Impact of Renal Transplantation on Chronic Kidney Disease-Associated Pruritus and Serum IL-31 Levels

Dear Editor,

Chronic pruritus (CP) is an unpleasant sensation causing itching for up to six weeks. Cholestasis, dermatological, endocrinological, hematological, neurological, psychiatric, malignant, or chronic kidney disease (CKD) can cause CP.[1] Pruritus linked to CKD without other identifiable causes is CKD-associated Pruritus (CKD-aP), also called uremic pruritus (UP). Prevalence estimates range from 18% to 80%, with ~40% of patients experiencing severe pruritus.[2]

CKD-aP has multiple pathophysiological mechanisms.[3] Systemic micro-inflammation is pivotal, with patients on HD having elevated inflammatory markers (C-reactive protein, ferritin) and cytokines (e.g., interleukin [IL]-6, IL-31). IL-31, nicknamed the "itchy cytokine," is secreted by T-cells and has been implicated in pruritus across dermatological and systemic disorders.[3-5]

Several instruments quantify pruritus severity, including the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), and Kidney Disease Quality of Life-Short Form (KDQOL-SF), but the 5-D Itch Scale is more nuanced, assessing duration, degree, direction, disability, and distribution.[6] Although studies have reported elevated levels in CKD-aP, the exact correlation between IL-31 and itch intensity remains uncertain. This study aimed to investigate whether serum IL-31 levels correlate with itch severity, measured by the 5-D Itch Scale, and how these parameters change pre- and post-transplant. The study design, inclusion and exclusion criteria, and pruritus assessment using the 5-D Itch Scale are detailed in Supplementary Material.

Of 202 screened patients with stage V CKD scheduled for renal transplantation, 89 had pruritus, and three were excluded due to primary skin disorders, leaving 86 (42.6%) for analysis. Among these, 82 were on HD, and four underwent preemptive transplantation. The mean age and dialysis vintage were 47.67 ± 2.35 and 2.56 ± 1.2 years, respectively. Based on the 5-D Itch Scale, 26 patients (30.23%) had mild, 36 (41.86%) had moderate, 16 (18.60%) had severe, and 8 (9.30%) had extremely severe pruritus. The overall mean itch score and serum IL-31 pre-transplant were 15.03 ± 4.06 and 145.02 ± 103.27 pg/mL, respectively.

Pre-transplant itch score and IL-31 levels showed a strong positive correlation ($r = 0.805$, $p = 0.001$) [Table 1]. The mild ($r = 0.399$, $p = 0.043$) and moderate ($r = 0.479$, $p = 0.003$) categories showed a moderate correlation. The severe and extremely severe groups showed weaker or non-significant relationships, likely reflecting smaller subgroup sizes. Parathyroid hormone (PTH) and ferritin differed significantly across pruritus categories ($p = 0.011$ and $p = 0.002$, respectively). Calcium, phosphorus, calcium-phosphorus product, and dialysis vintage remained stable.

Table 1: Comparison of patients based on itch category and mean pre-transplant IL-31 levels

Categories of Itch based on 5D score	No. of patients	Pre-transplant IL-31 (pg/mL)	P-value
Mild (9-11)	26 (30.2%)	75.2 ± 36.23	0.001
Moderate (12-17)	36 (41.9%)	117.54 ± 39.89	
Severe (18-21)	16 (18.6%)	212.82 ± 89.76	
Extremely severe (>21)	8 (9.3%)	364 ± 103.27	
Total	86 (100%)	145.02 ± 103.27	

IL-31: Interleukin 31

One month post-transplantation, 55 patients (63.9%) reported complete resolution, 25 (29.1%) had mild pruritus, and 6 (6.9%) had moderate pruritus [Supplementary Table 1]. Mean itch scores and IL-31 levels declined significantly in all categories ($p < 0.001$). The post-transplant overall correlation remained positive but more moderate ($r = 0.411$, $p = 0.001$) [Table 2]. No significant differences emerged in ferritin, PTH, phosphorus, calcium-phosphorus product, dialysis vintage, or diabetic status between fully recovered patients and those with persistent pruritus. Notably, reductions in itch scores and serum IL-31 showed a moderate positive correlation ($r = 0.464$, $p = 0.001$) pre- and post-transplant.

The pruritus rate in patients with stage V CKD (42.6%) may not reflect the broader CKD population but aligns with reports depicting highly variable pruritus prevalence (18-80%) in patients on HD.[2,S1-S3] The CKD Outcomes and Practice Patterns Study (CKDopps) found moderate pruritus and severe to extreme pruritus in 24% and 10–13% of non-dialysis patients with CKD, respectively. The intensity increased with advancing CKD.[S4]

Prior research has linked pruritus to depression, impaired sleep, increased mortality, and reduced quality of life.[S1-S3] In this study, sleep was the most affected aspect (75%), followed by leisure and social activities (14%). The nocturnal exacerbation of uremic pruritus is well documented.[S5]

The strong correlation between pre-transplant itch scores and IL-31 ($r = 0.805$, $p = 0.001$) indicated an immune-mediated role. Ko *et al*.[S6] also reported a positive relationship between IL-31 levels and pruritus severity. Other investigations have confirmed elevated IL-31 in CKD-

Table 2: Changes in Itch scores and serum IL-31 levels pre- and post-transplant, stratified by pruritus severity

Pre-transplant itch category	n	Pre-transplant Itch score	Post-transplant Itch score	p-value (Itch)	Pre-transplant serum IL-31 (pg/mL)	Post-transplant serum IL-31 (pg/mL)	p-value (IL-31)
Mild	26	10.15 ± 1.16	6.54 ± 1.56	<0.001	75.2 ± 36.23	37.31 ± 18.64	<0.001
Moderate	36	14.75 ± 1.73	7.69 ± 2.36	<0.001	117.54 ± 39.89	55.32 ± 26.56	<0.001
Severe	16	19.75 ± 1.24	8.31 ± 1.78	<0.001	212.82 ± 89.76	102.08 ± 33.74	<0.001
Very/extremely severe	8	22.75 ± 0.71	7.50 ± 2.39	<0.001	364 ± 103.27	133.25 ± 60.60	<0.001
Total	86	15.03 ± 4.36	7.44 ± 2.11	<0.001	145.02 ± 103.27	89.91 ± 59.51	<0.001

IL-31: Interleukin 31

aP, though not all established direct correlation with itch intensity, possibly due to small sample sizes or differing measurement scales.[S5,S7,S8]

Methodological differences often hinder cross-study comparisons; for instance, Ko *et al*.[S6] employed VAS, Haggag *et al*.[S5] used NRS, and we used the 5-D Itch Scale. Varying observation periods also introduce inconsistency.

Renal transplantation is the most definitive treatment for refractory pruritus. One month post-transplant, 63.9%, 29.1%, and 6.9% of our patients experienced complete resolution, mild pruritus, and moderate pruritus, respectively. Other studies noted similar or more pronounced improvements post-transplantation.[S9,S10] Krajewski *et al*.[S11] found decreased itching that remained above baseline population levels, possibly due to polypharmacy, drug allergies, or persistent neuropathic alterations. They also suggested that hyperparathyroidism and uremia, often corrected post-transplant, may be less involved in persistent itch than previously assumed.

We found a persistent moderate positive correlation ($r = 0.411$, $p = 0.001$) between itch scores and IL-31 post-transplant, implying that factors beyond uremia correction (e.g., immunological or neurological mechanisms) may sustain pruritus.[S8] Importantly, there was a significant decrease in mean 5-D Itch Scores and IL-31 levels pre- and post-transplant. The two variables also showed moderate correlation in their reductions ($r = 0.464$, $p = 0.001$).

To our knowledge, this is the first Indian study to track IL-31 and pruritus severity changes within a cohort of patients with CKD undergoing transplantation. One limitation is that all patients received calcineurin inhibitors (cyclosporine A or tacrolimus); its anti-inflammatory properties may have influenced pruritus.

Renal transplantation markedly alleviated CKD-aP, with most patients experiencing complete resolution or significant itch reduction. Serum IL-31 and pruritus severity are strongly correlated in the pre-transplant setting and show moderate association afterward, suggesting an ongoing immunological component. Future research should explore IL-31's long term trajectory and its potential as a therapeutic target for CKD-aP.

Conflicts of interest: There are no conflicts of interest.

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