The Relationship Between Serum Interleukin-31 Levels and Chronic Kidney Disease-Associated Pruritus in Patients Undergoing Hemodialysis

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ABSTRACT

Background: *Chronic kidney disease-associated pruritus (CKD-aP) has been linked to immune dysregulation, including elevated interleukin-31 (IL-31) levels. However, the limited research on serum IL-31 levels in patients with CKD-aP has yielded inconsistent findings due to heterogeneous patient populations and varied assessment methods. This study elucidated the relationship between serum IL-31 levels, CKD-aP, and its severity in patients undergoing routine hemodialysis (HD).* ***Methods:*** *This cross-sectional observational study included patients undergoing HD at Dr. Cipto Mangunkusumo Hospital between April and May 2024. Pruritus was assessed using the visual analog scale (VAS) and 5-D itch scale. Serum IL-31 levels were measured using enzyme-linked immunosorbent assay. Bivariate and multivariate analyses were performed.* ***Results:*** *Among 70 participants (54.3% male; median age, 52.5 years; median HD vintage, 57 months), 35 experienced CKD-aP. The median VAS and 5-D itch scale scores were 5.3 and 13, respectively, indicating moderate itching severity. Patients with CKD-aP had significantly higher serum IL-31 levels than those without CKD-aP ($p = 0.05$). Receiver operating characteristic analysis showed modest discriminatory ability (area under the curve = 0.64), with a sensitivity of 51.4% and specificity of 74.3% at a cut-off of 173 pg/mL. A significant association was observed between serum IL-31 levels and CKD-aP ($p = 0.03$). However, no significant correlation was found between IL-31 levels and pruritus severity as measured by the VAS ($p = 0.79$) or 5-D itch scale ($p = 0.44$).* ***Conclusion:*** *Serum IL-31 levels were higher in patients with CKD-aP, suggesting its potential association with pruritus. However,*

its modest diagnostic performance and lack of correlation with itch severity indicate that IL-31 is unlikely to serve as a standalone clinical biomarker and may have a limited role as an adjunctive or exploratory marker.

Keywords**:** *Chronic kidney disease-associated pruritus (CKD-aP), hemodialysis, interleukin-31, 5-D itch scale, visual analog scale (VAS) .*

INTRODUCTION

Chronic kidney disease-associated pruritus (CKD-aP), previously known as uremic pruritus, is an important but often overlooked symptom reported by 42–57% of patients on hemodialysis (HD).[1,2] This condition is highlighted as a priority by the Kidney Disease Improving Global Outcomes, detrimentally affecting the patients' overall well-being. CKD-aP contributes to sleep disturbances, anxiety, depression, reduced social function, and an increased risk of hospitalization and mortality. Despite its impact, CKD-aP remains underreported, underestimated, and underdiagnosed; its pathophysiological mechanisms remain unclear, with no standardized treatment protocols.[3-7]

Emerging theories suggested that several factors contributed to the development of CKD-aP, including insufficient dialysis, disrupted calcium and phosphate metabolism, opioid receptor imbalance, and immune dysregulation. This last theory is supported by evidence linking systemic inflammation and immune response dysregulation in patients undergoing HD to factors such as uremic toxins, oxidative stress, non-biocompatible dialysis materials, and infected vascular access.[8] Among the various cytokines, interleukin-31 (IL-31) has emerged as a key player, known for its role in other chronic pruritic conditions such as atopic dermatitis.[9,10]

However, current evidence regarding serum IL-31 levels in patients with CKD-aP remains limited and inconsistent. The variability in study findings may be attributed to heterogeneous patient populations and the use of non-standardized pruritus assessment tools.[11-15] Moreover, the clinical role of IL-31, whether as a pathophysiological mediator, a marker of disease presence, or a potential indicator of severity, has not been clearly established. Therefore, this study aimed to evaluate the relationship between serum IL-31 levels and CKD-aP, as well as their associations with pruritus severity in patients undergoing HD, using standardized assessment tools including the visual analog scale (VAS) and 5-D itch scale.

METHODS

Study Design and Patients

This cross-sectional observational study was conducted in the hemodialysis unit of Dr. Cipto Mangunkusumo Hospital, Indonesia, between April and May 2024. Participants were eligible for inclusion if they were over 18 years of age, had been undergoing regular HD treatment for more than three months, received HD sessions twice weekly for 5 h each, had not missed any HD sessions in the preceding month, demonstrated comprehension and adherence to the research protocol, and provided written consent to participate. The exclusion criteria were as follows: a history of primary skin diseases, active hepatitis B or C infection, chronic or cholestatic liver disease, active infections, or malignancy; recent use (within 3 days) of antihistamines or gabapentinoids; recent (within 1 week) phototherapy sessions; and recent (within 2 weeks) use of oral steroids or immunosuppressants.

Data Collection

Diagnosis of CKD-aP was established by clinical examination. The severity of pruritus was quantitatively assessed using the VAS and 5-D itch scale.[16,17] Using the VAS scores, pruritus was classified as mild (1.0–3.9), moderate (4.0–6.9), or severe (7.0–10).[18] Whereas using the 5-D itch scale scores, pruritus was categorized as mild (5–11), moderate (12–17), or severe (18–25).[19,20] Serum IL-31 levels were measured using the Abbexa enzyme-linked immunosorbent assay (ELISA) kit protocol, with venous blood samples collected before the initiation of HD sessions.[21]

Statistical Analysis

The relationship between serum IL-31 levels and CKD-aP was analyzed using bivariate analysis. The t-test was used for normally distributed data and the Mann–Whitney U test for non-normally distributed data, as appropriate. Variables demonstrating a significant relationship ($p \leq 0.25$) were subsequently analyzed using multivariate logistic regression. Receiver operating characteristic (ROC) curve analysis was used to determine the serum IL-31 cut-off value. The association between IL-31 levels and CKD-aP was analyzed using the chi-square test. The correlation between serum IL-31 levels and pruritus severity was examined using Spearman's correlation test because the data were not normally distributed. Since no variables showed significant correlations ($p \leq 0.25$), multivariate linear regression analysis was not performed. The Kruskal–Wallis test was used to evaluate differences in serum IL-31 levels by itch severity, with a significance level set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA).

Ethics Statement

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia, Dr. Cipto Mangunkusumo Hospital (No. UN2.F1/ETIK/PPM.00.02/2024). Written informed consent was obtained from all the participants before enrollment.

RESULTS

Study Participant Characteristics

Our analysis included 70 patients who underwent routine HD between April and May 2024 (**Figure 1**). Of these, 54.3% were male, with a median age of 52.5 years and a median HD vintage of 57 months. Among the participants, 35.7% had diabetes mellitus, and 90% had hypertension. Laboratory evaluations revealed an average hemoglobin level of 9.8 mg/dL, a median neutrophil-to-lymphocyte ratio of 2.9, an average creatinine level of 12.6 mg/dL, and a median estimated glomerular filtration rate of 3.8 mL/min/1.73 m^2. Iron status indicators showed an average serum iron level of 51 mg/dL, a mean total iron-binding capacity of 222 mg/dL, and a median transferrin saturation of 22%. Electrolyte analysis indicated a relatively stable median sodium level of 137 mmol/L, an average potassium level of 4.6 mmol/L, and an average chloride level of 102 mmol/L. Hypercalcemia was present in 15.7% of the patients, whereas hyperphosphatemia was noted in 72.9%. Serum IL-31 levels had a median of 146.0 pg/mL.

Among the 35 patients with CKD-aP, the mean itch severity, measured using the VAS, was 5.3. Additionally, an average score of 13 was obtained on the 5-D itch scale. Based on the VAS, 57.1% of the patients reported moderate itching, and an equal proportion (42.9%) reported mild and moderate itching according to the 5-D itch scale (**Table 1**).

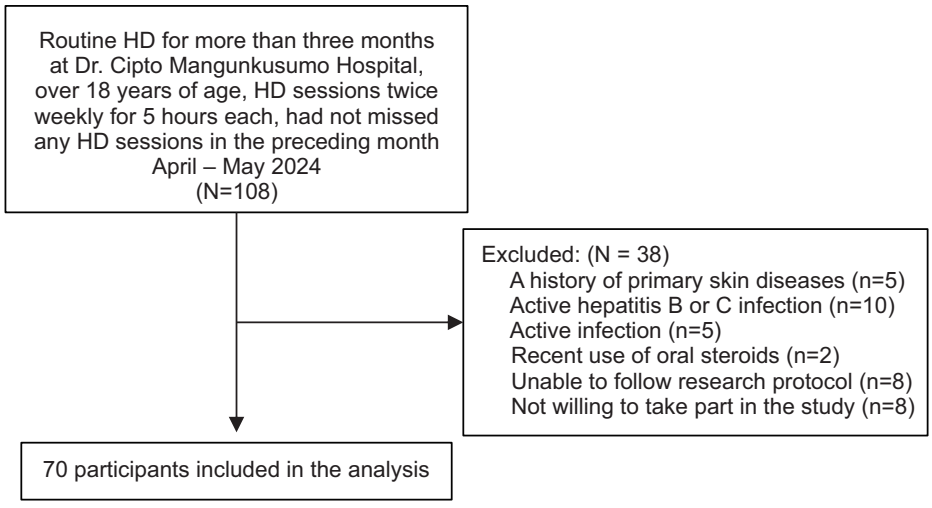

Figure 1. Flow chart of patient recruitment.

Table 1. Characteristics of the severity of CKD-aP.

Characteristics	n (%)
Visual analog scale	
Mild	10 (28.6)
Moderate	20 (57.1)
Severe	5 (14.3)
5-D itch scale	
Mild	15 (42.9)
Moderate	15 (42.9)
Severe	5 (14.2)

Serum IL-31 Levels in Patients Undergoing HD with and without CKD-aP

The analysis revealed that the median serum IL-31 levels were significantly higher in patients with CKD-aP than in those without (173.0 vs. 135.7 pg/mL, $p = 0.05$). ROC curve analysis identified a cut-off value for serum IL-31 levels at 173 pg/mL, with an area under the curve (AUC) of 0.64 (95% confidence interval [CI]: 0.51–0.77), $p = 0.05$, a sensitivity of 51.4%, and a specificity of 74.3% . Patients were categorized into high and low serum IL-31 groups based on this cut-off, which revealed a significant association between serum IL-31 levels and CKD-aP ($p = 0.03$) (**Table 2**).

The demographic and clinical characteristics did not differ significantly between patients with and without CKD-aP (**Table 3**). Confounding variables such as age, sex, HD vintage, absolute basophil count, absolute eosinophil count, urea, Kt/V, ferritin, and albumin levels were comparable between the groups. Other variable characteristics were also comparable between patients with and without CKD-aP.

Table 2. Bivariate analysis of serum IL-31 levels and CKD-aP.

Serum IL-31 groups	CKD-aP, n (%)		Prevalence ratio (95% CI)	*p*
	Yes (n=35)	No (n=35)		
High IL-31 levels	18 (66.7)	9 (33.3)	1.69 (1.07–2.66)	0.03[a]
Low IL-31 levels	17 (39.5)	26 (60.5)		

CI, confidence interval.
[a]Chi-square test.

Table 3. Comparison of study participants based on CKD-aP.

Characteristics	CKD-aP		*p*
	Yes (n=35)	No (n=35)	
Age (yr)	52 (41–62)	53 (35–63)	0.63[a]
Male	20 (57.1)	18 (51.4)	0.81[c]
HD vintage (mo)	57 (36–97)	57 (37–84)	0.94[a]
NLR	3.2 (1.8–5.3)	2.9 (2.0–3.9)	0.78[a]
Absolute basophil count (/μL)	30 (26–54)	35 (27–61)	0.63[a]
Absolute eosinophil count (/μL)	228 (130–428)	237 (127–410)	0.84[a]
Ureum (mg/dL)	135 ± 47	137 ± 48	0.89[b]
Kt/V	1.95 (1.79–2.18)	1.94 (1.80–2.20)	0.94[a]
Ferritin (mg/dL)	185 (53–460)	185 (50–554)	0.87[a]
Albumin (mg/dL)	4.0 (0.5)	4.2 (0.4)	0.21[a]
Diabetes	12 (34.3)	13 (37.1)	1.00[c]
Hypertension	33 (94.3)	30 (85.7)	0.43[c]
Absolute neutrophil count (/μL)	4541 (3427–6307)	4277 (3085–5809)	0.49[a]
Absolute lymphocyte count (/μL)	1520 (969–1903)	1438 (1116–1997)	0.70[a]
Hemoglobin (mg/dL)	9.7 ± 2.5	9.8 ± 2.0	0.78[b]
Leukocytes (x10^3/μL)	7.30 ± 2.39	7.19 ± 2.24	0.84[b]
Thrombocytes (x10^3/μL)	233 ± 76	232 ± 81	0.97[b]
AST (mg/dL)	17 ± 8	13 ± 5	0.04[b]
ALT (mg/dL)	12 (7–17)	8 (7–13)	0.13[a]
Creatinine (mg/dL)	12.4 ± 3.8	12.9 ± 4.3	0.61[b]
eGFR (ml/min/1.73m^2)	3.9 (2.9–4.9)	3.4 (3–4.5)	0.62[a]
Uric acid (mg/dL)	7.5 ± 1.9	7.9 ± 2.2	0.38[b]
Blood glucose (mg/dL)	91 (81–119)	89 (81–151)	0.67[a]
SI (mg/dL)	55 ± 26	46 ± 18	0.10[b]
TIBC (mg/dL)	221 (187–248)	225 (178–264)	0.88[a]

TSAT (%)	23 (16–33)	21 (16–24)	0.06[a]
Sodium (mmol/L)	137 ± 2	136 ± 4	0.06[b]
Potassium (mmol/L)	4.5 ± 0.7	4.7 ± 0.7	0.25[b]
Chloride (mmol/L)	102.4 ± 2.7	101.5 ± 3.7	0.26[b]
Hypercalcemia	7 (20.0)	4 (11.4)	0.51[c]
Hyperphosphatemia	29 (82.9)	22 (62.9)	0.11[c]

Data are expressed as median (interquartile range), number (%), or mean ± standard deviation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HD, hemodialysis; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; SI, serum iron; TIBC, total iron binding capacity; TSAT, transferrin saturation.
[a]Mann–Whitney U test. [b]Independent t-test. [c]Chi-square test.

Multivariate Analysis of Serum IL-31 and CKD-aP

In the multivariate logistic regression analysis, albumin was the only variable with a significance level of $p \leq 0.25$. However, the analysis indicated no significant confounding variables, as the change in the prevalence ratio was <10% (**Table 4**).

Correlation Between Serum IL-31 Levels and CKD-aP Severity

Bivariate analysis did not show a significant correlation between serum IL-31 levels and VAS scores ($r = 0.05$, $p = 0.79$; **Figure 2**) or between serum IL-31 levels and the 5-D itch scale scores ($r = 0.14$, $p = 0.44$; **Figure 3**). Further analysis assessing the relationship between serum IL-31 levels and itching severity categories (mild, moderate, and severe) revealed a non-significant trend, suggesting that higher serum IL-31 levels corresponded to a higher itch severity according to VAS ($p = 0.39$, **Figure 4**) and the 5-D itch scale scores ($p = 0.25$, **Figure 5**).

DISCUSSION

In the present study, we evaluated the association between serum IL-31 levels and

Table 4. Multivariate logistic regression analysis of CKD-aP.

Variable	Prevalence ratio (95% CI)	*p*	Delta prevalence ratio (%)
Crude : Serum IL-31 (>173 pg/mL)	1.69 (1.07–2.66)	0.03	
Adjusted :			
+ Albumin	1.66 (1.08–2.58)	0.02	1.38

CI, confidence interval.

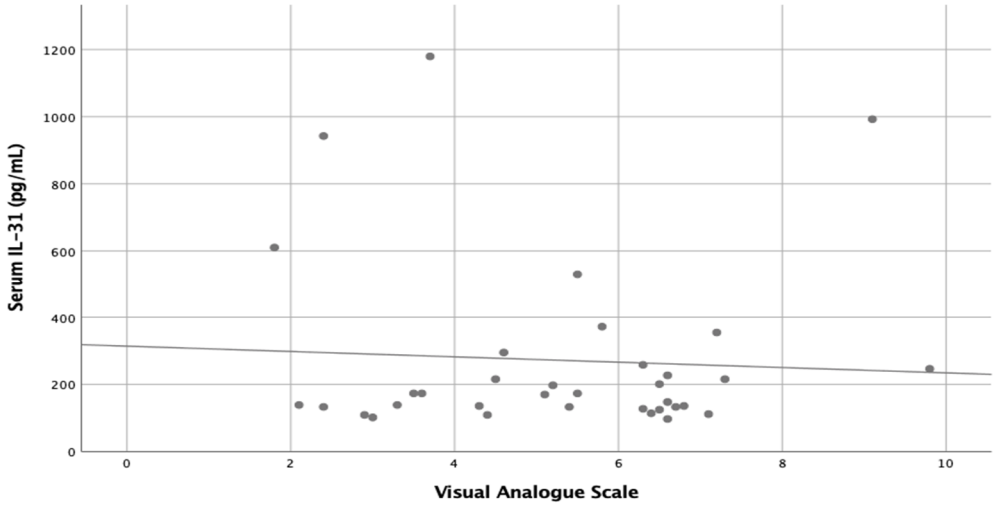

Figure 2. Scatter plot showing the correlation of serum IL-31 with the VAS score.

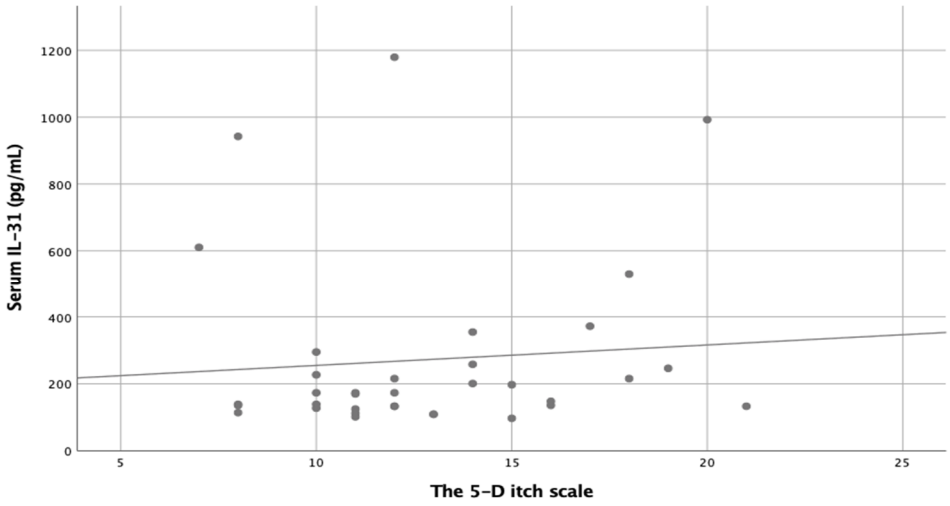

Figure 3. Scatter plot showing the correlation of serum IL-31 with the 5- D itch scale.

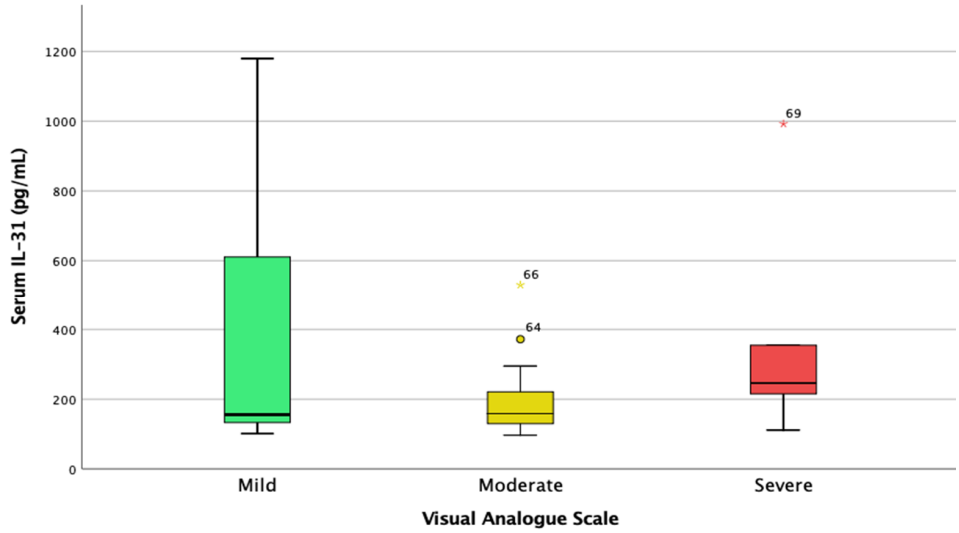

Figure 4. Boxplot of differences in serum IL-31 levels based on the severity of the VAS score.

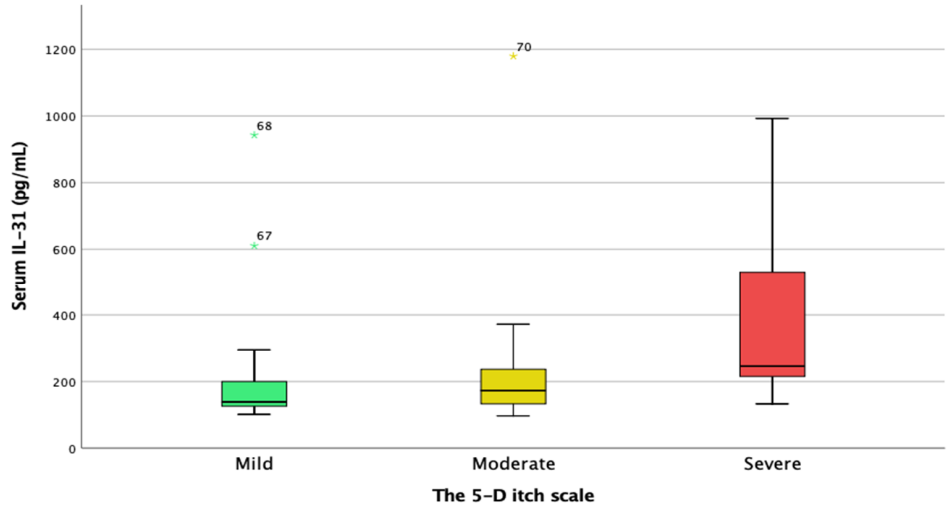

Figure 5. Boxplot of differences in serum IL-31 levels based on the severity of the 5-D itch scale.

CKD-aP in patients undergoing HD. The principal findings of this study identified a statistically significant difference in serum IL-31 levels between patients with and without CKD-aP (p = 0.05). The observed elevation in IL-31 levels in patients with CKD-aP is consistent with several previous studies reporting higher IL-31 levels in pruritic than in non-pruritic HD populations. In a Taiwanese cohort of 178 patients on routine HD, those with pruritus had significantly higher IL-31 levels than those without (median 8.68 vs. 4.91 pg/mL, p = 0.04).[11] Similarly, research conducted in Poland on a sample comprising 175 individuals, demonstrated that IL-31 serum levels in patients with CKD-aP (679.9 ± 1112.3 pg/mL) were substantially higher than those in patients without CKD-aP (176.1 ± 290.7 pg/mL) and healthy controls (57.3 ± 65.1 pg/mL), with p-values of <0.001 and 0.019, respectively.[15] A study from Iraq reported a significant difference in IL-31 levels between patients with CKD-aP (55.87 ± 5.36 pg/mL) and those without (39.01 ± 4.74 pg/mL), as well as compared to healthy individuals (25.49 ± 3.55 pg/mL), with p-values of 0.001 and 0.006, respectively, indicating a clear differentiation based on the presence of pruritus.[13]

However, contrasting outcomes were observed in studies conducted in Palestine and Egypt. A Palestinian study involving 172 patients on HD and 11 patients on peritoneal dialysis found no significant difference in mean IL-31 levels between patients with and without CKD-aP (4936.6 ± 33611.5 vs. 3919.2 ± 15914.4 pg/mL).[14] Similarly, an Egyptian study involving 88 patients revealed no significant variation in serum IL-31 levels within the HD groups, regardless of the presence of CKD-aP (6.44 ± 7.88 pg/mL for patients with CKD-aP vs. 3.58 ± 3.84 pg/mL for those without).[12] These disparities across geographical locations and patient populations highlight the complexity of the role of IL-31 in pruritus among patients undergoing HD.

Importantly, the diagnostic performance of IL-31 in this study was limited, with an AUC of 0.64 and a sensitivity of 51.4%, indicating a poor discriminatory ability. Interleukin-31 alone is insufficient as a reliable diagnostic biomarker for CKD-aP. Although a statistically significant association was observed using the identified cut-off value, this finding should be interpreted with caution, given its modest predictive performance. A Taiwanese study conducted on patients undergoing regular HD three times a week proposed a lower cut-off point. Serum IL-31 assessments were performed after a fasting period of at least 8 hours using the Mabtech kit from Sweden.[11] In contrast, the present study involved patients on regular HD twice a week, without the requirement of fasting before the tests, and employed ELISA kits manufactured by Abbexa (United Kingdom). The variability in the reported cut-off values across studies may be attributable to differences in patient characteristics, dialysis regimens, and assay methodologies.

A decline in kidney function leads to the accumulation of uremic toxins, which precipitate oxidative stress and prompt the release of inflammatory cytokines.[22] A noteworthy finding across several studies is the overexpression of IL-31, which is implicated in the exacerbation and growth of sensory nerves, thereby enhancing the sensitivity to minimal itch-provoking stimuli.[9,23] This phenomenon contributes to the development of persistent pruritus. Specifically, IL-31 expression in the skin correlates with reduced filaggrin levels, a pivotal protein in keratinocyte differentiation and skin barrier maintenance.[12] From a mechanistic perspective, IL-31 has been implicated in pruritus through its role in neuroimmune interactions. It is thought to promote the activation and sensitization of sensory nerve fibers and contribute to the itch–scratch cycle via inflammatory pathways.[24] However, CKD-aP is a multifactorial condition involving additional mechanisms such as uremic toxin accumulation, opioid receptor imbalance, and other inflammatory mediators.[25,26] This complexity likely explains the limited correlation between IL-31 levels and the clinical manifestations observed in this and other studies.

The lack of a significant correlation between IL-31 levels and pruritus severity further limits its clinical applicability. Similar findings have been reported in several studies, whereas a positive correlation has been demonstrated in others. This discrepancy may be attributed to

the heterogeneity in study design and assessment tools. The study conducted in Iraq, utilizing the VAS, found no significant association between IL-31 levels and pruritus severity. These findings align with research from Egypt and Poland using the Numerical Rating Scale (NRS).[12,13,15] However, Ko et al. have reported a significant relationship between serum IL-31 levels and VAS scores.[11] Histopathological examination of the skin also revealed a significant association between IL-31 expression and the VAS score.[27]

These results suggest that although IL-31 may contribute to pruritus, it does not adequately reflect symptom intensity. Therefore, IL-31 may be considered a pathophysiological or exploratory marker rather than a marker of disease severity. The lack of a consistent relationship between serum IL-31 levels and pruritus severity could stem from several factors, including patient population diversity, differences in itch scales, increased IL-31 receptor activity reducing circulating IL-31 levels, and the role of IL-31 in activating the JAK/STAT intracellular signaling pathways.[28] Among the variable itch assessment instruments used across studies, the VAS and 5-D itch scale are validated and reliable tools for measuring pruritus. Notably, the 5-D itch scale is recommended by the International Forum for the Study of Itch for its multidimensional assessment capabilities and applicability to a range of diseases.[17,29] Moreover, the 5-D itch scale has been translated into multiple languages, including Indonesian, ensuring high validity, reliability, and ease of self-administration with minimal instructions.[20] Future investigations involving larger, more heterogeneous cohorts are warranted to verify the potential role of IL-31 in predicting pruritus severity.

In the present study, the multivariate analysis did not identify significant confounding variables, although albumin levels were initially considered. Additionally, the bivariate analysis revealed that potential confounding factors, including dialysis adequacy (Kt/V), ferritin levels, and dialysis vintage, were not significantly different between the two patient cohorts. The prevalence of hyperphosphatemia and diabetes was comparable between groups. However, the absence of key inflammatory biomarkers, such as C-reactive protein and other cytokines, limits the comprehensive assessment of systemic inflammation and should be considered when interpreting these findings. Only a few studies have used multivariate analysis to evaluate IL-31 levels in patients with CKD-aP.

This study had several limitations. First, its cross-sectional design precludes causal inferences. Second, the relatively small sample size may limit the statistical power, particularly for ROC and multivariate analyses. Third, the adjustment for confounding variables was limited. Finally, the absence of additional inflammatory biomarkers restricted a more comprehensive evaluation of systemic inflammation. Despite these limitations, this study contributes to the growing body of evidence suggesting a role of IL-31 in CKD-aP. However, given its modest diagnostic performance and lack of association with pruritus severity, IL-31 is unlikely to serve as a standalone clinical biomarker. Future studies with larger sample sizes, longitudinal designs, and broader biomarker panels are required to define its role in the complex pathophysiology of CKD-aP.

CONCLUSION

In patients with CKD-aP undergoing routine HD, serum IL-31 concentrations were markedly elevated compared with those in patients without CKD-aP, supporting a potential association with immune-related pathomechanisms of pruritus. However, the modest discriminatory performance and absence of a correlation with itch severity suggest that IL-31 has limited utility as a diagnostic biomarker. Its role may be considered as an adjunctive or exploratory marker, and further longitudinal studies incorporating broader inflammatory profiles are warranted.

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CONFLICT OF INTERESTS

All the authors declare that there are no conflicts of interest.

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