



MALAYSIAN JOURNAL OF BIOCHEMISTRY & MOLECULAR BIOLOGY

The Official Publication of The Malaysian Society For Biochemistry & Molecular Biology
(MSBMB)
<http://mjbmb.org>

DIAGNOSTIC AND PROGNOSTIC VALUE OF INTERLEUKIN-6 FOR PRURITUS IN PATIENTS WITH END STATE RENAL DISEASE UNDERGOING REGULAR HEMODIALYSIS

Riri Andri Muzasti* and Dewi Fuji Lestari

Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas of Sumatera Utara

*Corresponding Author: riri.andri@usu.ac.id

History

Received: 4th January 2020
Accepted: 13th February 2020

Keywords:

Interleukin-6, pruritus, end state renal disease, hemodialysis

Abstract

Chronic kidney disease (CKD) is a national health problem because the incidence tends to increase, has a poor prognosis, and requires high costs. Pruritus is estimated to occur in 20% - 90% of patients with end-stage renal disease (ESRD) undergoing dialysis. Hemodialysis (HD) patients tend to develop inflammation, which involves several proinflammatory cytokines, such as Interleukin-6 (IL-6). Previous studies have shown that IL-6 is a central regulator of the inflammatory process and is found in dermal nerve fibers. We conducted a cross-sectional analytic study to determine the cut-off value of IL-6 levels as a marker of pruritus in ESRD patients undergoing HD. Patients were asked to fill out a Pauli-Magnus questionnaire, and we checked their serum IL-6, calcium, phosphate, and parathyroid hormone levels. Out of the 100 patients who met the inclusion and exclusion criteria, we found that age, HD frequency, and IL-6 levels were significantly associated with pruritus ($p = 0.003$; $p = 0.021$ and $p = 0.001$). The cut-off value of IL-6 as a predictor of pruritus in ESRD patients undergoing regular HD was 101.55 mg/ml, with a sensitivity of 98.1% and specificity of 95.8%. From this study, we conclude that IL-6 levels >101.55 mg/ml was a powerful predictor of pruritus in ESRD patients undergoing regular HD

INTRODUCTION

Chronic kidney disease (CKD) is a national health problem because the incidence tends to increase; it has a poor prognosis and requires high costs. The most commonly used modality for renal replacement therapy in Indonesia is hemodialysis. The Indonesian Renal Registry (IRR) in 2018 reported that 92% of patients undergoing hemodialysis were CKD patients. There was a consistent increase in the number of new and active patients. The number of new patients has doubled compared to 2017 (from 30,832 patients to 66,433 patients). Likewise, the number of active patients increased sharply compared to the previous year (from 77,892 patients to 132,142 patients). In line with the increasing number of patients, the number of HD centers also increased to 797 units spread across various regions in Indonesia^{1,2}.

Hemodialysis patients often complain of itching. Pruritus is estimated to occur in 20% - 90% of dialysis patients. In large-scale studies of the Dialysis Outcomes and Practice Patterns Study (DOPPS), I and DOPPS II reports that $> 40\%$ of patients undergoing HD suffer from chronic pruritus^{3,4}. Although pruritus can be temporary for several months, these symptoms are more frequent last more than one year^{5,6}.

Inflammation is considered to have an essential role in the pathogenesis of pruritus in HD patients. Among several proinflammatory cytokines, research shows that IL-6 is a central regulator of the inflammatory process and is found in dermal nerve fibers. Research conducted by Kimmel et al. stated that serum IL-6 levels were significantly increased in the group of patients with pruritus compared with patients without pruritus^{7,8}.

Based on this background, we conducted a study to determine the relationship between IL-6 levels and the occurrence of pruritus in ESRD patients undergoing regular HD.

MATERIALS AND METHODS

Study Sample

The population in this study were all ESRD patients who underwent HD at the Rasyida Renal Hospital in Medan. Patients who had undergone regular HD \geq three years, \geq 18 years old, and had given written consent to participate were included in the study. Patients with primary skin disease and changing dialysis modalities within three months were excluded from this study.

Study Design

This research is an analytic study with a cross-sectional design. The sampling technique used was consecutive sampling. After obtaining approval from the ethics committee, subjects who met the inclusion and exclusion criteria were asked to give written consent to participate in this study. Demographic and clinical data are obtained from medical records or interviews. Pruritus, which is associated with CKD diagnosed based on the criteria in Table 1.

Table 1. Diagnostic Criteria of Pruritus Associated with CKD³⁴

1.	Pruritus occurred just before the onset of dialysis, or occurred at any time, without evidence of other underlying active diseases.
2.	More than or equal to three episodes of pruritus within <2 weeks, which occur several times a day, last for at least several minutes, and interfere with the patient's daily life.
3.	Pruritus occurs in a regular pattern over six months but is less frequent than mentioned above.

Patients were asked to fill out the Pauli-Magnus questionnaire (Table 2) and undergo laboratory tests to check serum IL-6, calcium, phosphate, and parathyroid hormone levels. Interleukin-6 levels were measured using the turbidimetry method (Architect of CRP Harmonization MultiKent 6K26-30, Indonesia). Calcium levels were determined based on the cresol phthalein complex method (ADVIA 03932883 RevA, Indonesia), whereas phosphate levels were determined by the phosphomolybdate method (ADVIA 024220623 Reva, Indonesia)

Statistical Analysis

Univariate analysis was performed to obtain a general description of each variable studied. An unpaired t-test was used to determine the relationship between numerical variables and categorical variables.

Diagnostic analysis of Area Under Curve (AUC) with a 95% confidence interval (95% CI) was used to determine the sensitivity and specificity of the IL-6 cut-off points. The diagnostic analysis is also to determine the value of Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR), and Negative Likelihood Ratio (NLR) from IL-6 levels.

Table 2. Scoring of Symptoms in Each Questionnaire Parameters

Parameters	Score
Degree of Severity	
Minimal itching, without the desire to scratch	1
Desire to scratch, but without skin damage	2
Scratching and skin damage	4
Bothersome itching	5
Location	
Less than 2 locations	1
2 locations	2
More than 2 locations	3
Sleep Disturbance	
Scratching episodes at night causing skin damage	1-5
Pruritus attack woke the patients from sleep	2-10

RESULTS AND DISCUSSION

Characteristics of Participants

The study was conducted in April 2018, involving 100 patients who met the inclusion and exclusion criteria. The majority of participants were male (60%) with an average age of 57 years old. This finding was in line with the study of Muzasti et al.⁹. Women are protected by estrogen during reproductive age. CKD often occurs in patients who smoke and drink alcohol, which is often found in men. Most of the patients were in \geq 55 years old group (53%). These results are consistent with the 2015 IRR, where the proportion of patients in the 45-64 years old category. Most of the participants underwent HD twice a week (75%)⁵. A total of 53 patients (53.0%) consumed calcium-based phosphate-binder medicine.

From the laboratory tests, we found that the mean level of leukocyte and phosphate were 10,813 cells/mm³ and 5.44 mg/dL. The median level of urea, IL-6, calcium, parathyroid hormone and absolute eosinophil were 113 mg/dL, 120 mg/dL, 9.8 mg/dL, 69.72 pg/dL, and 0.07x10³/uL (Table 3).

Table 3. Characteristics of Participants

Variable	n = 100
Sex, n (%)	
Male	60 (60,0%)
Female	40 (40,0%)
Age, median (min-max), years	57 (22 – 78)
Age, n (%)	
<45 years	18 (18,0%)
45-54 years	29 (29,0%)
≥55 years	53 (53,0%)
Hemodialysis vintage, n (%)	
≤ 5years	69 (69,0%)
>5 years	31 (31,0%)
Frequency of Hemodialysis, n (%)	
Twice a week (10 hours)	75 (75%)
Three times a week (12 hours)	25 (25%)
Comorbidity, n (%)	
Diabetes Mellitus	
Yes	21 (21,0%)
None	79 (79,0%)
BMI Classification, n (%)	
Normal	69 (69,0%)
Underweight	2 (2,00%)
Overweight	29 (29,0%)
History of Medicine (Yes), n (%)	
Calcium based phosphate binder	53 (53,0%)
Non-Calcium based phosphate binder	10 (10,0%)
Gabapentin	67 (67,0%)
Laboratory Tests	
Urea, median (min-max), mg/dL	113 (6-158)
IL-6 Level, median (min-max), mg/dl	120 (35,8-
Calcium Level, median (min-max), mg/dL	665,0)
Phosphate Level, mean (±SB), mg/dL	9,8 (8-10,9)
Parathyroid Hormone Level, median (min-max), pg/dL	5,44 (0,624-
Albumin Level, median (min-max), mg/dL	69,72 (35,7-
Ca*P Level, median (min-max) mg/dL	132,5)
Absolute Eosinophil Count, median (min-max) 10 ³ /uL	3,90 (2,90-
Leukocyte, mean (±SB), cells/mm ³	4,90)
Leukocyte Level, cells/mm ³	52,90(34,44-
4.000-11.000	69,36)
>11.000	0,07 (0,00-
Pruritus, n (%)	10,813)
Yes	(1.777,85)
No	
Yes	61 (61,0%)
No	39 (39,0%)

Out of 100 participants, 52% of them had pruritus. Most of the patients had a mild intensity of pruritus (48%). Weiss's study concluded that the prevalence of pruritus differs based on its intensity. Mild pruritic intensity occurred in 22 - 52.6% of patients, moderate pruritus in 22.6 - 40% of patients, and severe pruritus in 8 - 40% of patients⁹. Most complaints of pruritus in this study were felt at night, with an average score

of 19.32. These results are in line with previous studies conducted by Min. et al. They found that patients with a VAS score > four more experienced pruritus at night¹⁰ (Table 4).

Bivariate Analysis

Table 5 showed that there was a significant difference in the mean of IL-6 levels among pruritus events (p = 0.001). Inflammation plays a vital role in the pruritus pathogenesis in HD patients, where a series of inflammatory factors such as IL-6, IL-2, and histamine, are reported to be associated with pruritic¹¹. IL-6 and leukocytes are found to be increased in pruritic patients. Interleukin-6 is reported to be most associated with inflammation than other cytokines and C-reactive protein because it is the central regulator of the inflammatory process^{12,13}.

Age was statistically related to pruritus (p = 0.003), where the group of patients ≥55 years old had more pruritus events compared to other age groups (57.69%). In addition to decreased immunity, the aging process also reduces the metabolism of the immune system, making it possible to increase the sensation of pruritus in HD patients^{14,15}.

Statistically, we found that the frequency of HD was associated with pruritus (p = 0.021). Reddy et al. concluded that the frequency of HD was related to pruritus because when blood products circulate during the HD process, it will stimulate acute immune reactions. So, the more often the patients undergo HD, the higher the blood contact with foreign substances such as bioincompatible elements, dialysate contamination, which is a potential source of inflammation¹⁶.

On the other hand, statistically, the hemodialysis vintage was not associated with pruritus in our result (p = 0.703). This may be because some patients took Gabapentin therapy. Gabapentin has been used to treat pruritus by blunting the transmission of C nerve fibers, modulating pain and itching sensation^{3,4,6}.

Our study found that patients taking calcium-based phosphate binders had more pruritus than those none calcium-based (61.5% vs. 9.6%). However, statistically, this was not significantly different (p > 0.05). According to Ji-Won Min et al., the administration of phosphate binder drugs can reduce phosphate levels so that the incidence of pruritus also decreased. Gatmiri et al. 's study showed that phosphate levels of <7 mg/dl did not trigger pruritus. Conversely, the phosphate levels of > 7 mg/dl would trigger pruritus¹⁷.

Our study also found that the mean of leukocyte count in patients with pruritus was not significantly different from those without pruritus. We conclude that statistically, the leukocytes count is not related to pruritus (p > 0,05). This is because pruritus in CKD patients is a chronic process so that the leukocytes count can be normal¹⁸.

Urea levels are not statistically related to pruritus in our result (p > 0.05). It is consistent with previous studies by Ji-Won Min et al. They showed that urea was not directly playing a role in the pathogenesis pruritus but rather are

caused by the accumulation of uremic toxins such as β 2-microglobulin is¹³.

Serum calcium level in patients with pruritus was not too different from those without pruritus (9,756±0,67 mg/dl vs. 9,652±0,812 mg/dL); therefore, it was concluded that serum calcium levels were not statistically related to pruritus (p=0,631). This is per previous studies by Ji-Won Min et al.,¹³. Although microprecipitation of ionic calcium can modulate the conduction of itching sensations and trigger the release of histamine from mast cells in the skin^{17,19}, but the calcium levels in this study (9,756 mg/dl) did not cause

pruritus as it needs to reach the cut-off points of 10.2 mg/dl causing pruritus¹⁷.

In our study, the mean phosphate level of patients with pruritus was almost the same as those without pruritus (70.67 ± 17.89 mg/dL vs. 68.48 ± 17.89 mg/dL). Based on statistical analysis, we concluded that serum phosphate levels were not significantly associated with pruritus (p= 0.194). This might be because some of the patients had a history of taking phosphate binding agents (Table 5).

Table 5. Comparison of pruritus proportion based on participant characteristics

Variable	Pruritus		P
	Yes (n=52)	No (n=48)	
Age, n (% within)			
< 45 years old	3 (5,8%)	15 (31,3%)	0,003 ^a
45-54 years old	19 (36,5%)	10 (20,8%)	
≥ 55 years old	30 (57,7%)	23 (47,9%)	
Hemodialysis vintage, n (%)			
≤ 5 years	35 (67,3%)	34 (70,8%)	0,703 ^a
> 5 years	17 (32,7%)	14 (29,2%)	
Frequency of Hemodialysis, n (%)			
Two times a week (10 hours)	34 (65,4%)	41 (85,4%)	0,021 ^a
Three times a week (12 hours)	18 (34,6%)	7 (14,6%)	
History of Medicines (Yes), n (%)			
Calcium based Phosphate-binder	32 (61,5%)	21 (43,8%)	0,075 ^a
Non-Calcium Phosphate-binder	5 (9,6%)	5 (10,4%)	0,894 ^a
Laboratory Tests			
Leukocyte, cell/mm ³	10.598,08±1776,2	11.045,83±1768,5	0,210 ^f
Urea, mg/dL,	113,5±13,73	112,79±19,64	0,560 ^c
IL-6, mg/dl	135,77±25,15	77,68±88,13	0,001 ^c
Calcium, mg/dL	9,756±0,67	9,652±0,812	0,631 ^c
Phosphate, mg/dL	70,67±17,89	68,48±17,89	0,194 ^t
Parathyroid Hormone, pg/dL	5,521±0,580	5,358±0,664	0,712 ^c
Leukocyte count, cell/mm ³			
4.000-11.000	36 (59,0%)	25 (41,0%)	0,079 ^a
>11.000	16 (41,0%)	23 (59,0%)	

AUC Score

Based on the AUC value (0.964) in the ROC analysis (Figure 1), we suggested that the IL-6 level was a powerful predictor of pruritus in ESRD patients with HD (p<0,001). The cut-off point of IL-6 levels is 101,550 mg / ml with a sensitivity of 98.1% and specificity 95.8% (CI 95% 0.917 - 1,000).

Based on the value of the IL-6 cut-off point, we could determine the positive predictive value (PPV) and the negative predictive value (NPV) of IL-6. The ability of IL-6 level in detecting patients who had pruritus is stated as Positive Predictive Value (PPV), which is 96.2%. While the ability of IL-6 levels in detecting patients, who do not have pruritus is stated as a Negative Predictive Value (NPV),

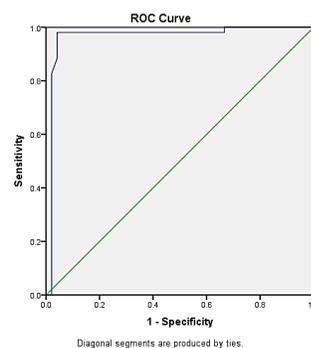


Figure 1. ROC analysis

which is 97.9%. The Positive Likelihood Ratio (PLR) value is 2.33%, and the Negative Likelihood Ratio (NLR) is 1.98%.

It can be concluded that IL-6 is a powerful predictor of the incidence of pruritus in ESRD patients undergoing regular HD.

ACKNOWLEDGMENT

The authors would like to thank Rasyida Renal Hospital Medan, for facilitated this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

REFERENCES

1. IRR IRR-. (2017) 10th Report of Indonesian Renal Registry. Indonesia.
2. IRR IRR-. (2018) 11th Report of Indonesian Renal Registry. Indonesia.
3. Mettang, T., Kremer, A.E. (2015) Uremic pruritus. *Kidney Int* 87(4), 685-691.
4. Shirazian, S., Aina, O., Park, Y., Chowdhury, N., Leger, K., Hou, L., et al. (2017) Chronic kidney disease-associated pruritus: impact on the quality of life and current management challenges. *International Journal of Nephrology and Renovascular Disease* 10(1), 11–26.
5. Pisoni, R.L., Wikstrom, B., Elder, S.J., Akizawa, T., Asano, Y., Kern, M.L., et al. (2006) Pruritus in hemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 21, 3495-3505.
6. Aramwit, P., Supasyndh, O. (2015) Uremic Pruritus; Its Prevalence, Pathophysiology, and Management. In: Suzuki, H. *Update in Hemodialysis*. Croatia. InTech, 19-41.
7. Filho, R.P., Lindholm, B., Axelsson, J., Stenvinkel, P. (2003) Update on interleukin-6 and its role in chronic renal failure. *Nephrol Dial Transplant* 18, 1042-1045.
8. Kimmel, M., Alscher, D.M., Dunst, R., Braun, N., Machleidt, C., Kiefer, T., et al. (2006) The role of micro-inflammation in the pathogenesis of uremic pruritus in hemodialysis patients. *Nephrol Dial Transplant* 21, 749-755.
9. Muzasti, R.A., Lubis, H.R. (2018) Association of phase angle on bioelectrical impedance analysis and dialysis frequency with the survival of chronic hemodialysis patients. *Earth and environmental science*, 125(1).
10. Min, J.W., Kim, S.H., Young, O.K., Jin, D.C., Song, H.C., Choi, E.J., et al. (2016) Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. *Kidney Res Clin Pract* 35, 107-113.
11. Wu, H.Y., Peng, Y.S., Chen, H.Y., Tsai, W.C., Yang, J.Y., Hsu, S.P., et al. (2016) A Comparison of Uremic Pruritus in Patients Receiving Peritoneal Dialysis and Hemodialysis. *Medicine* 95(9), 1-6.
12. Shafei, N.K., Nour, A. (2016) Observations on the Association of Serum histamine, Interleukins, and Other Serum Biochemical Values with Severity of Pruritus in Chronic Hemodialysis Patients. *Nanomed Nanotechnol* 7(1), 1-6.
13. Atmojo, D.S. (2000) Prinsip dan Indikasi Hemodialysis. *Pertemuan Ilmiah Tahunan Ilmu Penyakit Dalam* 3(1), 1-8.
14. Ascioglu, E, et al. (2011) Uremic Pruritus: Still Itching. *Turkish Nephrology, Dialysis, and Transplantation Journal* 20(1), 7-13.
15. Magnus, C.P., Mikus, G., Alscher, D.M., Kirschner, T., Nagel, W., Gugeler, N., et al. (2000) Naltrexone Does Not Relieve Uremic Pruritus: Results of a Randomized, Double-Blind, Placebo-Controlled Crossover Study. *J Am Soc Nephrol* 11, 514-519.
16. Santoro, A., Mancini, E. (2014) Is hemodiafiltration the technical solution to chronic inflammation affecting hemodialysis patients? *Kidney International* 86, 235-237.
17. Gatmiri, S.M., Mahdavi, M., Parezkeski, T.M., Abbasi, M. (2013) Uremic Pruritus and Serum Phosphorus level. *Acta Med Iran*.
18. Suzuki, H., Omata, H., Kumagai, H. (2015) Recent Advances in Treatment for Uremic Pruritus. *Open Journal of Nephrology* 5(1), 1-13.
19. Akhyani, M., Ganji, M.R., Samadi, N., Khamesan, B., Daneshpazhooh, M. (2005) Pruritus in hemodialysis patients. *BMC Dermatology*.
20. Brennan, F. (2016) The pathophysiology of pruritus – A review for clinicians. *Progress in Palliative Care* 24(3), 133-146.