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Serum Level of Interleukin-31 in Patients with Uremic Pruritus Undergoing Hemodialysis

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Abstract:

Background: Uremic pruritus is a common symptom in patients with end-stage renal disease who are undergoing maintenance hemodialysis. This symptom is frequently refractory to most treatments, and is associated with substantial medical, psychological, and social disturbances in patients receiving dialysis. This study aimed to estimate serum level of IL31, in patients with uremic pruritus and to relate it with different clinical parameters. **Methods:** This was a prospective case-control study conducted on participants recruited from the hemodialysis unit of the Urology and Nephrology Center, Mansoura University. **Results:** serum IL-31 is significantly higher in patients receiving hemodialysis with pruritus symptoms, along with a positive exposure-response relationship between serum IL-31 and pruritus intensity. **Conclusion:** Uremic pruritus, is a distressing symptom in end-stage renal disease patients on hemodialysis, which lacks a definitive explanation, though factors like immune processes and IL-31 are considered. Its impact on patients' quality of life varies, making it challenging to characterize. Unraveling mechanisms like IL-31 may guide future treatments for this condition, which significantly affects patients' well-being.

Keywords: Interleukin-31; Uremic Pruritus; Hemodialysis.

Introduction

Uremic pruritus is a common symptom in patients with end-stage renal disease who are undergoing maintenance hemodialysis. This symptom is frequently refractory to most treatments, and is associated with substantial medical, psychological, and social disturbances in patients receiving dialysis. [(1)]

Multiple hypotheses and parameters have been postulated for the pathophysiology of uremic pruritus. Among them, some evidence supports a central role of an immune hypothesis, based on the findings that serum levels of high-sensitivity C-reactive protein (hsCRP) and some inflammatory cytokines, such as interleukin (IL)-2 and IL-6, were elevated in patients with uremic pruritus. However, a consensus has not been reached among these studies, and uremic pruritus remains poorly characterized [(2)].

Intensity and spatial distribution of pruritus in patients with chronic renal insufficiency may vary significantly over time. The degree of chronic kidney disease associated pruritis (CKD-aP) may range from sporadic discomfort to complete restlessness during day- and nighttime strongly reducing the patient's quality of life. The skin of affected patients is often unchanged, resembling that of patients without pruritus, which in most cases presents dry and scaly. In contrast to dermatological pruritus, primary skin lesions are not observed in patients with CKD-aP [(3)].

Up to 50% of patients with CKD-aP complain of generalized pruritus (25). In the remaining patients, CKD-aP seems to affect predominantly back, face, and shunt arm (a surgically created connection between vein and artery. It allows direct access to the bloodstream for dialysis.) , respectively. In about 25% of patients, pruritus is reported to be most severe during or immediately after dialysis. Once patients have developed CKD-aP, this symptom will in most cases last for months or years [(4)].

It has been shown that a novel T-cell-derived cytokine called IL-31 can cause severe pruritus and dermatitis in transgenic mice. This is accomplished by signaling through a heterodimeric receptor that is made up of the IL-31 receptor A and the oncostatin M receptor. This receptor is present on epithelial cells and keratinocytes [(5)].

It is possible that IL-31 is involved in the recruitment of polymorphonuclear cells, monocytes, and T cells to the skin, as it has been shown to exhibit direct immunomodulatory effects in vitro [(6)]. Scratching NC/Nga mice (compared to non-scratching NC/Nga mice were shown to have considerably increased expression of skin IL-31 messenger RNA [(7)]. In mice with chronic scratching behavior, there is a correlation between the number of scratches and the amount of IL-31 messenger RNA expressed in the skin [(8)].

In human subjects, enhanced expression of IL-31 is associated with the induction and persistence of pruritus and chronic skin inflammation, such as atopic dermatitis and allergic contact dermatitis [(9)].

The purpose of this study was to estimate serum level of IL31, in patients with uremic pruritus and to relate it with different studied clinical parameters.

Patients and methods

This was a prospective case-control study conducted on participants recruited from the hemodialysis unit of the Urology and Nephrology Center, Mansoura University. It was performed from October 2017 till November 2023.

The study enrolled two groups: Patients' group: patients with chronic renal failure undergoing hemodialysis and presented with uremic pruritis (40 patients). Control group (age and gender not matched): patients undergoing hemodialysis not suffering from uremic pruritis (40 patient).

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study

was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University (MS.11.12.2017).

Inclusion criteria were patients on regular HD three times weekly, patients with normal serum calcium, phosphorus levels, patients with serum PTH within target limits 150-300pg/ml, patients with hemoglobin level between 10-11 g/dl and patients with no skin xerosis.

Exclusion criteria were patient with systemic pruritic diseases such as hepatic disease and Drug-induced pruritus, pruritic dermatological diseases such as eczema, lichen simplex, urticaria and infections, immunosuppressive disease such as HIV infection and neoplastic diseases and immunosuppressive therapy in the past 3 months.

All patients were subjected to: Complete history taking including personal history, complaint & its duration, present history, past medical history, past Surgical history. Physical examinations including complete general examination, Local examination: Complete cutaneous examination for exclusion of other causes of pruritus.

Pruritus Assessment: A detailed scoring system modified by Pauli-Magnus was used to assess the characteristics of pruritus including; intensity, scratching activity, pruritus distribution, and the frequency of pruritus-related sleep disturbances [(10)].

Investigational Studies including Routine laboratory investigations as CBC, ESR, CRP, PT, PTT, INR, Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvate transaminase (SGPT), Urea, creatinine, uric acid (UA), Calcium, phosphorus (P).

Serum levels of IL-31 were measured with a commercially available enzyme-linked immunosorbent assay kit: In the IL-31 detection process, serum samples are initially prepared by collecting and isolating the liquid serum portion through centrifugation. A 96-well microtiter plate is then coated with an IL-31-specific antibody, and the prepared serum samples, controls, and known IL-31 standards are added to the plate wells for incubation, allowing IL-31 binding. Following incubation, a thorough washing step is performed to eliminate unbound substances and contaminants. A secondary antibody labeled with an enzyme is introduced, triggering a color-producing reaction upon exposure to a substrate. The color intensity of the resulting product is subsequently measured using a spectrophotometer or plate reader, with the intensity directly correlating with the amount of IL-31 in the samples. By comparing measured absorbance values to a standard curve generated from known IL-31 concentrations, the IL-31 concentrations in the serum samples are determined through data analysis.

Uremic Pruritus Assessment Tools: In addition to the questionnaire, the following assessment tools can be used to further evaluate and measure uremic pruritus in patients. Visual Analog Scale (VAS): The VAS is a horizontal line with anchors at each end representing the extremes of the symptom being measured (e.g., itching severity). Patients mark their level of itching intensity on the line, with 0 representing no itching and 10 representing the worst imaginable itching.

Statistical analysis

The data analysis involved descriptive statistics (mean, SD, percentage), with significance set at a 2-sided P value ≤ 0.05. For normally distributed continuous variables, data were presented as mean ± SD. Univariate analysis employed the 2-sample t-test, Wilcoxon rank sum test, and Pearson chi-squared test. Non-normally distributed continuous variables were compared using the Kruskal-Wallis rank sum test, and Spearman rank correlation assessed relationships. Multivariate linear regression identified predictive factors for uremic pruritus, with SPSS software (version 20.0, Chicago, IL, USA) used for all analyses.

Results

The current study was conducted on 80 participants (40 patients with chronic renal failure undergoing hemodialysis and presented with uremic pruritis and 40 controls undergoing hemodialysis not suffering from uremic pruritis). Participants were recruited from the hemodialysis unit of the Urology and Nephrology Center, Mansoura University.

Table 1: Pruritus severity and intensity among patients' group.

	Patients group (n =40)
Pruritus severity	
- A slight pruritus sensation without the need to scratch	9 (22.50%)
- With the need to scratch but without excoriation	15 (37.50%)
- Persistent and severe pruritus request	9 (22.50%)
- Scratching accompanied by excoriation	4 (10%)
- Pruritus causing overwhelming restlessness	3 (7.50%)
Time of most intense	
- On the day after hemodialysis	6 (15%)
- In the evening before hemodialysis	19 (47.50%)
- All the time	15 (37.50%)
Sleep deprivation	
- Awakening	16 (40%)
- Sometimes awakening	14 (35%)
- Not awakening	10 (25%)
Pruritus distribution	
- Local area	8 (20%)
- One site	11 (27.50%)
- Two sites	7 (17.50%)
- Three sites	5 (12.50%)
- More than three	5 (12.50%)
- All the body	4 (10%)
Pruritus area	
- Fistula arm	2 (5%)
- The back	17(42.50%)
- Legs	3 (7.50%)
- Head	2 (5%)
- Arm	1 (2.50%)
- Front part of the body	15(37.50%)
Medication for pruritus	
- Antihistamine tablets	19(47.50%)
- Antihistamine tablets and lotion	12 (30%)
- Steroid ointment	9 (22.50%)
Patients beneficial from pruritis medication	
- Post-treatment (patient with improvement after medication)	22 (55%)
- Pre-treatment (patient without improvement after medication)	18 (45%)
Non-pharmacological treatment of pruritis	
- Moisturizer	24 (60%)
- Cologne	8 (20%)
- Cold application	5 (12.50%)
- Vinegar water	3 (7.50%)

Table 1 showed severity and intensity of pruritus among patients' group. Number of patients with a slight pruritus sensation without the need to scratch in the study population was 9 patients (22.50%). Number of patients whose time of most intense pruritis on the day after hemodialysis in the study population was 6 patients (15%) (Figure 8). Number of patients with awakening sleep deprivation in the study population was 16 patients (40%). Number of patients with local area pruritus in the study population was 8 patients (20%). Number of patients with fistula arm (a surgically created connection between vein and artery. It allows direct access to the bloodstream for dialysis.) pruritus in the study population was 2 patients (5%). Number of patients who was using antihistamine tablets for pruritus in the study population was 19 patients (47.50%). Number of patients with a drug beneficial in the study population was 22 patients (55%). Number of patients who were using moisturizer in the study population was 24 patients (60%).

Table 2 showed blood pressure measurements among the study groups. Regarding SBP and DBP, patients' group had significantly higher SBP and DBP compared to controls ($p<0.001$).

Table 3 showed laboratory data results among the study groups. Regarding SGOT (U/L) and SGPT (U/L) in patients' group, there was no statistically significant difference between the two groups. Regarding PO4 (mg/dL) in patients' group there was no statistically significant difference between the two groups. Regarding uric acid (mg/dL) and serum Ca (mg/dL) significantly higher levels were presented in patients' group compared to control group ($p<0.001$) (Figures 23 & 24). Serum level of IL-31 was significantly higher in patients' group compared to control group ($p<0.001$). It also showed clinical data of pruritus among patients' group. Number of patients with previous pruritus in the study population was 16 (40%). Duration of pruritus (m) in the study population ranged from 15 to 37 with mean ± SD = 26.3 ± 5.43. Visual Analog Scale (VAS) of pruritus intensity among patients' group. VAS score in the study population ranged from 2 to 5 with mean ± SD = 3.25 ± 0.87.

Table 2: Blood pressure measurements among the study groups.

	Patients' group (n = 40)	Control group (n = 40)	Test of Sig.	*p*
SBP				
Mean ± SD.	123.35 ± 4.2	117.1 ± 4.09	t = 6.742	**<0.001**
Median (IQR)	123 (121 - 126.25)	117 (113.75 - 120.25)		
Range (Min-Max)	18 (114 - 13)	16 (110 - 126)		
DBP				
Mean ± SD.	82.12 ± 1.99	78.18 ± 2.1	t = 8.639	**<0.001**
Median (IQR)	82 (81 - 84)	79 (76 - 80)		
Range (Min-Max)	7 (78 - 85)	7 (75 - 82)		

t: Independent T test, SD: standard deviation, IQR: interquartile range, t: Independent T test, *p* : *p* value for comparing between the studied groups. Min-Max

Table 3: Laboratory and Clinical data results among the study groups.

	Patients' group (n = 40)	Control group (n = 40)	Test of Sig.	*p*
SGOT (U/L)				
Mean ± SD.	28.95 ± 8.64	27.58 ± 8.07	t = 0.736	0.464
Median (IQR)	29 (22.75 - 35.2)	26 (22.75 - 33.25)		
Range (Min-Max)	32 (14 - 46)	30 (13 - 43)		
SGPT (U/L)				
Mean ± SD.	32.25 ± 10.68	30.75 ± 9.41	t = 0.666	0.507
Median (IQR)	31 (24.5 - 38.25)	31.5 (24 - 36.5)		
Range (Min-Max)	36 (16 - 52)	32 (13 - 45)		
Uric acid (mg/dL)				
Mean ± SD.	5.13 ± 0.44	4.89 ± 0.41	t = 2.587	**0.012**
Median (IQR)	5.1 (4.84 - 5.4)	4.86 (4.58 - 5.22)		
Range (Min-Max)	1.62 (4.3 - 5.92)	1.76 (3.98 - 5.74)		
Serum Ca (mg/dL)				
Mean ± SD.	9.79 ± 0.44	9.27 ± 0.4	t = 5.513	**<0.001**
Median (IQR)	9.7 (9.4 - 10.1)	9.4 (8.95 - 9.52)		
Range (Min-Max)	1.4 (9.2 - 10.6)	1.7 (8.5 - 10.2)		
Serum PO4 (mg/dL)				
Mean ± SD.	6.62 ± 1.49	6.96 ± 1.52	t = -1.025	0.309
Median (IQR)	6.6 (5.4 - 7.72)	6.95 (5.88 - 7.78)		
Range (Min-Max)	5.9 (3.9 - 9.8)	6.1 (3.4 - 9.5)		
IL-31 (pg/mL)				
Mean ± SD.	11.1 ± 6.78	5.58 ± 2.83	t = 4.75	**<0.001**
Median (IQR)	9.37 (6.76 - 13.78)	5.14 (3.67 - 6.27)		
Range (Min-Max)	27.52 (1.65 - 29.17)	11.51 (1.77 - 13.28)		
		Patients' group (n = 40)		
Previous pruritus				
- Severe		16 (40%)		
- Mild		24 (60%)		
Duration of pruritus (m)				
Mean ± SD.		26.3 ± 5.43		
Median (IQR)		26.5 (22 - 29)		
Range (Min-Max)		22 (15 - 37)		
VAS score				
Mean ± SD.		3.25 ± 0.87		
Median (IQR)		3 (3 - 4)		
Range (Min-Max)		3 (2 - 5)		

;t: Independent T test, SD: standard deviation, IQR: interquartile range, t: Independent T test, p: p value for comparing between the studied groups. VAS. visual analogue score. Min-Max

Table 4 showed Pearson's correlation coefficients (r) between VAS score of pruritus intensity and other variables. Pearson's correlation coefficients (r) between VAS score and IL-31 (pg/mL) were 0.086 with a weak positive relationship between the two variables. Pearson's correlation coefficients (r) between VAS score and UA (mg/dL) were -0.165 with a weak negative relationship between the two variables. Pearson's correlation coefficients (r) between VAS

score and Ca (mg/dL) were 0.188 with a weak positive relationship between the two variables. Pearson's correlation coefficients (r) between VAS score and PO4 (mg/dL) was -0.292 with a weak negative relationship between the two variables.

Table 5 shows that the predictive value of IL-31 for pruritis severity was assessed using Receiver Operating Characteristic (ROC) curve. Area Under the Curve of IL-31 =.90 (95 % C.I = .77-1.00). Sensitivity and specificity values were 100 % & 75.3 % respectively. Diagnostic accuracy of Pruritus causing overwhelming restlessness, positive predictive value and negative predictive value were 65%,17.6% and 100% respectively. The predictive value of IL-31 for time of most intense pruritis was assessed using Receiver Operating Characteristic (ROC) curve. Area Under the Curve of IL-31 = 0.881 (95 % C.I = .717-.905). Sensitivity and specificity values were 100 % & 64.6 % respectively. Diagnostic accuracy of time of most intense pruritis (all the time), positive predictive value and negative predictive value were 65%,51.7% and 100% respectively. Also, the predictive value of IL-31 for pruritis distribution was assessed using Receiver Operating Characteristic (ROC) curve. Area Under the Curve of IL-31 = .79 (95 % C.I = .607-.977). Sensitivity and specificity values were 100 % & 64% respectively. Diagnostic accuracy of pruritis distribution (all the body), positive predictive value and negative predictive value were 67.5%,23.5% and 100% respectively.

Age, BMI, systolic blood pressure, diastolic blood pressure, SGOT, SGPT and duration of pruritis are highly significant predictors of VAS score (P< .001) (Figure 1).

Table 4: Pearson's correlation coefficients (r) between VAS score of pruritus intensity and other variables

	VAS score of pruritus intensity	
	Pearson's correlation coefficients (r)	**P**
IL-31 (pg/mL)	0.086	0.599
UA (mg/dL)	-0.165	0.308
Ca (mg/dL)	0.188	0.246
PO4 (mg/dL)	-0.292	0.067

p value. Probability , UA. Uric acid, Ca .calcium, PO4.phosphoroux

Table 5: Diagnostic accuracy of IL-31 for pruritis severity (pruritus causing overwhelming restlessness), pruritis severity time of most intense pruritis (all the time) and for pruritis distribution.

Pruritis severity (Pruritus causing overwhelming restlessness)	**AUC**	**95% CI**	**Cutoff point (pg/ml)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Serum IL-31	0.90	0.77-1.00	9.63	100%	75.3%	17.6%	100%	65%
Time of most intense pruritis (all the time)								
Serum IL-31	.811	.717-.905	6.84	100%	64.6%	51.7%	100%	65%
Pruritis distribution (All the body)								
IL-31	0.79	.607-.977	9.63	100%	64%	23.5%	100%	67.5%

AUC: Area Under the curve; PPV: positive predictive value; NPV: negative predictive value; CI: Confidence interval.

Age, gender, BMI, systolic blood pressure, diastolic blood pressure, SGOT, SGPT, uric acid level, Ca level, PO4 level, IL-31, history of pruritis and duration of pruritis are nonsignificant predictors of pruritis severity (P>.05). Also, age, gender, BMI, systolic blood pressure, diastolic blood pressure, SGOT, SGPT, uric acid level, Ca level, PO4 level, IL-31, history of pruritis and duration of pruritis are non significant predictors of pruritis severity (P>.05) (Table 6).

Table 6: Univariate and multivariate logistic regression of pruritis severity with different variables.

Variables		Univariate logistic regression OR (95% CI)	P value
Age (years)		1.776 (1.063-2.967)	.028
Gender	**Female**	2.500 (.162- 38.59)	.512
	Male	**Reference category**	
BMI (kg/m^2)		1.097(.000-.000)	.874
SBP(mmHg)		11871 (1039 - 13561)	.673
DBP (mmHg)		16321 (1.181-22557)	.546
SGOT(U/L)		95782 (9578-957823)	.993
SGPT(U/L)		1518 (1518- 15181)	.997
UA(mg/dL)		47.427 (1.481-1518)	.029
Ca(mg/dL)		179.68 (6.463-4995)	.002
PO4(mg/dL)		.469 (.179-1.233)	.125
IL-31(pg/ml)		1.882 (1.382-2.563)	.001
History of pruritus	**No**	1.350E-16 (.000-.000)	
	Yes	**Reference category**	
Duration of pruritis (months)		41385 (.000-.000)	.998
Variables		**Multivariate logistic regression OR (95% CI)**	**P value**
Age (years)		3.079 (.000-.000)	1.00
Gender	**Female**	2.406 (.000-.000)	.993
	Male	**Reference category**	
BMI (kg/m2)		8.682 (.000-.000)	.997
SBP(mmHg)		.009 (.000-.000)	.998
DBP (mmHg)		6509.2 (.000-.000)	.996
SGOT(U/L)		.031 (.000-.000)	.998
SGPT(U/L)		4 .944 (.000-.000)	.997
UA (mg/dL)		239742 (.000-.000)	.998
Ca(mg/dL)		31176 (2814-1664)	.901
PO4(mg/dL)		.000 (.000-.000)	.998
IL-31(pg/ml)		.690 (.000-.000)	1.00
History of pruritus	**No**	41583(.000-.000)	.999
	Yes	**Reference category**	
Duration of pruritis (months)		3.206 (.000-.000)	1.00

CI: Confidence interval

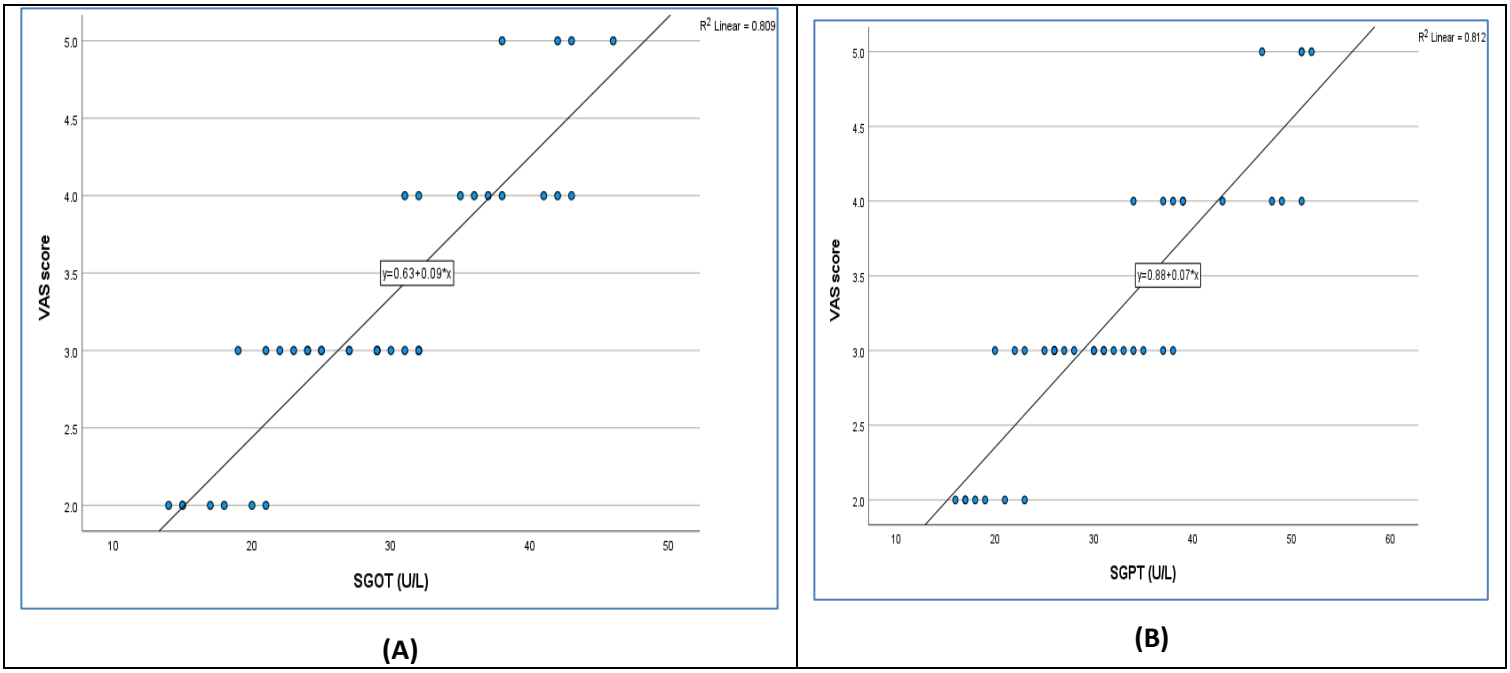

Figure 1: (A) Scatter graph showing significant positive correlation between serum SGOT and VAS score, the regression coefficient (R^2) and equation are also shown. (B) Scatter graph showing significant positive correlation between serum SGPT and VAS score, the regression coefficient (R^2) and equation are also shown.

Discussion

This prospective case control study was conducted on 80 participants divided equally into 2 groups: Patients' group: 40 patients with chronic renal failure undergoing hemodialysis presented with uremic pruritis. Control group: 40 patients undergoing hemodialysis not suffering from uremic pruritis.

Our results were in accordance with a previous study that stated that pruritus was associated with sleep abnormalities in most of the patients, 61% reported having difficulties falling asleep and 44% were awakened frequently or occasionally by pruritus [(11)]. The build-up of uremic toxins across the night may explain these results. Sleep is responsible for multiple homeostatic functions, deprivation of which can have drastic consequences. Pruritus often intensifies in the evenings, thereby interfering with sleep quality [(12)].

Regarding pruritus distribution areas, a study found that 83% from patients' pruritus involved large, no dermatomal areas with striking bilateral symmetry [(13)]. Another study revealed that among the pruritic patients, 45.2% had more than 25% of body surface area involvement and 30.6% had symmetric distribution of pruritus symptoms (14). This research reported that the patients described the pruritus as involving all areas of the body and the areas most involved were back, 70%; abdomen, 46%; head, 44%; and arms, 43%. In 80% of the patients the involvement was symmetrical. More than one third of the patients had generalized pruritus that affected more than one third of their body surface area [(11)].

According to pruritus medication among patients' group, a study revealed that 60.9% of patients used medications, such as oral antihistamines or topical therapies, for their pruritus and there was no significant relationship between the type of medication and the pruritus severity [(15)]. Another study demonstrated that 67 % of patients were taking medications for pruritus. Those with greater UP severity were more likely to take medications. All patients with severe pruritis (representing 25% of the study population) reported that

the medications "did not help at all" or only "helped a little," compared with two thirds of patients with mild pruritis. Consistent with reports of medication ineffectiveness, pruritus intensity was high and associated symptoms were frequent despite medication use among most patients [13].

Regarding blood pressure measurements, our results were parallel to a study reported that in hemodialysis patients the mean systolic BP (mmHg) was (144.0 ± 21.0) and diastolic BP (mmHg) was (75.0 ± 14.0) [16].

Regarding laboratory data, our results were supported with a study reported that there was no significance between the studied groups regarding AST (SGOT) while there was a significance regarding SGPT alanine transaminase (p = 0.03) [14].

Our results came in agreement with research which demonstrated that patients with pruritus also had higher blood levels of uric acid, calcium and PO4 with a significance difference [14]. Similarly, a study reported that patients with UP had significantly higher blood levels of calcium and PO4 compared to patients on HD without UP [17].

The current study showed that serum level of IL-31 was significantly higher in patients' group compared to control group. Same findings were reported by a study; they also reported that IL-31 serum level was significantly higher in the HD itchy group ($p < 0.001$) in comparison to the HD patients free from pruritus (18). Another study reported that IL-31 level was significantly higher in HD patients than in the control healthy group [19].

As regards the predictive value of IL-31 for time of most intense pruritis, IL – 31 is an inflammatory and pruritogenic cytokine produced by a variety of cells, mainly TH2 cells and expressed mainly in non-hematopoietic tissue, skin and in the endothelium. Thus, over-expression of IL − 31 has a pruritic role in different diseases such as atopic dermatitis, psoriasis and others as was described based on skin biopsies through activating sensory neurons to promote itching [20-22]. Therefore, a study concluded that IL-31 plays an important role in several inflammatory skin diseases, and treatment targeting IL-31 is expected to contribute meaningfully to the clinical management of a wide range of diseases [22].

IL-33 "alarmin" cytokine is another inflammatory marker, usually secreted by damaged tissues and cells which promotes the release of IL-4 dependent release of IL-31 by TH cells [23]. It is usually elevated in diseases like atopic dermatitis [21], multiple studies have shown a higher level of IL-31 and IL-33 and pruritus, which might suggest close correlation between these interleukins in different pathologies [20-22].

Regarding history of previous pruritus and duration of pruritus, a study reported that the median duration of HD was 42 months. There were 60 cases of UP (prevalence rate, 40.54%), including 22 mild cases (14.86%), 30 moderate cases (20.27%), and 8 severe cases (5.41%) [24].

Regarding Visual Analog Scale (VAS) of pruritus intensity among patients' group, a study demonstrated that there was not a significant correlation between the IL-31 serum levels and the pruritus intensity (VAS) score of pruritus intensity [18].

Contradicting our results, a study reported that higher serum levels of IL-31, hsCRP, and alanine transaminase, and lower Kt/V, were independent predictors for higher VAS scores of pruritus intensity. Higher levels of the product of calcium and phosphorus, and lower white blood cell counts, were borderline significantly associated with pruritus intensity [14].

A recent study reported that independent predictors of UP included associated hypertension, higher calcium levels, higher phosphorus levels and higher high-sensitivity C-reactive protein (hsCRP) levels. Independent predictors of significant UP included longer HD duration, lack of vitamin D

supplementation, lower albumin levels and higher hsCRP levels [(17)].

In contrast, a study reported that the OR for WBC count was 1.730 (95% CI), while the other variables did not have a statistically significant effect on the possibility of pruritus development [(15)].

Our study showed that BMI, systolic blood pressure, diastolic blood pressure, SGOT, SGPT, uric acid level, Ca level, PO4 level, IL-31, history of pruritis and duration of pruritis were non-significant predictors for pruritis severity.

Also, a study revealed that there was no significant correlation between gender, DM, HTN and different laboratory tests (like hemoglobin, parathyroid hormone, calcium, phosphorus and alkaline phosphatase) with the levels of IL-31 [(19)].

Also, a study revealed that Ca level and PO4 level were non-significant predictors for pruritis severity [(15)].

Conclusion

Uremic pruritus, a distressing symptom in end-stage renal disease patients on hemodialysis, lacks a definitive explanation, though factors like immune processes and IL-31 are considered. Its impact on patients' quality of life varies, making it challenging to characterize. Unraveling mechanisms like IL-31 may guide future treatments for this condition, which significantly affects patients' well-being.

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