



A Scoping Review: Factors Associated with Pruritus in CKD (Chronic Kidney Disease) Patients Undergoing Dialysis

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ABSTRACT

Chronic Kidney Disease (CKD) is characterized by progressive loss of kidney function over time due to kidney damage or reduced glomerular filtration rate (GFR) $<60 \text{ mL/min/1.73m}^2$ for >3 months. The increased levels of urea in patients with chronic kidney failure can cause pruritus known as uremic pruritus or chronic kidney disease associated pruritus (CKD-ap). The research method that will be used is PRISMA. These scoping reviews will use a systematic approach and selection process. Library sources were traced from the Proquest, PubMed, Scopus and Google Scholar databases. This scoping review examines the associated factors with pruritus in patients undergoing dialysis. Factors related to uremic pruritus, namely based on analysis through scoping reviews that have been carried out on 8 articles, it was found that the most widely used study design was cross-sectional, the most widely used type of dialysis is hemodialysis with the number of articles is 3 articles and the number of patients that is male 505 samples (60.4%) and women 331 samples (39.6%) with the Total is 836 samples. Factors associated with uremic pruritus are gender, age, dialysis dose, duration of dialysis, urea/urea, C-Reactive Protein (CRP), and parathyroid hormone (PTH). The conclusion is that the factor that most dominant factor affecting pruritus is the factor of laboratory results, which is a factor that can be modified

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Kata kunci:

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ABSTRAK

Chronic Kidney Disease (CKD) ditandai dengan hilangnya fungsi ginjal secara bertahap dari waktu ke waktu karena kerusakan ginjal atau ketika laju filtrasi glomerulus (LFG) $<60 \text{ mL/menit/1,73 m}^2$ selama >3 bulan. Peningkatan kadar ureum pada penderita gagal ginjal kronik dapat menyebabkan pruritus yang dikenal dengan istilah pruritus uremik atau chronic kidney disease associated pruritus (CKD-ap). Metode penelitian menggunakan PRISMA. Scoping review ini menggunakan pendekatan dan proses seleksi yang sistematis. Sumber pustaka ditelusur dari database Proquest, PubMed, Scopus dan Google Schoolar. Scoping review ini bertujuan untuk menelaah faktor-faktor yang berhubungan dengan pruritus uremik pada pasien yang menjalani dialisis. Faktor yang berhubungan pruritus uremik yaitu berdasarkan analisis melalui scoping review yang telah dilakukan pada 8 artikel maka didapatkan hasil bahwa desain penelitian paling banyak digunakan yaitu cross sectional, tipe dealisis paling banyak digunakan yaitu hemodialisis dengan jumlah artikel yaitu 3 artikel dan jumlah pasien yaitu Laki-laki 505 sampel (60,4%) dan perempuan 331 sampel (39,6%) Total 836 sampel. Faktor yang berhubungan dengan pruritus uremik adalah jenis kelamin, umur, dosis dialisis, lama dialisis, urea/ureum, C-Reactive Protein (CRP), dan hormon paratiroid (PTH). kesimpulan yang paling dominan mempengaruhi pruritus adalah faktor hasil laboratorium yaitu faktor yang mampu untuk dimodifikasi

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INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by progressive loss of kidney function over time due to kidney damage or reduced glomerular filtration rate (GFR) <60 mL/min/173m² for >3 months. CKD is a kidney disease in which there is a gradual decline in kidney function over several months or years (>3 months) (Hasan & Obeed, 2021; Swarna et al., 2019).

The prevalence of CKD worldwide reaches 9.1%, which is estimated at around 700 million. The Riskesdas report (2018) shows that the prevalence of chronic kidney disease in Indonesia is 0.38% or 713,783 cases. The Data from PERNEFRI states that the prevalence of kidney disease is quite high, reaching 30.7 million (Nurmansyah & Arofiati, 2019). Data from *Dialysis Outcomes and Practice Patterns Study* (DOPPS), which is an study observational, revealed that 67% of the 23,264 patients undergoing hemodialysis experienced problems, namely chronic pruritus. (Locatelli & Legat, 2021).

Patients with chronic kidney failure will experience an increase in urea and creatinine caused by failure of the kidney function to secrete the remains of metabolic substances in the body (Smeltzer & Bare, 2013). An increased level of urea in the body can cause organ function disorders such as fluid and electrolyte disturbances, skin, endocrine metabolism, neuromuscular, cardiovascular, lung, gastrointestinal, hematological, and immunological (Jameson et al., 2015).

Pruritus is a skin problem that interferes with the quality of sleep and daily activities of patients with chronic kidney failure due to the itchiness that appears (Shaikh et al., 2019). Not only that, Juanda research (2017) states that pruritus gives patients a feeling of discomfort, embarrassment, and lack of confidence. It is feared that things like this can lead to more severe psycho-social problems and also do not rule out the possibility that patients will experience mental disorders (Oxtavia et al., 2017). Apart from the psychological impact, Yonathan & Darmawan (2021) stated that patients with chronic kidney disease with symptoms of pruritus are more

at risk of infection, injury, calciphylaxis, *acquired perforating dermatosis*, and *nephrogenic systemic fibrosis*.

Considering the high incidence of uremic pruritus and complications resulting from uremic pruritus in CKD patients, this scoping review intends to examine what factors cause pruritus in patients undergoing dialysis.

METHODS

The research method that will be used is PRISMA. This scoping review uses a systematic approach and selection process. Library sources were traced from national and international *databases* including Proquest, PubMed, Google Scholar, and Scopus. The keywords that will be used in the search are (etiology AND pruritus AND uremic AND patients AND dialysis AND Chronic kidney disease). This *scoping review* aims to examine the associated factors with pruritus in patients undergoing dialysis. Therefore the inclusion criteria used to determine that an article is eligible to be included in the review are as follows: patients experiencing uremic pruritus, CKD patients undergoing dialysis, journal publications for the last 5 years (2018-2022), and the study design, which is cross sectional, cohort, and descriptive studies.

RESULTS AND DISCUSSIONS

Based on the search results for articles through the database, namely Proquest, Pubmed, Google Scholar, and Scopus, 13,081 articles were shows high relevance to the topics reviewed between 2018-2022, totaling 3,149 articles. After article check for duplicates, abstracts, and titles 19 articles were entered the next stage of full text and eligibility studies based on the criteria inclusion and exclusion set by the researcher. The 8 research articles that met the criteria inclusion were then reviewed for quality and synthesized into the final report of this scoping review.

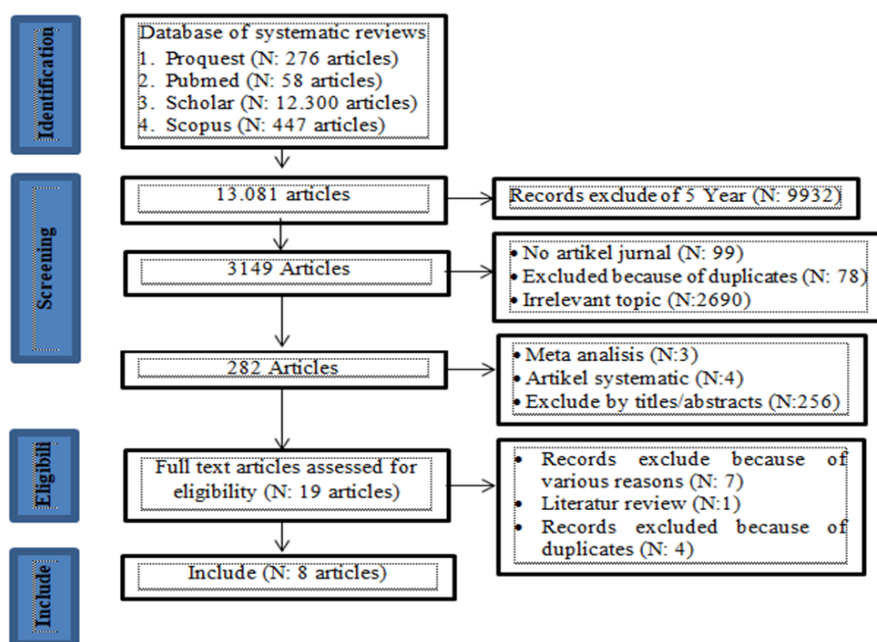


Chart 1
Prism Diagrams

Table 1 List of research articles in *scoping review* on factors causing pruritus in CKD patients undergoing dialysis

No	Author (Year)	Title	Country	Study Design	Dialysis Type	Number Of Samples	Outcome
1	(Hasan & Obeed., 2021)	Pruritus occurs in patients with chronic kidney disease: Features and associated factors	Iraq	Cross-sectional	Hemodialysis	53 patients	1. Gender 2. Age
2	(Minato et al., 2020)	Factors associated with uremic pruritus in patients undergoing peritoneal dialysis	Japan	Cross-sectional	Peritoneal Dialysis	46 patients	Gender (male)
3	(Zhao et al., 2021)	Determinants of the intensity of uremic pruritus in patients receiving maintenance hemodialysis: A cross-sectional study	India	Cross-sectional	Hemodialysis	148 patients	1. High-Sensitivity C-Reactive Protein 2. (Blood Urea Nitrogen)
4	(Wu et al., 2018)	Prognostic importance and determinants of uremic pruritus in patients receiving peritoneal dialysis: A prospective cohort study	Taiwan	Cohort study	Peritoneal Dialysis	85 PD patients	1. Duration of dialysis 2. Total dialysis adequacy (dialysis dose) ≤ 18 Kt/V 3. Parathyroid Hormone 4. C-Reactive Protein (CRP)
5	(A Harlim., 2020)	Factors associated with uremic pruritus in chronic kidney failure patients	Indonesia	Cross-sectional	Hemodialysis	33 patients	Hemodialysis duration
6	(Kumar et al., 2020)	Uremic Pruritus and associated factors in Chronic Dialysis Patients: An Observational Study in Western Nepal	Nepal	Cohort study	Hemodialysis and Peritoneal Dialysis	59 patients	Urea Serum
7	(Hu et al., 2019)	Clinical features and risk factors of pruritus in patients with chronic renal failure	China	Cohort study	Hemodialysis and Peritoneal Dialysis	382 patients	PTH (Parathyroid Hormone)
8	(Mehr Kash et al., 2021)	Pruritus Features in Children with End-Stage Renal Disease Underwent Dialysis: A Cross-Sectional Study	Iran	Cross-sectional	Hemodialysis and Peritoneal Dialysis	30 patients	1. Age 2. PTH Serum (Parathyroid Hormone)

Table 2 Characteristics Description

No	Characteristics	Frequency (N)	Percentage (%)
1	Design Studies		
	Cross-Sectional	5 articles	62,5%
	Cohort Study	3 articles	37,5%
2	Dialysis Type		
	Hemodialysis	3 articles	37,5%
	Peritoneal Dialysis	2 articles	25%
	Hemodialysis and peritoneal dialysis	3 articles	37,5%
3	Country		
	West Asia		
	Iraq	1 article	25%
	Iran	1 article	
	East Asia		
	Japan	1 article	37,5%
	Taiwan	1 article	
	China	1 article	
	South Asia		
	India	1 article	25%
Nepal	1 article		
Southeast Asia			
Indonesia	1 article	12,5%	
4	Gender		
	Male	505 sample	60,4%
	Female	331 sample	39,6%

Table 3 Factors Associated with Uremic Pruritus

No	Characteristics	Results Summary	Frequency (N)
1	Gender	Male 72 patients (72,7%)	2 articles
		Female 27 patients (27,3%)	
2	Age	Age ≥ 45 Years	1 article
3	Dialysis Dosage	HD Adequacy value $< 1,88$ Kt/V	1 article
4	Duration of dialysis	Duration of dialysis > 4.1 Year	1 article
5	Laboratory Results	Urea/ureum	Mean ureum 19.95 mmol/L or in the range of 18.28–21.65 mmol/L
			Mean ureum 122,4 mg/dl with SD 36,1
		C-Reactive Protein (CRP)	2.00 (1.00–3.00) > 0.16 (mg/L)
		Parathyroid Hormone (PTH)	Mean 251,2 (pg/ml)
			Mean 608.15 (pg/ml) with SD 514.44
		Mean 524.12 pg/ml with SD 313,53	3 articles

Patient characteristic factors

a. Gender

The results of a cross-sectional study showed that the male sex experienced the most uremic pruritus, namely 72 patients (72.7%) compared to women (Hasan & Obeed 2021). This is in line with Hasan & Obeed (2021) cross-sectional study which states that gender is associated with uremic pruritus with a value ($p < 0.017$).

This is related to the high incidence of CKD in men due to unhealthy lifestyles, such as frequent smoking, drinking coffee and energy drinks, and rarely consuming water. Other causes that increase the exacerbation of uremic pruritus in men, namely men have a high level of physical activity, which causes more sweat production than women, and low skincare habits are also reasons for the high effect of uremic pruritus in men because uremic pruritus occurs more easily in men with dry skin. (Fauziah & Soelistyowati, 2018).

b. Age

The results of a cross-sectional study showed that ≥ 45 years of age experienced uremic pruritus the most, namely 46 patients (86.8%). Hasan & Obeed (2021) cross-sectional study states that age is associated with uremic pruritus with a value ($p < 0.034$).

Most of the uremic pruritus patients are in middle adulthood, aged 41-60 years. This may be due to the unhealthy lifestyle of the middle adulthood group, such as eating fast food, stressful activities, sitting in the office all day, consuming coffee and energy drinks frequently, and rarely drinking water. This bad habit is a risk factor for kidney damage. Kidney damage is the main cause of uremic pruritus. In addition, the decreased ability of the body to metabolize substances that cause uremic pruritus between the ages of 41 and 60 years is also the reason for the high incidence of uremic pruritus in this age group (Fauziah & Soelistyowati, 2018).

c. Dialysis dose

Dialysis doses with HD adequacy values < 1.88 Kt/V can be a factor causing pruritus. This is in line with a *cross-sectional study* conducted by Kossuth Cabrejos et al (2020) which stated that there was a relationship between dialysis dose and uremic pruritus as indicated by the value ($p < 0.002$).

In the study, Wu et al (2018) Severity of uremic pruritus was greater in patient with weekly total KT/V < 1.88 (HD work capacity value or urea clearance ratio) than in patients with high solute clearance. According clinical guidelines, target dose of total weekly Kt/V ≥ 17 Kt/V to ensure adequate clearance of the solution in peritoneal dialysis. The higher the total weekly Kt/V value, it will show that the cleanliness of the solute is higher, so it can remove more pruritogenic substances. Pruritogenic substances that can be dialyzed with optimal dialysis targets can reduce uremic pruritus (Wu et al., 2018).

d. Duration of dialysis

The length of the duration of undergoing hemodialysis is one of the factors causing the problem of uremic pruritus. This is supported by the research of Wu et al (2018) which states that there is a relationship between the duration of dialysis and uremic pruritus with an indicated value ($p < 0.032$).

Uremic pruritus is related to the duration of dialysis. This is affected by further damage to kidney function. In theory, it is explained that uremic pruritus usually occurs in patients undergoing dialysis for a long time. The researchers find duration dialysis affected the severity of uremic pruritus symptoms, namely the longer the dialysis treatment was carried out, the more severe the uremic pruritus. This is further exacerbated by impaired kidney function. Therefore, people with CKD are expected to follow and adhere to a predetermined diet so that kidney function does not worsen and uremic pruritus does not get worse (Fauziah & Soelistyowati, 2018).

Laboratory result factor

a. Urea/ureum

Urea levels that exceed normal limits, namely 7-30 mg/dl or 2.5-10.7 mmol/L, are trigger factors for uremic pruritus. This is in line with the research of Zhao et al (2021) which states that there is a relationship with uremic pruritus, namely a value ($p < 0.028$).

Urea is a substance that is not charged (uncharged), not bound in plasma, soluble in water, easily diffuses between water compartments, easily dialyzed, and dispersed in body fluids. In addition to its low toxicity, urea is a good marker of uremic conditions because it is a product of protein degradation. Uremia is the most common cause of metabolic pruritus in uremic pruritus. Complaints of pruritus are thought to be related to the release of histamine from mast cells in the skin. Histamine is released by mast cells and directly stimulates H1 receptors on specific C fibers. The number of mast cells and basophils increases, resulting in uremic pruritus (Ago Harlim & Yogyartono, 2012; Pardede, 2010; Roswati, 2013).

b. C-Reactive Protein (CRP)

CRP level > 0.16 (mg/L) is a factor for uremic pruritus. In line with the *prospective cohort study* conducted by Wu et al (2018) which states that CRP levels are associated with uremic pruritus as evidenced by the results of the multivariate test with a value ($p < 0.032$).

Uremic pruritus is also known as a systemic disorder associated with inflammation. Inflammation is a marker associated with uremic pruritus in both hemodialysis and peritoneal dialysis patients. Uremic pruritus is considered a skin reaction to an ongoing inflammatory process characterized by increased levels of high-sensitive reactive protein C. The state of uremic inflammation also explains the high number of mast cells in the dermis which eventually results in uremic pruritus (Pardede, 2010; Sarhan et al., 2020; Tseng et al., 2018).

c. Parathyroid Hormone (PTH)

Parathyroid hormone (PTH) affects the occurrence of uremic pruritus. According to Hu et al (2019), there is a relationship between PTH and uremic pruritus as evidenced by the value ($p < 0.001$).

Hyperparathyroidism can trigger mast cells to release histamine, causing microprecipitation of calcium and magnesium salts in the skin. However, not all patients with severe hyperparathyroidism experience uremic pruritus. One study reported that pruritus disappeared completely after parathyroidectomy. It was further noted that there was no

relationship between plasma PTH (parathyroid hormone) levels and dermal cell proliferation, nor was there a difference in the number of mast cells or PTH levels between patients with and without pruritus (Roswati, 2013).

LIMITATION OF THE STUDY

This article only uses search sources from four databases and all literature sources obtained in this search are only articles in English.

CONCLUSIONS AND SUGESTIONS

Based on the analysis through scoping review that has been done, it can be concluded that the most dominant factor affecting pruritus is the factor of laboratory results, which is a factor that can be modified. It is recommended to change lifestyles so that the results of the laboratory experience change.

ETHICAL CONSIDERATIONS

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Conflict of Interest Statement

No conflict of interest

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