancers. Globocan reported that in Indonesia there were 34,783 or 8.8% of new cases, with details of 25,943 (14.1%) occurring in men, while the number of deaths was 30,843 or 13,300 in men, while the number of deaths was 30,843 or 13,300. 2%) and a 5-year prevalence of 37,662 (13.77%). Data on the incidence of lung cancer at a young age, description of characteristics, risk factors, incidence rates, and therapeutic outcomes obtained (outcome) do not have as much data when compared to data for the older age group.

Method

Method The study is a retrospective cohort study, which examines backwards using secondary data, specifically medical records of patients at Persahabatan Hospital in Jakarta from January 2023, with a total sample of 45 respondents.

Result

In this study, the number of samples was 45, univariate analysis was carried out, and the results showed that the average age of the sample in the study was 37 years with an average of 25 men and 20 women, the average had a genetic history of 16 and did not have genetic 29, the average exposure to carcinogens was 29 and not exposed to carcinogens 16, the average smoker is 24 and does not smoke 21, the average performance status 1 is 21 people, performance status 2 (16), performance 3 (7), and performance status 4 (1), the average has a subjective response in the form of complaints 45, the average has a subjective response in the form of complaints 45, the average objective response is partial disease (6), stable disease (28) and progressive disease (11), mean positive EGFR mutation (35) and the (7), the average (8), and the Stage II B (16) Stage III A (12), Stage III B (13), Stage IVa (3), and Stage IVb (1), all patients received 100 chemotherapy treatment regimens. To assess the correlation of these factors to survival rates, a correlation test was carried out, and c-squared obtained facto r that significantly influences the survival rate is the stage of cancer with a P value of 0.024 and exposure to outdoor carcinogens in the workplace with a P value of 0.005.

Conclusion

The results of the statistical tests showed that most of the clinical factors and modalities of therapy did not affect the survival rate of lung cancer patients. What affected the survival rate of young patients with lung cancer were staging factors and exposure to carcinogens

Keywords: *Lung Cancer, Young Age, Clinical Outcome, Survival Rate*

CASE REPORT : SECONDARY SPONTANEOUS RIGHT PNEUMOTHORAX EC. SUSP. TB DD/ PNEUMOTHORAX CATAMENIAL

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ABSTRACT

Background: Catamenial pneumothorax is a pneumothorax that occurs repeatedly and spontaneously in women, recur within 24 to 72 hours before or after menstrual onset. incidence of 3-6% in women aged 30-35 years often associated with endometriosis.

Case : A 42 year old woman came to the emergency room with complaints of coughing up yellow-green sputum that had been coming and going since ± 5 months. During last 2 months fever, cough, shortness of breath while doing light activities were felt 1-2 days before menstrual cycle and improved when it was over, had history of endometriosis. Respiration rate increased, vesicular sounds decreased throughout the right hemithorax and asymmetrical chest expansion. Chest x-ray result: right pneumothorax, with collapsed right lung. Thoracic CT result: right pneumothorax, ground glass opacity in 6th segment of right and left lung, lesion of the lung-pleura of 3-5 segments right lung and 3rd left lung, DD/ endometrial nodules. Therapy given oxygen on nasal cannula and insertion of water sealed drainage (WSD) the symptoms recovered.

Discussion: Pneumothorax catamenial considered as a differential diagnosis in the assessment of pneumothorax cases in female patients of fertile age who have a history of endometriosis.

Conclusion: Catamenial pneumothorax is a rare disease. In this case, there is improvement after pharmacological therapy and insertion of water sealed drainage (WSD).

Key words: *catamenial pneumothorax, endometriosis*

ANTIBIOTIC SENSITIVITY PATTERN OF BACTERIAL PATHOGENS IN THE INTENSIVE CARE UNIT OF GATOT SOEBROTO:A RETROSPECTIVE STUDY

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ABSTRACT

Introduction: Bronchoalveolar lavage (BAL) has been established for diagnostic purposes in critically ill ventilated patients in intensive care units (ICUs) with minimally invasive procedure that involves instillation of sterile normal saline into a subsegment of the lung, followed by suction and collection of the instillation for analysis. To determine the pattern of bacteria from the result of BAL culture in ICU Rspad Gatot Soebroto.

Method: This study used retrospective data taken from medical records of BAL culture results from Microbiology Laboratory of RSPAD Gatot Soebroto from January 2022 until Desember 2022

Result: Specimens were collected from 2379 patients who were given antimicrobial treatment, of which 1556 (64.68%) were cultured positive and 832 (35.32%) were negative. The most bacterial found in BAL culture were Acinobacter baumani 38 %, Klebsiella pneumoniae 20.5%, and Pseudomonas aeruginosa 5.4%. Acinebacter baumannii isolates showed high rate of resistance to cefazoline (100%), ceftriaxone (99.1%), ciprofloxacine and piperacilin or tazobactam (96.1 %). Amikacin was the most effective (39.4%) antibiotic against A.baumannii followed by fosfomycin (22.2%), and trimethoprim (20.8%).

Conclusion: Most bacteria isolated from ICU of Gatot Soebroto Hospital were resistant to the third generation of cephalosporins, and quinolone antibiotics and bacteria found mostly Gram negative. Regular surveillance of antibiotic susceptibility patterns is very important for setting orders to guide the clinician in choosing empirical or directed therapy of infected patients.

Keywords: Bronchoalveolar lavage, Intensive care unit, Bacteria Pattern

SURVIVAL RATE OF LUNG CANCER RECEIVING ANTICANCER THERAPY IN WEST NUSA TENGGARA (NPTB) PROVINCE

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ABSTRACT

Background:
Lung cancer has highest mortality rates in the world. Data from the Persahabatan Hospitals shows that the 1-year survival rate were 31.6% in NSCLC patients treated with conventional chemoterapy. Data regarding the outcomes of lung cancer management in Indonesia is still limited. Especially in NTB province. This data willl be an additional reference regarding the outcome of cancer treatment and supporting data in the management of lung cancer in Indonesia.

Methods:
This is an observational analytic study using data of lung cancer patients who were treated at the NTB Provincial General Hospital from January 2018 to April 2023. Exclusion criteria included incomplete media record data. Observations were made for 64 months, but there were a few that exceeded 64 months.

Results:
This study found that the mean age was 55.36 years (95% CI 53.78-56.94), most were male (68.1%), had no family history of cancer (75.8%), non-smokers (98.3%), Sasak ethnicity (74.7%) and had adenocarcinoma lung cancer (55.2%), with 99.4% is advanced stage. Most of Lung cancer therapy is conventional chemotherapy (79.5%). The 1-year survival rate of patients receiving anticancer therapy is 35%; The 2-year survival rate was 18% with a hazard ratio of 42% ($p<0.001$, 95% CI 0.26-0.68), whereas without anticancer therapy were 8% and 2% for 1 year and 2-years survival respectively.

Conclusions:
This is the first data regarding the survival rate of lung cancer patients in NTB province which shows benefit of those who were treated with anticancer therapy.

Keywords: *lung cancer, anticancer, lung-cancer survival*

CARBOPLATIN AND PAKLITAKSEL CHEMOTHERAPY RESPONSE IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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ABSTRACT

Background : This is a preliminary study to determine the chemotherapy response in non small cell lung cancer patients at Mohammad Hoesin hospital.

Methods: This study used a retrospective cohort design in lung cancer patients who received carboplatin and paklitaksel chemotherapy at Mohammad Hoesin Hospital between June 2021-December 2022. Data collection was selected through medical records and then survival analysis was carried out to obtain progressive free survival and overall survival rates.

Results : Exist 40 lung cancer patient were filled inclusion criteria. Characteristics of subjects included ages 51-60 (39%), men (80%), smoking history (80%), moderate IB (55%), adenocarcinoma (70%) and stage IV (90%). The most RECIST evaluations based on RECIST 1.1 are stable resposes. Chemotherapy side effects include anemia (70%), nausea (27.5 %) and hair loss (22.50%). The median and mean progressive free survival (PFS) was 6 months and 7.5 months. There was a significant difference between the mean of progressive free survival and the type of cancer ($p<0.001$). The median and mean overall survival (OS) was 10.91 months and 11.7 months. There was a significant difference between the mean of overall survival and the type of cancer ($p<0.001$). The median time to progression is 9 months.

Conclusion: The most common carboplatin and paklitaksel chemotherapy response in lung cancer patients after receiving 3 cycles of chemotherapy based on RECIST 1.1 was a stable response. There were significant differences between cancer types with PFS and OS. Median PFS and OS were 6 months and 10.91 months.

Keywords : *Lung cancer, Chemotherapy response, Progressive free survival*

A CHALLENGING CASE OF PNEUMOCYSTIS PNEUMONIA MANAGEMENT SUPERIMPOSED WITH DRUG INDUCED LIVER INJURY

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ABSTRACT

Introduction

Pneumocystis pneumonia (PCP) and Mycobacterium tuberculosis (TB) infection are opportunistic infections that often occur in immunocompromised patients. More attention is needed while undergoing PCP and pulmonary TB therapy to evaluate response to therapy. The authors would like to present a case report of therapy adjustment in HIV patient with PCP and pulmonary TB.

Case Illustration

A 21-year-old male patient came to the Emergency Room with complaints of severe shortness of breath. These symptoms begin with a productive cough accompanied by shortness of breath, night sweats, and fever started 3 weeks before hospital admission. This is followed by symptoms of prolonged diarrhea and the appearance of thrush in the mouth. The patient also lost 30 kg in 4 months. One week earlier the patient had been hospitalized for a similar complaint and was diagnosed with pulmonary TB, currently undergoing Category 1 Anti Tuberculosis therapy.

The diagnosis of PCP, relapsed pulmonary TB and HIV co-infection was established during the treatment based on clinical manifestations, history and radiological findings. While undergoing PCP and TB therapy, the patient experienced hypersensitivity reactions to drugs and DILI (Drug Induced Liver Injury). Treatment was then adjusted by changing PCP therapy from Cotrimoxazole to Primaquine and Clindamycin. After undergoing adjustments in therapy, liver function markers decreased gradually and the patient's clinical condition improved without any hypersensitivity reactions.

Conclusion

HIV, PCP, and Pulmonary TB co-infection should be considered in patients with TB symptoms and who are immunocompromised. Adequate treatment and management of side effects play an important role in determining the outcome. Primaquine and Clincamycin may be considered as an effective alternative when Cotrimoxazole cannot be given.

ONE YEAR SURVIVAL RATE IN NSCLC PATIENTS WITH POSITIVE EGFR MUTATIONS RECEIVING FIRST-LINE OSIMERTINIB THERAPY

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ABSTRACT

Background

Osimertinib has become standard of care for the firstline treatment for EGFR mutation positive NSCLC in Indonesia. Herewith we reported 1 year survival of Patient with Osimertinib firstline in EGFR mutation positive stage IV NSCLC.

Method

This is a retrospective study from medical records of Osimertinib fristline in EGFR mutation positive advanced stage NSCLC until December 2022. Inclusion criteria includes all patients with Osimertinib treatment as firstline therapy started prior to January 2022.

Result1

Nineteen (19) subjects were included in this study. Five (5/19 % were male), 14/19 female, 1 dari 19 heavy smoker, all patients were harboring sensitizing EGFR mutation (exon 19 or exon 21 L858R). One year overall survival (1 Year OS) was 89.4%.

Conclusion

In this study we showed 1-Year OS of Osimertinib as firstline therapy of EGFR mutation positive NSCLC was 89.4.6

REVEALING THE DIAGNOSIS OF ADENOCARCINOMA IN PATIENT WITH MASSIVE PLEURAL EFFUSION CONCOMITANT WITH MORBUS HANSEN A CASE REPORT

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ABSTRACT

Background

Diagnostic of lung cancer is like a rocket science, where multi-modalities and multi-disciplinary teamwork are often required. Consider that the respiratory tract is the main entry site for Mycobacterium Leprae, we may curious about how Morbus Hansen can relate to Lung Cancer.

Case

A 61 years old man, came to the emergency room with shortness of breath caused by massive pleural effusion on left hemithorax. He also appeared to be in medication of Morbus Hansen. Serial evacuation had performed but the sitology result was unconcluded as a malignancy. Bronchoscopy and Video-Assisted Thoracoscopy Surgery (VATS) had performed, acid-fast bacilli staining returned negative, two times Chest CT-Scan both showed for lung mass, and eventually, re-bronchoscopy had to be conducted. The result came out positive for Adenocarcinoma without driver mutation. Later the patient had chemotherapy, while also took the medication for Morbus Hansen.

Discussion

Morbus Hansen, at some point, could play a role in patient to have Lung Cancer. Diagnostic of Lung Cancer could face difficulties, especially if the patient came with other pathological conditions. The diagnostic process could spend a lot of sources to increase the diagnostic yield.

Conclusion

Lung biopsy, either with closed or open method, is really important to diagnose Lung Cancer. Morbus Hansen can contributes to Lung Cancer, consider that its main entry site is through the respiratory tract.

Keywords

Lung Adenocarcinoma, Lung biopsy, Re-bronchoscopy, Lung Cancer Diagnosis, Morbus Hansen.

PULMONARY EMBOLISM MIMICKING LUNG TUMOR IN A PATIENT WITH ANTIPHOSPHOLIPID SYNDROME: A CASE REPORT

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ABSTRACT

Background

Antiphospholipid Syndrome (APS) is a rare disease with an incidence rate of around 50 per 100.000 population. APS is a multisystem autoimmune disease. APS can cause various organ complications, including pulmonary thromboembolic disease. The thromboembolic condition may give an appearance resembling a lung tumor.

Case Presentation

A 29-year-old female came with chest pain and a chronic cough. She had a history of abortus twice with a gestational age below three months. CT Scan Thorax with contras showed cavitating mass in the posterobasal inferior lobe of the right lung. A needle biopsy was not performed due to no representative lesions on CT Scan Thorax. The laboratory result showed high lupus anticoagulant (LA) ratio (2,64), the ANA test result was high (104), the COOMB test result was positive, and the echocardiography showed a thrombus in the right ventricle. The primary management is anticoagulants or antiplatelet therapy. After the treatment of the anticoagulant, the cavitating mass disappeared.

Discussion

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by thrombus formation (arterial and venous) related to heart disease, neurological features, and abortion pregnancy-related complications, with increased antiphospholipid antibodies (APLAs). Multiple thrombi in APS can resemble lung tumours.

Conclusion

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease. Antiphospholipid syndrome (APS) management needs multiple modalities and a multidiscipline team for a better outcome.

Keywords

Antiphospholipid syndrome (APS), Lung Tumor, Thromboembolism

SILICOTUBERCULOSIS AS A FATAL DISEASE WITH VARIOUS COMPLICATIONS: A CASE REPORT

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ABSTRACT

Background

Silicotuberculosis can lead to severe complications, including bilateral pneumothorax, bronchopleural fistula, and pneumonia which causes sepsis and respiratory failure.

Case Presentation

A 60-year-old man construction worker presented with progressive dyspnea and chronic cough. The patient had bilateral pneumothorax and severe pneumonia. Sepsis was indicated by sofa score 3. GeneXpert sputum showed *Mycobacterium tuberculosis* (MTB) detected rifampicin resistance not detected. Blood gas analysis showed type 1 respiratory failure. High Flow Nasal Cannula (HFNC) was performed to treat respiratory failure. Chest computerized tomography scan showed bronchopleural fistula. Thoracic surgery was planned for fistula repair, but the fistula closed spontaneously. Spectrophotometry of the pleural fluid obtained silica material. The patient was discharged with Long- Term Oxygen Therapy (LTOT).

Discussion

Silicosis is a common disease among construction workers and a risk factor for pulmonary tuberculosis. Both diseases can cause pneumothorax as a complication. Bronchopleural fistula should be treated surgically, but in some cases, it could close spontaneously. Treatment for silicosis focuses on preventing the patient from further exposure to silica. Supportive therapy involving infection prevention, breathing exercises, bronchodilators, and oxygen supplementation are the mainstays of treatment.

Conclusion

Silicosis is a risk factor for pulmonary tuberculosis. Silicotuberculosis can cause many complications with severe morbidity and mortality. Management of silicotuberculosis needs multiple modalities and a multidisciplinary team for a better outcome.

Keywords

Silicotuberculosis, Pneumothorax, Bronchopleural Fistula, Sepsis, Respiratory Failure.

A SUCCESSFUL MANAGEMENT OF PULMONARY TB ALONG WITH PLEURAL TB AND RECURRENT COLLAPSED LUNG IN A CKD STAGE V PATIENT: A CASE REPORT

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is often associated with an increased risk of active tuberculosis (TB) due to immune dysfunction induced by urea level.

Case Report: A 50 year old male TB patient with CKD was referred to our hospital due to subcutaneous emphysema and puss in the water seal drainage (WSD) wound. This patient had undergone WSD installation twice prior to admission. Chest CT-scan revealed a solid mass in the superior lobe of the posterior segment of the right lung with collapsed lung. Puss culture of the WSD wound obtained Staphylococcus haemolyticus. This patient was then diagnosed with pyopneumothorax with collapsed lung and secondary infection. Thoracotomy was performed for decortication, biopsy showing granulomatous suppurative inflammation, and wet resection of caseosa. However, the subcutaneous emphysema was persistent and even worse than the previous one. Thus, we conducted thoracotomy again for bronchopleural fistula ligation. We administered anti TB drug and performed dialysis. The condition improved evidenced by good clinical improvement, expanded right lung, and absence of subcutaneous emphysema, so that we discharged the patient.

Discussion: Patients with CKD have 6.9 – 52.5 folds higher risk of TB. Bronchopleural fistula occurs 2.74 times more frequently in patients with pyopneumothorax. Delayed management of pulmonary TB can lead to significant damage of lung tissue, which may require invasive approach. In this case decortication, routine administration of anti TB drug, and dialysis resulted in significant improvement.

Keywords: *ckd, tuberculosis, pyopneumothorax.*

LUNG CANCER MIMICKING PULMONARY TUBERCULOSIS: CHALLENGES TO DIAGNOSE IN ARIFIN ACHMAD GENERAL HOSPITAL PERIOD AUGUST 2022 TO JANUARY 2023

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ABSTRACT

Background: Lung cancer and pulmonary tuberculosis are similar, but there aren't as many diagnostic enforcement facilities. This delays diagnosis and prevents lung cancer patients from receiving the best treatment, leading to a worse prognosis and reduced survival rate. Differential diagnosis of lung cancer should be taken into account.

Methods: This research is a descriptive cross-sectional approach with a total sampling data collection technique. The samples were collected for 6 months according to the inclusion criteria and the results are presented in the form of a distribution table.

Results: The results of the study found 17 samples with the highest male sex with the highest type of cancer diagnosed with the type of adenocarcinoma (70.6%). The duration of delay is less than 6 months (58.8%) being the highest number in this study. As a result of the delay in diagnosis, patients diagnosed with lung cancer were diagnosed with Stage 4 in all samples.

Discussion: With Indonesia having the highest TB prevalence in the world, evaluating diagnoses and treatments might be difficult. Patient survival is significantly impacted by diagnostic delays. The underlying causes of this disorder include a lack of diagnostic resources and a poor assessment of TB therapy. To decrease the prevalence of lung cancer owing to a late diagnosis of pulmonary TB, more research and policy from all stakeholders are required.

Keyword : *Lung Cancer, Pulmonary TB, Lung Cancer Mimicking Pulmonary Tuberculosis*

NOVEL UTILITY AND ASSOCIATION OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO WITH ACUTE RESPIRATORY FAILURE IN ACUTE EXACERBATION OF COPD PATIENTS

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ABSTRACT

BACKGROUND: Acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) is the major cause of hospitalization. It entails increased inflammatory responses. Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are inflammatory markers obtained from low-cost procedure, but the study regarding their usage for AE-COPD in Indonesia is still limited. Thus, we investigated their possible roles in AE-COPD.

METHODS: We assessed 156 medical records of hospitalized AE-COPD from January-December 2022 in this retrospective study, and included 60 patients who met research criteria. Patients were categorized as Group 1 without acute respiratory failure (ARF) and Group 2 with ARF. NLR and PLR between two groups were analyzed by Mann-Whitney test. Relationships of NLR/PLR and ARF were evaluated by Spearman test. Receiver operating characteristics (ROC) curve and area under the curve (AUC) were used to assess NLR and PLR's ability to predict ARF in AE-COPD.

RESULTS: Group 2 had higher NLR and PLR values (p=0.001, p=0.021; respectively). NLR (r=0.44, p=0.001) and PLR (r=0.30, p=0.019) have strong and moderate correlations with ARF. To predict ARF in AECOPD, ROC curves analysis offers ideal NLR cut-off of 4.90 with 71.4% sensitivity and 72% specificity (AUC 0.760, p=0.001), along with PLR cut-off of 163.85 with 60% sensitivity and specificity (AUC 0.677, p=0.021).

DISCUSSION: Results were consistent with previous studies. Immune system deprivation during exacerbation, including neutrophil migration, lymphopenia, and platelet activation, are what prompted the alterations in peripheral blood.

CONCLUSION: NLR and PLR are convenient and reliable indicators to assess inflammatory response and severity, including ARF, of AE-COPD.

CORRELATION OF DAILY WORK DURATION AND BURNOUT SYNDROME INCIDENCE OF COVID-19 REFERRAL HOSPITAL HEALTH WORKERS AT JEMBER

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ABSTRACT

Background: The COVID-19 pandemic has increased the workload of health workers, especially the duration of daily work. This increased work duration will result work stress and lead to mental health problems, which known as burnout syndrome. This study aims to determine whether there were relationship between the duration of daily work and burnout syndrome of COVID-19 referral hospital health workers at Jember.

Method: This research method was observational analytic with a cross-sectional and conducted at RSD dr. Soebandi, Jember Klinik Hospital, and Kaliwates General Hospital in May 2021-June 2022. The respondents of this study were health workers at the COVID-19 referral hospital at Jember. Data collection was used a demographic data questionnaire and Maslach Burnout Inventory (MBI) questionnaire was used to measure the degree of burnout syndrome. The data from this study were analyzed using the Chi-square and Spearman correlation.

Result: Data from 213 health workers who work as doctors and nurses had shown there were no correlation between the duration of daily work and burnout syndrome in during the COVID-19 pandemic with -value of 0.699 ($\rho > 0.05$)

Conclussion: No correlation between the duration of daily work and burnout syndrome in health workers during the COVID-19 pandemic in Jember

Keywords: *COVID-19, Burnout Syndrome, Duration of Daily Work, Health Workers.*

ASSOCIATION OF COVID-19 VACCINE WITH SEVERITY OF SYMPTOMS AND MORTALITY RATE: A COHORT RETROSPECTIVE STUDY

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ABSTRACT

Background: Various type of COVID-19 vaccine has been developed using various methods. Several studies that had been carried out to study vaccines againts severity symptoms and mortality rates of COVID-19, but with quite limited study. In this study, we aim to explore the association between COVID-19 vaccination status againts severity of symptoms and mortality. Method: This study is an analytic observational study with a retrospective cohort design, with inclusion criteria All COVID-19 patients aged over or equal to 18 years who were treated in the period December 2021 to February 2022 at Prof IGNG Ngoerah Hospital, Denpasar. The data were then analyzed using the Cox proportional hazard method.

Result: Patients who had never been vaccinated before, tends to be more at risk of experiencing severe-critical symptoms, but not statistically significant (HR 1.2; 95% CI 0.6-2.3; p = 0.614; adjusted HR 1.3 95% CI 0 ,7-2,6; p= 0.413). The relationship between vaccination and mortality tends to be with a higher risk of mortality, but it is not statistically significant (HR 1.5; 95% CI 0.8-2.9; p=0.180; adjusted HR 1.5 95% CI 0.8-2, 8; p = 0.175). Analysis based on frequency found that subjects who had not been vaccinated, vaccinated once and twice, tends to have a higher risk of mortality compared to subjects who were vaccinated three times but not statistically significant with HR each of 2,3 (IK95% 0,3-17,4; p=0,410; adjusted HR 2,4((IK95% 0,3-18,0; p=0,401)), 1,4 (IK95% 0,1-13,9; p=0,753; Adjusted HR 1,5 (IK95% 0,2-14,2; p=0,743)); and 1,6 (IK95% 0,2-12,1; p=0,637; Adjusted HR 1,6 (IK95% 0,2-12,3; p=0,633)) respectively. Patients without history of COVID-19 infection tend to have a higher risk of mortality but not statically significant (HR 1.7 (95% CI 0.9-3.1; p=0.092; adjusted HR 1.7 95% CI 0.9-3.1; p=0.90).

Conclusion: COVID-19 vaccine status is not associated to the severity of symptoms and mortality. Based on a history of previous COVID-19 infection, vaccine status was not associated with symptom severity and mortality.

Key Words: *COVID-19 Vaccine, Severity of Symptoms, Mortality.*

COMPARISON OF SURVIVABILITY FACTORS ON LUNG CANCER PATIENTS IN RSUP IGNG NGOERAH DENPASAR BALI

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ABSTRACT

Introduction: Lung cancer has the highest mortality rate in the world for both female and male populations. Significant developments in cancer diagnosis and therapy have increased lung cancer survivability rates, but analysis of survival in age groups and the factors that influence it is still very rarely done in Indonesia. Therefore, this study was conducted to understand the difference in survival and to analyze the age category most susceptible to lung cancer as well as the factors that influence it.

Methods: A cross-sectional study was conducted at RSUP I.G.N.G Ngoerah Denpasar Bali from November 2022 to February 2023. A total of 304 data from subjects with lung cancer were used in this study and data regarding gender, age, histological type, EGFR expression, symptoms, stage and type of therapy were collected. Analysis was carried out using SPSS ver 21.

Results: The subject's mean age in this study was 57.25±9.91 years with 53.9% male (164 subjects). Adenocarcinoma was the major histological type in this study (84.9%) and the majority of patients had stage IV (87.8%). EGFR mutations were detected in 34.9% of the study subjects with the majority of patients being treated with chemotherapy and best supportive care (BSC). In terms of median survival, we found that patients younger than 45 years old had significantly lower median survival compared to those who older than 45 years (14 weeks vs. 24 weeks; p: <0.000). Further analysis showed that brain metastasis, pleural metastasis, gender, and therapy were independent factors that influence patient's survival. Conclusion: Younger age was associated with lower survival in lung cancer patients which was influenced by metastasis location, gender, and therapeutic options.

Keywords: *Lung Cancer, Survival, Characteristics.*

EFFECTS OF TIME INTERVALS FROM DIAGNOSIS TO TREATMENT ON NON-SMALL CELL CARCINOMA PATIENTS

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ABSTRACT

Background: Lung cancer is an abnormal, uncontrolled growth of cells that starts from lung tissue. About 80% of lung cancers are non-small cell lung carcinomas. (NSCLC). Time intervals between diagnosis and treatment are suspected to reduce the congestion of NSCLC patients due to the progressive disease. The aim of this study was to evaluate the influence of the time interval from diagnosis to treatment on NSCLC patient contraction.

Material and Method: This study is an analytical observational study with a retrospective cohort design. The sample of the research was 25 non-small cell lung carcinoma patients at RSUP Prof Dr. IGNG Ngoerah who met the inclusion criteria. Data collection is carried out through data extraction on the medical record installation. The analysis is done using SPSS ver. 25.

Result: Based on the analysis of 25 NSCLC patients in this study, dignificant differences were found in the rate of diagnosis-treatment intervals in patients who lived 18.44 ± 32.958 days, compared to patients who died 147.33 ± 172.916 days. Significant relationship was found between the time intervals from diagnosis to treatment and the incidence (HR = 2,098; CI95% = 2,843 – 4,029; p = 0,009) of all time interval of more than 7 days compared with the subgroup of subgroups between cancer diagnosis and treatment <7 days.

Conclusion: Based on the results of the analysis, it was found that there is a significant relationship between internal time from diagnosis to treatment to NSCLC patients.

Keywords: *Time interval, diagnosis, treatment, NSCLC*

CORRELATION OF ASYMPTOMATIC AND SYMPTOMATIC HYPERURICEMIA WITH SPUTUM CONVERTION TIME AND OUTCOME IN DRUG RESISTANCE TUBERCULOSIS PATIENTS IN DR MOEWARDI HOSPITAL SURAKARTA

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ABSTRACT

Background: Drug-resistant tuberculosis (DR TB) patients often experience either asymptomatic or symptomatic hyperuricemia as a side effect of DR TB treatment. This study investigated the corellation between clinical manifestations of hyperuricemia and sputum conversion time as well as the outcome of DR TB patients.

Methods: An analytic observational study using a retrospective cohort design was conducted on DR TB patients undergoing treatment in Dr. Moewardi Hospital, Surakarta, from January 2018 to December 2022. The data were taken from the medical records of patients and statisfically analysed with Spearman Correlation test. The significance level was determined with $p < 0.05$

Results: Hyperuricemia occurred in 90 of 313 subjects (28,7%), comprising 58 subjects (64.4%) with asymptomatic hyperuricemia and 32 (35.6%) subjects with symptomatic hyperuricemia. The Spearman correlation test obtained no correlation between clinical manifestations of hyperuricemia and sputum conversion time ($p = 784$) as well as outcome ($p = 0.821$). Our analysis found no difference in terms of outcome and sputum conversion time among DR TB patients either with asymptomatic or symptomatic hyperuricemia who were on short term regimens (STR) using kanamycin/amikacin as well as all oral regimens and long term regimens ($p = 0.357$ and $p = 0.141$; $p = 0.619$ and $p = 0.478$; $p = 0.255$ and $p = 0.938$, respectively).

Conclusion: Clinical manifestations of hyperuricemia do not affect the conversion time or outcome of DR TB patients undergoing treatment.

Keywords: *hyperuricemia, drug resistance tuberculosis, outcome, sputum conversion time*

CORRELATION BETWEEN D-DIMER AND BRIXIA SCORE TO MORTALITY OF COVID-19 PATIENTS

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a severe and highly contagious acute respiratory syndrome caused by SARS-CoV-2 virus. A variety of factors can increase a patient's risk of death, including coagulopathy characterized by increased D-dimer levels. D-dimer could be one of the determinants of COVID-19 severity, as assessed by chest radiographs. This study aimed to analyze chest radiographic severity based on Brixia score at degree of coagulation based on D-dimer in mortality COVID-19 patients who was hospitalized.

Method : The retrospective study was conducted at Dr. Saiful Anwar hospital by an observational cross-sectional design that included of 300 medical records COVID-19 patients who passed away while hospitalized. Data were analyzed using the Wilcoxon test, and the results were also tested for Spearman correlation to determine relationships between variables.

Result : A comparison of initial D-dimer and final admission D-dimer by Wilcoxon test showed that the median initial D-dimer of 1.4 (0.24-79.27) was lower than the median final D- dimer of 4.33 (0.63-470.6), with significant difference (p=0.000). Comparison of initial and final Brixia scores showed that mean initial Brixia scores of 15.0 (6.0-18.0) were lower than final Brixia scores of 16.0 (6.0-18, 0), although there was no significant difference (p=0.165).

Conclusion : Increased D-dimer and Brixia scores were significantly correlated with mortality in COVID-19 patients.

Keyword : *COVID-19 mortality, D-dimer, Brixia score*

FACTORS ASSOCIATED WITH LATENT TUBERCULOSIS INFECTION IN HEALTH WORKERS AT THE WEST SUMATRA CENTER OF LUNG DISEASE HOSPITAL

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ABSTRACT

Introduction: The risk of latent tuberculosis (LTBI) in health workers is higher compared to other professions because the chances of contact with tuberculosis (Tb) patients are more frequent. The risk of LTBI is higher in people living in countries with a high Tb burden. Health workers in Indonesia have both risks.

Methode: A cross-sectional study design, we examined 31 health workers at the West Sumatra Lung Hospital using tuberculin skin test (TST) with PPD RT 23 and then measuring TST after 48- 72 hours. Tuberculin skin test results with induration of more than 10 mm, no Tb symptoms and a normal chest X-ray and normal genexpert test will be determined as LTBI.

Result:
The prevalence of LTBI was 32.2%, 31 out of 95 health workers performed TST. There was a significant difference between health workers who worked using N95 mask (p:0.004). Health workers who do not use N95 masks have a higher risk of LTBI (95% CL: 1.58-69.1). Conclusions: This study showed an increased risk of LTBI in health workers who do not use N95 masks.

Keywords: *Health workers, LTBI, N95 Mask*

RELATIONSHIP BETWEEN PROCALCITONIN LEVELS AND CLINICAL SEVERITY AND OUTCOME IN COVID-19 PATIENTS

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ABSTRACT

BACKGROUND: The clinical severity of COVID-19 varies form asymptomatic to critically ill. The underlying pathophysiology is the release of inflammatory cytokines notably in severe and critical patients, that could lead to raise in inflammatory markes such as procalcitonin. This study aims to investigate the relationship between procalcitonin levels with clinical severity and outcome in COVID-19 patients.

MATERIAL AND METHOD: A cross-sectional study with retrospective approach in 449 COVID-19 patients at Dr. M Djamil Hospital from January 1st 2021 to December 31st 2021. Result were analyzed using Chi-Square and multinomial logistic regression. Outcomes were the odds of patients present with poorer clinical severity as well as inpatient mortality.

RESULT: Most of the patients were in the 18-49 years old group (39,42%), female (56,12%), had obesity as comorbid (30,28%), present with critically ill severity (50,33%), and had PCT levels < 0,5 ng/mL (77,06%). Based on outcome, age were the characteristics that is not homogen. This study found that PCT levels had relationship with clinical severity and outcome (p=0,000). Patients with PCT levels ≥ 0,5 ng/mL were more likely present with poorer clinical, and had higher chance of mortality.

CONCLUSION: There is significant relationship between elevated PCT levels ≥ 0,5 ng/mL and poorer clinical severity and mortality in COVID-19 patients

KEYWORD : *procalcitonin, COVID-19, outcome, clinical severity, relationshi*

DIAGNOSTIC PERFORMANCE OF CHEST CT COMPARED TO RT-PCR FOR COVID-19: AN EVIDENCE-BASED CASED REPORT

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ABSTRACT

Background: One of the challenges in managing coronavirus disease 2019 (COVID-19) is the identification of a swift and reliable diagnostic modality that could serve as an alternative to reverse-transcriptase polymerase chain reaction (RT-PCR). The use of chest computed tomography (CT) for COVID-19 diagnosis or triage in health care settings with limited PCR capacity is controversial. This study aimed to determine the diagnostic performance of chest CT compared to RT-PCR in diagnosing COVID-19.

Methods: The search was conducted on PubMed, Cochrane and ScienceDirect according to clinical question. The studies were selected based on inclusion and exclusion criteria and led to four useful articles. The selected studies were critically appraised for their validity, importance, and applicability.

Results and Discussion: Four studies were found with comparable validity. Khatami's study showed 87% sensitivity, 46% specificity, 69% positive predictive value (PPV), 89% negative predictive value (NPV). Herpe's study showed 90% sensitivity, 91% specificity, 92% PPV, 89% NPV. Falaschi's study showed a sensitivity of 90.7%, specificity 78.8%, PPV 86.4%, NPV of 85.1%. He's study showed a sensitivity of 77%, specificity 96%, PPV 92.95%, NPV 85.2%. One of the advantages of chest CT was it could show the extent of infected lung and predict the patient's prognosis.

Conclusion: Chest CT had good diagnostic performance in diagnosing COVID-19. We highly suggest the use of non-contrast chest CT to diagnose COVID-19 in patients showing moderate symptoms with any vague findings from chest x-ray despite a negative outcome for RT-PCR.

Keywords: *COVID-19, chest CT, RT-PCR*

BRONCHOSCOPY IN KEROSENE INGESTION: A CASE REPORT

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ABSTRACT

Background: Kerosene ingestion cases can be found in developing countries which still commonly used as a household material and stored in unsafe place. Kerosene ingestion causes serious morbidity and mortality due to aspiration pneumonitis. There is no specific guideline for managing kerosene ingestion. Bronchoscopy is a non-invasive modality used for performing several diagnostic and therapeutic procedures, including in aspiration pneumonitis cases. Bronchoscopy could benefit the outcome by removing aspirated liquid from the airway thus can reduce inflammatory reaction, preventing atelectasis, and reducing risk of infection.

Case presentation: A 3-years-old boy was brought to the emergency room because he had a severe cough and shortness of breath after accidentally drinking about 15 ml of kerosene 1 hour before went the hospital. The patient was unconscious with kussmaul breathing pattern, SpO2 was 61% room air, bilateral rhonchi were found. The patient was immediately intubated and performed cito bronchoscopy. Based on bronchoscopy examination, the mucosa in the trachea and carina was hyperemic and there was mucoid secretion in lower lobe of left lung. Bronchial toilette was performed and bronchial washing samples were collected. The patient was given sedative, symptomatic agents and antibiotics. After treated for 3 weeks, radiographic evaluation showed significant improvement. The child clinically active, eating and drinking well. The patient was allowed to discharge.

Conclusion: Respiratory complications such as pneumonitis and hypoxia can occur due to ingestion of kerosene. However, prompt recognition, treatment and performing bronchial toilette using bronchoscopy can improve the outcome.

Keywords: *kerosene, aspiration pneumonitis, bronchoscopy*

CLINICAL OUTCOME ADENOCARSINOMA LUNG CANCERS PATIENTS EGFR POSITIVE AND NEGATIVE MUTATIONS WITH BRAIN METASTASES

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ABSTRACT

Introduction

Lung cancer is a major problem since it has become more prevalent than other types of cancer in both developing and developed nations. Lung cancer caused roughly 50.9 million deaths globally in 2012. 10 % of patients have brain metastases when they are first diagnosed, and 40 % of lung cancer patients have brain metastases at some time in the course of their illness. Contrary to routinely prescribed conventional medications, the usage of TKI inhibitor pharmaceuticals especially extends the life expectancy of lung cancer patients. Contrary to routinely prescribed conventional medications, the usage of TKI inhibitor pharmaceuticals especially extends the life expectancy of lung cancer patients.

Method :

The layout of this observe is an analytical description of the secondary information taken in March - April 2023 from the scientific facts of Persahabatan Hospital sufferers from January 2020 - December 2022 the usage of a retrospective cohort method.

Results :

In this study, with a sample of 46 people, bivariate analysis was performed for OS (Overall Survival) using the graphix cox statistical test. It was found that there was a correlation. In this study the most respondents were aged over 45 years (43 respondents) with the most sex being male 38 respondents (82.6 %), positive EGFR mutations as many as 30 patients (82.6 %) and the average number of patients with brain metastases with negative EGFR mutations (16.7 %) and those with a genetic history were 27 respondents (58.7 %). Brain metastases in lung cancer patients with positive EGFR on TKI occurred at the eighth month, while brain metastases in individuals with negative EGFR adenocarcinoma receiving platinum-based chemotherapy occurred at the fifth month. The survival rate was 24 months for lung adenocarcinoma with a positive EGFR mutation and 23 months for adenocarcinoma with a negative EGFR mutation.

Conclusion :

It has been found that from 46 research samples, lung adenocarcinoma patients experienced metastases to the brain due to a non optimal response and also resistance to therapy given an average of Five months for negative EGFR mutation adenocarcinoma on platinum-based chemotherapy with a survival rate of approximately 23 months, and an average of the eight month for adenocarcinoma patients with positive egfr mutations on TKi with a longer survival rate than negative egfr mutations, namely 24 months.

Keywords: *Lung Adenocarcinoma, Brain Metastases, EGFR Mutations*

KNOWLEDGE, ATTITUTE, AND BEHAVIOUR LEVEL OF HEALTHCARE WORKERS WHO MANAGE PREGNANT WOMEN WITH COVID-19 IN A HOSPITAL IN JAKARTA, INDONESIA

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ABSTRACT

COVID-19 is caused by a novel coronavirus, which discovered in China in 2019 and announced as global pandemic in March 2020. Healthcare worker's knowledge about COVID-19 can influence their attitude and behavior in dealing with COVID-19 patients, which plays an important role in preventing the transmission of COVID-19.

Objective : To determine the level of knowledge, attitudes, and behavior of health workers who treat pregnant women with COVID-19 at hospitals in Jakarta

Methods : This was a cross-sectional descriptive study at Cipto Mangunkusumo National General Hospital, Persahabatan General Hospital, and Fatmawati General Hospital within April 2021 – June 2022. We conducted online survey using google form. Bivariate analysis was used to determine association between knowledge, attitude, and practice towards COVID-19 by chi square method.

Results: The knowledge regarding standard precautions, COVID-19 in general and the handling of COVID-19 patients were good (99.8%, 66%, 56.7). Respondents' attitudes towards COVID-19 transmission in hospitals and COVID-19 pandemic were good (79.4%, 89.2%). Respondents' behavior when handling COVID-19 were good (90.2%). Bivariate analysis between knowledge about COVID-19 in general and attitudes towards COVID-19 transmission in hospitals showed significant results (OR = 2.06, 95% CI = 1.01 – 4.17, p = 0.043).

Conclusion : Overall healthcare worker's knowledge, attitude, and were good. Knowledge of health workers about COVID-19 is associated to attitudes towards the transmission of COVID-19 in hospitals. There is a association between the level of education and job to general knowledge of COVID-19.

Keywords: *knowledge attitude behavior level, healthcare workers, pregnant patients, COVID-19*

BRONCHODILATOR TEST REVERSIBILITY (BDR) PROFILE OF ASTHMA PATIENTS IN RSUP PERSAHABATAN

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ABSTRACT

Background

Asthma is affecting 1-18% of the population, characterized by variable symptoms and expiratory airflow limitation, that may resolve after some medication.1 Current asthma diagnosis is based on the clinical in addition to presence of airway obstruction with a significant change in forced expiratory volume in 1 second (FEV1) or force vital capacity (FVC) after bronchodilator (BD) administration.2 The ATS defined a 'reversible' criteria as an increase in FEV1 of 200 ml or greater and 12% improvement from baseline after inhalation of BD.3,4 However we also found that asthma patients had an 'ireversible' results after BD administration.

Method

This study was conducted in RSUP Persahabatan using medical records data. We took all patients diagnosed with asthma who underwent spirometry test from January until December 2022. There are 204 patients, but 4 patients were excluded because unable to finish the manuever.

Result

Only 43 out of 200 patients in this study had reversible result, while 157 (81,5%) shown ireversible result. There are 31 (20,3%) female with reversible result. The comorbidities from both reversible and ireversible group were cardiovascular 10 (25,6%) and 29 (74,4%) respectively. There are 164 patients with no smoking history, and 27 out of 36 who had smoking history came with reversible results. Out of patients with reversible results, 19/43 (27.9%) had moderate persistent asthma severity comprising other severity. Among the other 157 patients with irreversible, 64 (82.1%) had mild persistent asthma severity. The eosinophil ≥300 106/μL found in 26.6% reversible patients and 73.3% ireversible patients, although there were more irreversible patients with eosinophil count <300 106/μL. From the ACT score thus with reversible results demonstrated uncontrolled asthma 11 (30,6%) and the irreversible results dominantly had partially controlled asthma 68 (86,1%).

Conclusion

In this study most of the asthma patients had ireversible results after bronchodilator test. Even though the patients had ireversible results, this doesn't match with the improvement on clinical symptoms. While theoritically asthma is a reversible airway disease, some factors may contribute to this results. However, a further study is required to analyze those factors that may affect to this results.

Keywords: *Asthma, Spirometry, Bronchodilator test*

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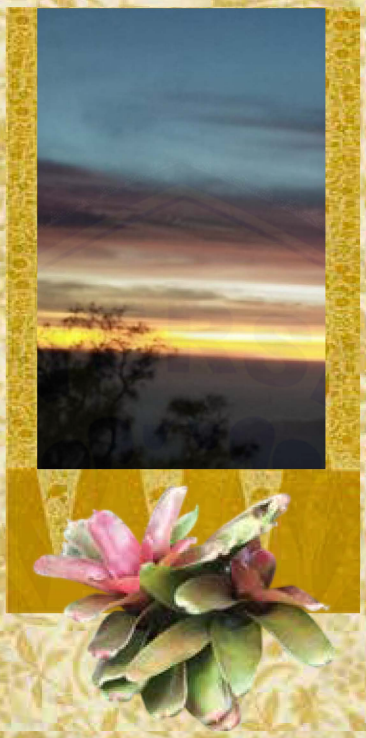

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