

Risk Factors Of Uremic Pruritus In Hemodialysis Patients :Narrative Literature Review

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Abstract

Uremic pruritus is a dermatological manifestation that common and disturbing problem in patients on hemodialysis with an incidence of 20% - 90%. The pathogenesis of uremic pruritus is complex and not understood. This review study aimed to identify factors of uremic pruritus in hemodialysis patients. A review searched three database (Proquest, NCBI, and Google Scholar) for previous studies using sectional, case control, and descriptive kuantitative design published between 2015-2020. The checklist guided by year, title, abstract, and full text. The JBI Critical Appraisal Tools are used to assess quality of articles. A total of thirteen articles which met inclusion criteria in this study. Each article identified different risk factor for uremic pruritus with at least one risk factor identified by the two articles. The type of study designs were cross-sectional with eleven articles. The average number of participants were fifty. A total of five risk factors that contributing of uremic pruritus: 1) clinical features (increased creatinin, hemoglobin, protein C reaktif, Interleukin (IL)-2 dan Interleukin (IL)-6), 2) dialysis duration of hemodialysis, 4) gender, and 5) age. Increased of urea level were indicated as the most risk factor because it acts as an intermediary for others.

Keywords: clinical features, hemodialysis, risk factors, uremic pruritus

Date of Submission: 20-03-2021

Date of acceptance:

I. Introduction

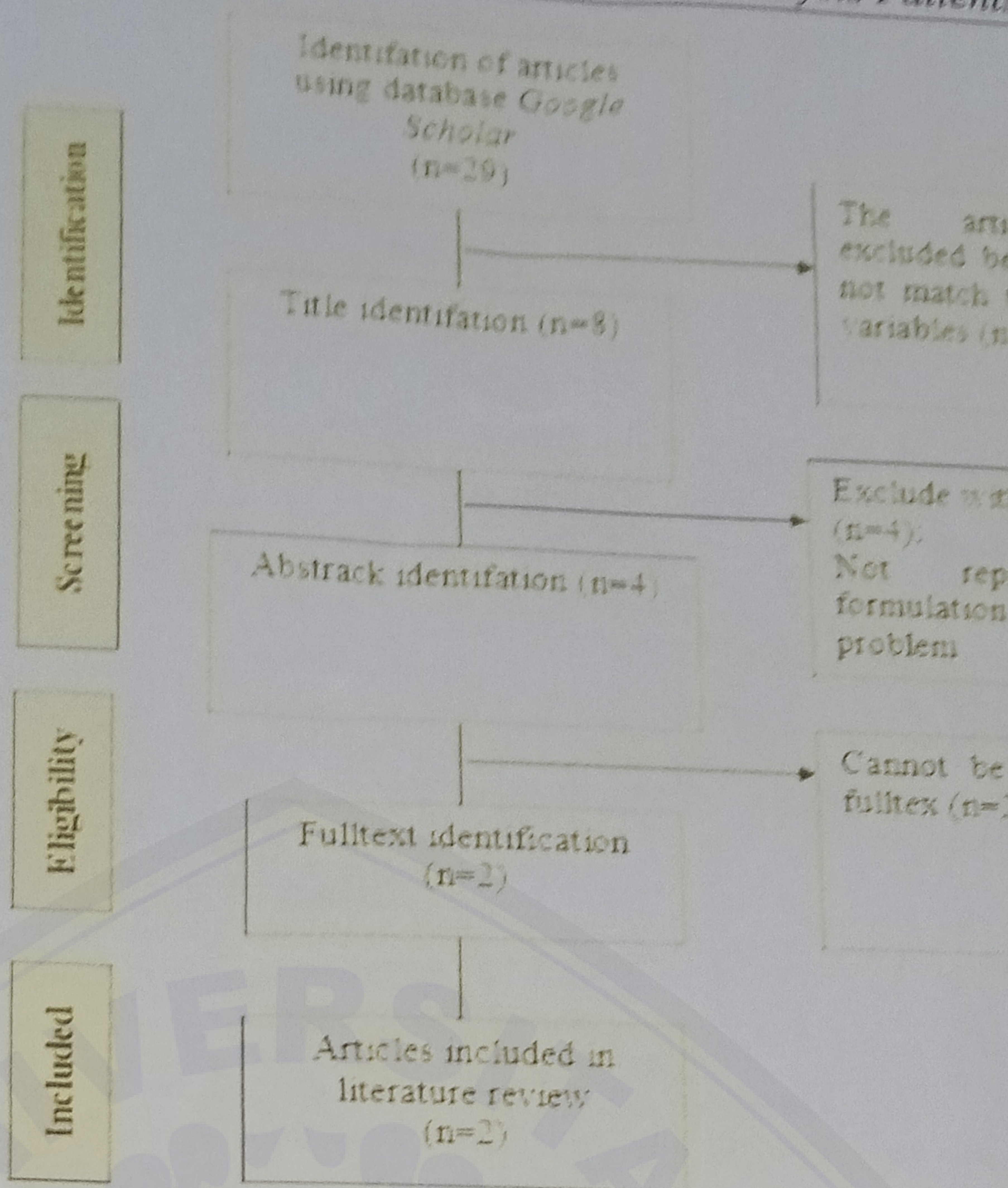
Chronic Kidney Disease (CKD) is a systemic disease that has many clinical signs. Glomerular Filtration Rate (GFR) is $<15 \text{ mL / minute / } 1.73\text{m}^2$, it is included in category of kidney failure, which where the kidneys unable to carry out their main function as an excretory system (Rachmadi, 2017). In this condition, therapy needs to be done to sustain the patient's life, namely by maintaining the process of removing metabolic waste (Widianti, 2017).

Hemodialysis (HD) is the most preferred therapy for CKD patients other than peritoneal dialysis and kidney transplants (Haryanti, I. A. P., 2015). Among other therapies, hemodialysis is more believed to be able to sustain a patient's life longer (Bayhakki & Hasneli, 2017). However, this therapy does not guarantee that patients will avoid a number of other potential health problems. Pruritus is a common complaint of by hemodialysis patients with a high incidence rate of up to 90%.

Pruritus is defined as an unpleasant sensation on the skin area which then triggers itching (Rachmadi, 2017). Meanwhile, pruritus that occurs in chronic kidney failure is defined as an itching on the skin which is probably caused by the accumulation of toxic uremia due to kidney failure and protein metabolic waste (Wu, 2015).

The incidence of uremic pruritus is high and even triggers an increase in mortality rate. A cohort study of 724 hemodialysis patients with itching recorded from 2013 - 2017, as many as 50% accompanied by skin lesions due to itching. This mortality rate is related to the intensity of depression, stress, and sleep disturbances (Grochulska, 2019). A recent study by (Kunung, 2019) on 77 patients, as many as 37 (63%) had pruritus. Likewise research by Kadam (2018) on 77 patients, more than half of the sample (57.2%) complained of pruritus. Research in Indonesia also reported pruritus experienced by the majority of HD patients. Wahyuni (2019) stated that out of 83 HD patients, 70% experienced pruritus.

With a relatively high incidence rate, pruritus should be a concern and maximum attention should be done. However, in reality the treatment of pruritus is not yet effective because the factors are not clear. Hu (2019), in the conclusion of their research said that it is very difficult to say the effect of a single factor. Based on these results, the researcher is interested in conducting a literature review and summarize the risk factors for the appearance of uremic pruritus in patients undergoing hemodialysis.



Gambar 2.2 Flow Diagram of Articles Selection with Indonesia

III. Result

From the two process of searching articles using keywords in researchers got a total of 13 articles. A total of 13 articles were then taken literature review study. The followings are summary if articles that had been

Table 1. Summary Of Articles

Author	Title and Identity of Article	Method (Design, Sample, Variable, and Analysis)
Hu, T., et al (2019)	Title: Clinical features and risk factors of Experimental And Therapeutic Medicine pruritus in patients with chronic renal failure. Identity: 18: 964-971, 2019 Doi: 10.3892/Etm.2019.7588	D: Cross-sectional study S: 382 patients: 138 HD, 41 Dialysis peritoneal, 203 CKD V: socio demographics, clinical parameters (serum urea nitrogen, creatinine, serum phosphorus, calcium phosphorus, and parathyroid hormone (PTH)) A: Chi-square test was used for comparisons of numerical variables.
Shafei, N. K dan A. Nour. (2016)	Title: Observations on the Association of Serum histamine, Interleukins and Other Serum Biochemical Values with Severity of Pruritus in Chronic Hemodialysis Patients Identity: Journal of nanomedicine & Nanotechnology	D: Cross-sectional study S: 50 hemodialysis patients V: uremic pruritus and clinical parameters A: comparison with the ANOVA test

<p>Onigbode, O., C. I. Otene (2016)</p>	<p>City, Edo State, Nigeria Identity: Journal of Integrative Nephrology and Andrology October-December 2016 Vol 3 Issue 4 DOI: 10.4103/2394- 2916.193498</p>	<p>V: uremic pruritus and clinical parameters A: Pearson for assess the association between pruritus and clinical parameters.</p>	<p>show urea, durat</p>
<p>Oliveira, M. G., at al. (2017)</p>	<p>Title: Factors Associated with Uremic Pruritus Identity: International Archives of Medicine Vol. 10 No. 178 doi: 10.3823/2448</p>	<p>D: cross sectional study S: 164 hemodialysis patients over 18 years old V: uremic pruritus, demographics, and clinical value A: Multivariate linear regression test</p>	<p>From pruri incre hem prur resp Sign</p>
<p>Ghassan, B at al. (2015)</p>	<p>Title: Relationship of Pruritus with Biochemical and Haematological Parameters in Haemodialysis Patients (A Single Center Study) Identity: J Fac Med Baghdad Vol. 57 No. 4</p>	<p>D: cross sectional study S: 103 hemodialysis patients V: uremic pruritus and clinical parameters A: -</p>	<p>Fr exp Cli dif 0.2 co ur</p>
<p>Sarhan, I. I., at. al. (2020)</p>	<p>Title: Association Of High Sensitive C Reactive Protein And Dialysis Adequacy With Uremic Pruritus In Hemodialysis Patients Identity: Alexandria Journal Of Medicine 2020, Vol. 56, No. 1, 111-117 Doi:1080/20905068.2020.1786 620</p>	<p>D: Case control study S:100 hemodialysis patients: 50 Patients HD with pruritus dan 50 nonpruritus. V: demographic data, adequacy of dialysis, uremic pruritus A:Chi-squares were used for group comparisons of qualitative data. Independent t-test for comparison of independent groups with quantitative data and parametric distribution. Mann- Whitney was used for comparison of non-parametric distribution data.</p>	<p>TI w be pr R w b S</p>
<p>Malekmakan, L., at. al. (2015)</p>	<p>Title:Association of High- Sensitive C-Reactive Protein and Dialysis Adequacy with Uremic Pruritus Identity: Saudi Journal of Kidney Diseases and Transplantation, Vol. 26 No. 5 Hal. 890-895</p>	<p>D: Case control study S: 241 patients aged ≥ 18 years and having undergoing HD ≥ 3 months V: uremic pruritus, demographic data, and clinical value (Kt/V or hemodialysis adequacy) A: Independent t test for quantitative data test and Chi- square for comparison.</p>	
<p>Rusyati, Y. Kandarai, dan N. T. Priliawati (2020)</p>	<p>Title: High serum interleukin-2 levels are associated with pruritus in chronic kidney disease undergoing regular hemodialysis Identity: Bali Medical Journal Vol. 9 No. 3 doi: 10.15562/bmj.v9i3.2018</p>	<p>D: Cross-sectional study S: 72 hemodialysis patients: 36 with pruritus and 36 without pruritus V: characteristics (age, sex, HD duration) and serum interleukin-2 A: Normality test with Kolmogorov Smirnov, Independent t-test for interleukin-2 differences between groups</p>	
<p>Abdelsalam, M., at. al (2019)</p>	<p>Title: Insulin Resistance and Hepatitis C Virus-Associated Subclinical Inflammation Are Hidden Causes of Pruritus in Egyptian Hemodialysis Patients: A Multicenter Prospective Observational Study Identity: Nephron DOI: 10.1159/000501409</p>	<p>D: Cross-sectional study S:193 hemodialysis patients V:risk factors and uremic pruritus A:Shapir-Wilk for normality Comparison of the two groups test (parametric data) and Mann- Whitney (non-parametric) ANOVA for comparisons more than two groups. Spearman to assess the relationship betwe</p>	

Author(s)	Title	Methodology	Significance
Kaur, S., et al (2019)	Title: Prevalence of Uremic Pruritus, Its Risk Factors and Impact on Health-Related Quality-Of-Life in Patients on Maintenance Hemodialysis Identity: Academia Journal of Medicine Vol. 2 No. 2	D: Cross-sectional study S: 164 hemodialysis patients V: risk factors and uremic pruritus A: Anova test for comparison of quantitative data and Chi-square test for comparison of categorical data.	signifikansi A total of 88 pruritus with moderate (n=22.7%). Patients aged 60 and above (n=42) was statistically significant (p<0.05)
Vracinic et al., (2015)	Title: Pruritus In Hemodialysis Patients: Results From Fresenius Dyalysis Center, Banja Luka, Bosnia And Herzegovina Identity: Our Dermatol Online. 2015;6(3):252-256	D: Cross-sectional study S: 62 hemodialysis patients V: uremic pruritus, age, sex, HD duration, and laboratory characteristics A: Mann-Whitney and t-test to compare between patients with or without pruritus. Wilcoxon and Chi-square test to assess of correlation of variables	Significant Of 34 males and 28 females, 15 (22.7%) had pruritus. Significant difference was found between patients with and without pruritus (p<0.05)
Wahyuni, A.,U. Z. Lawati, dan E. Gusti (2019)	Title: Korelasi Lama Menjalani Hemodialisa Dengan Pruritus Pada Pasien Hemodialisa Identity: Jurnal Endurance : Kajian Ilmiah Problema Kesehatan Vol 5 No 1	D: cross sectional study S: 83 hemodialysis patients V: Duration of hemodialysis and uremic pruritus A: Chi square for assess the correlation of variable	A total of 83 patients had uremic pruritus. There was a significant correlation between long duration of hemodialysis and uremic pruritus (p<0.05)
Sembiring, F., S. S. Nasution, dan Y. Ariani (2020)	Title: GambaranPruritusUremikPasienGagalGinjalKronikDiUnitHemodialisaRumahSakitUmumPusatHajiAdam Malik Medan Identity: Jurnal Perawat Indonesia Vo. 4 No. 1	D: descriptive quantitative S: 49 hemodialysis patients V: uremic pruritus A: -	A total of 49 patients (56% of sample) had uremic pruritus. The prevalence of pruritus was significantly higher in patients aged 60 and above (p<0.05)

IV. Discussion

1. Clinical Features

1.1 Urea

Uremia is the most common cause of pruritus because it has a fair correlation between urea levels in the blood and pruritus. Increased urea levels in the blood can endanger the patient's survival and interfere with their quality of life. Increased levels of urea in the blood can be a factor in the emergence of pruritus in patients. Urea, which should be excreted in the urine in the metabolic process, becomes toxic to the detriment of patients. Increased urea levels were found to be significantly correlated with the incidence of pruritus (Unuigbo, 2020);(Shafei, N. K., 2016);(Hu, 2019).

Research in Nigeria by Odonmeta (2016) on 50 hemodialysis patients reported that 25% experienced pruritus with urea levels far above normal values, namely 25 mg/dL. The study found that the increase in serum urea levels was associated with the frequency of pruritus. An uncontrolled increase in urea levels was caused by the patient not understanding the importance of dialysis due to the cost factor that was borne by the patient himself. The irregularity of dialysis causes the process of eliminating metabolic waste to stop as a result of which metabolic waste accumulated.

1.2 Creatinine

Creatinine in the blood is constant, namely 0.6 - 1.3 mg / dL, but a decrease in kidney function. Creatinine is excreted by the renal glomerulus. A decrease in creatinine value has a relationship with a decrease in Glomerular Filtration Rate (GFR). According to Oliveira (2017), HD patients with pruritus have a high creatinine level compared to those without pruritus. This indicates that kidney function will affect creatinine levels. High creatinine levels occur in the blood and becomes a risk factor for pruritus.

The results of research by Oliveira (2017) reported that creatinine levels in patients with pruritus were significantly higher (p<0.05) than in patients without pruritus. The average creatinine level in the group with pruritus was 7.4 to 11.6 mg / dL with an average of 9.9 mg / dL, while in the group without pruritus it was 6.6 to 10.6 mg / dL. A significant difference was also above the normal value, namely the range of 6 - 10.6 mg / dL.

pruritus.

Hu et al. (2019) reported that in pruritic patients, the creatinine value was $\mu\text{mol} / \text{l}$ in non-pruritic patients (normal creatinine in $\mu\text{mol} / \text{l}$ was 80-115 $\mu\text{mol} / \text{l}$). That an increase in creatinine value will cause the occurrence of pruritus.

1.3 Hemoglobin

The process of abnormal hemoglobin levels associated with uremic pruritus. One of the pathophysiologies that can be proposed for the theory of the hemoglobin is related to the incidence of anemia in dialysis patients (Pisani, 2006) blood cells is insufficient, the process of spreading hemoglobin will be hampered are disrupted including glomerular function because erythropoietin is produced by endothelial cells of the kidney cells. This situation will affect the emergence of complications that can arise are uremic pruritus (Olievera, 2017).

1.4 Interleukin (IL)-2 dan Interleukin (IL)-6

Serum Interleukin (IL) -2 and Interleukin (IL) -6 are indicated as because they are associated with inflammation. (Kimmel, 2006) study of 13 patients without pruritus. The cytokines IL-2 and IL-6 are important immunoregulatory central nervous system. The cytokines IL-2 and IL-6 can affect the physiological modulate several neurotransmitter systems in the central nervous system, thereby CNS function. This condition can then cause neurological effects and neuropathic itching or pruritus (Gaspari, 1987 in (Fallahzadeh, 2011). According to Sarhan (2020), interleukin-2 and 6 are associated with uremic pruritus.

Another study by Rusyati (2020) related to IL-2 with pruritus showed an increase in IL-2 values to 17.1 pg / ml while the value for patients without pruritus (normal range of 5-15 pg / ml). The results of this study concluded that there is a relationship between an increase in serum interleukin-2 values and pruritus in hemodialysis patients.

1.5 Protein C Reaktif (CRP)

Serum CRP is an important marker in identifying inflammation in hemodialysis patients. It has a role in the emergence of uremic pruritus with inflammation as the research by Chiu (2008), severe pruritus had significantly higher serum CRP (CRP value = 1.00-3.00 mg / L; $p = 0.017$). Logistic regression analysis showed CRP as a meaningful as independent predictors of uremic pruritus with adjustments for other factors (Chiu, 2008).

Likewise research by Sarhan et al. (2020) who also stated that the presence of pruritus. Highly sensitive reactive protein C was statistically positively correlated with pruritus as measured by a visual analog scale (p value = 0.001). Research by Sarhan (2020) reported that CRP was a predictor of pruritus ($p < 0.0001$).

2. Hemodialysis Adequacy

The increase of urea can be caused by other factors, such as inadequate hemodialysis will affect the amount of urea in the body. Hemodialysis patients have a strong potential to experience uremic pruritus (Sarhan et al., 2020). In a study of 241 HD patients, as many as 97 (40.2%) patients had pruritus. Sarhan (2020) reported that the difference between pruritic and non-pruritic patients was 63% versus 60%.

Likewise, the results of research from Malekmakan et al., (2015) showed a difference between adequate hemodialysis and uremic pruritus. Among other variables such as urea data and body mass index, there was no correlation with pruritus, that pruritus and non-pruritic groups. The differences between groups appeared in urea clearance values (> 1.2) were significantly associated with the occurrence of pruritus in hemodialysis patients (Malekmakan et al., 2015). The same result was reported by Hu et al. (2019), namely the value of urea clearance (Kt / V) in pruritic patients was 1.5 vs 1.5) with a significance value ($p = 0.0001$). This value indicates that there is a higher risk of dialysis patients experiencing pruritus.

3. Duration of Hemodialysis

Several studies have shown that the length of time undergoing hemodialysis is a risk factor for the appearance of uremic pruritus. Research by Wahyuni, A., et al (2018) on 83 hemodialysis patients, a bivariate analysis showed that there was a relationship between the two, where the correlation coefficient was positive, which meant that there was a relationship between the length of hemodialysis and the appearance of pruritus ($p = 0.023$).

Other studies that support the assumption that the length of time undergoing hemodialysis is a risk factor for the appearance of pruritus reported by Sembiring, F., et al. (2020) and Odor, C. I. Otene (2016), and Abdelsalam, M., et al (2019). Sembiring, F., et al (2020) analyzed 49 hemodialysis patients and found that all samples had mild pruritus and the length of hemodialysis for more than one year. Of the 49 respondents observed, 39 respondents had pruritus for more than 6 months.

Odonmeta, B. A., E. Unuigbo, and C. I. Otene (2016), stated that patients with a risk of developing pruritus because of the risk of skin disorders. These results indicate that the length of time on hemodialysis has a greater potential for patients to experience pruritus. Abdelsalam, M., et al (2019) stated the same thing that patients who had longer undergone HD pruritus had pruritus for a shorter duration (36.5 months vs 27 months).

4. Gender

Sex differences have also been of concern to some investigators regarding pruritus and its association with uremic pruritus. Research by Vrucinic et al., (2015) regarding uremic pruritus and its risk factors was examined from 62 HD patients and it was found that pruritus appeared more in men, namely 21 of 34 patients (61.8%) in men and 13 patients (45.2%) in women. The correlation between pruritus and other variables such as laboratory values did not show any significant association. Male gender had a higher prevalence of appearance of pruritus ($p = 0.005$). Vrucinic et al., (2015) concluded that gender is a risk factor for the emergence of pruritus but how the mechanism is not explained with certainty.

Research in Indonesia by Sembiring, F., et al (2020), also showed that there was more pruritus in men than women. Of the 49 respondents who were observed, as many as 39 respondents had pruritus. This study concluded that gender has a role in the emergence of pruritus in hemodialysis patients, a vulnerable group.

5. Age

Older people are considered susceptible to decreased immune system function, a condition is assumed to be one of the factors for the emergence of pruritus. Research by Rroji's (2015) study stated that the elderly (≤ 72 years) have a higher prevalence of pruritus because they experienced a downturn in the immune system. When there was a reaction on the skin and for a long time, the patient experience pruritus (Ersoy, N. A., dan A. I., 2019) dan (Kaur, 2019). According to Weiss (2019), pruritus is mostly complained of by patients aged 70-80 years. Age is a risk factor for the emergence of disease. As we get older, the immune system is also indicated to have decreased function, so that we age to have a greater risk of developing pruritus symptoms.

V. CONCLUSION

Thirteen articles were identified and analyzed, proving that uremic pruritus in hemodialysis patients. From the study summary, the results provide related factors for the emergence of uremic pruritus are multifactorial. Uremic pruritus arises because of risk factors such as dialysis, length of time on dialysis, age, and sex. The clinical values refer to Urea Reduction Ratio, Clearance, Interleukin-2, Interleukin-6, and C-Reactive Protein.

It is necessary to do more research on the accuracy of hemodialysis parameters that can be excreted and the hemodialysis frequency.

This research is important because it is still unclear about the management of pruritus in hemodialysis patients, which is not sufficient and is still different. In accordance with the continuous kidney disease management guidelines, pruritus management must be applied.

Future research is also expected to be broader, including the prevalence of uremic pruritus is also a complaint by dialysis patients although the prevalence of uremic pruritus factors is expected to improve management abilities.