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RESEARCH ARTICLE OPEN ACCESS

Serum levels of TNF-α, IL-1β, and IL-33 in patients with ascending pyelonephritis: A case-control study in Al-Najaf City

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Abstract
Objective: Ascending pyelonephritis (APN) is a serious upper urinary tract infection that may lead to immune-mediated inflammation. This study aimed to compare the serum levels of three cytokines, tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-33 (IL-33), in patients with pyelonephritis versus healthy individuals. The study also assessed differences between acute and chronic pyelonephritis cases and evaluated the diagnostic utility of these cytokines using receiver operating characteristic (ROC) analysis.
Methodology: A case-control study was conducted from September 2024 to January 2025, enrolling 120 participants: 60 patients with pyelonephritis (30 acute, 30 chronic) and 60 healthy controls. Serum levels of TNF-α, IL-1β, and IL-33 were measured using enzyme-linked immunosorbent assay (ELISA).
Results: TNF-α levels were significantly elevated in patients compared to controls (36.23 ± 64.12 pg/ml vs. 21.68 ± 18.52 pg/ml; p = 0.023). IL-1β levels also showed a significant increase (15.17 ± 27.82 pg/ml vs. 8.04 ± 7.00 pg/ml; p = 0.001). Similarly, IL-33 levels were higher in patients (23.19 ± 36.88 pg/ml) compared to controls (12.52 ± 8.96 pg/ml; p = 0.001). Chronic cases exhibited significantly higher cytokine levels than acute cases. ROC analysis revealed that TNF-α and IL-1β had strong diagnostic potential, while IL-33 demonstrated limited utility.
Conclusion: TNF-α and IL-1β are promising biomarkers for the diagnosis and monitoring of pyelonephritis, whereas IL-33 may have limited diagnostic relevance. TNF-α and IL-1β may serve as adjunct biomarkers for diagnosing pyelonephritis, particularly in chronic cases.

Keywords: TNF-α, IL-1β, IL-33, Ascending pyelonephritis, ELISA, Cytokines

Plain English Summary

Pyelonephritis is a kidney infection that starts in the lower urinary tract and ascends to the kidneys. This infection activates the immune system and causes the release of molecules called cytokines. This study investigated three cytokines, TNF-α, IL-1β, and IL-33, to understand their levels in infected versus healthy individuals. We also compared short-term (acute) and long-term (chronic) infections. Blood samples were tested using a lab method called ELISA.

Our findings showed that people with kidney infections had higher levels of TNF-α and IL-1β compared to healthy individuals. These two molecules were especially elevated in chronic cases, suggesting they might be useful in diagnosing or tracking the progression of the infection. IL-33 levels were also higher but did not show strong reliability as a diagnostic tool. We conclude that TNF-α and IL-1β could help identify and manage pyelonephritis, while IL-33 might not be suitable for that purpose.

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Introduction

Ascending pyelonephritis (APN) is a severe form of kidney infection that originates from the lower urinary tract. If not promptly treated, it may result in renal damage or systemic complications (1). Clinical symptoms include flank pain, fever, chills, nausea, vomiting, and dysuria (2). Risk factors include diabetes, anatomical abnormalities, immunosuppression, and hospital-acquired infections (2). Differentiating between APN and chronic pyelonephritis (CPN) is critical for clinical management.

Acute Pyelonephritis (APN) is characterised by an abrupt onset of high fever and flank pain, typically due to bacterial invasion of the renal parenchyma (3). It is often reversible in immunocompetent patients (4). Whereas Chronic Pyelonephritis (CPN) may result from repeated infections or unresolved acute infections. It may lead to complications like hypertension or renal scarring (5). Emphysematous Pyelonephritis: A life-threatening infection with gas-forming bacteria and high mortality (6). Xanthogranulomatous Pyelonephritis: A rare form characterised by granulomatous inflammation, often associated with renal calculi (7).

TNF-α is a crucial pro-inflammatory cytokine involved in pathogen clearance and immune regulation (8, 9). IL-1β enhances inflammation by recruiting immune cells (10, 11, 12). IL-33, a nuclear cytokine, participates in tissue repair and Th2 responses, but its exact role in pyelonephritis remains unclear (13, 14, 15).

Despite the availability of clinical diagnostic tools, the accurate and timely identification of pyelonephritis remains a challenge, particularly in distinguishing acute from chronic forms. Previous studies have highlighted the role of inflammatory cytokines as biomarkers for infection and tissue damage, but few have systematically compared the profiles of TNF-α, IL-1β, and IL-33 in pyelonephritis patients (8, 9, 10, 11, 12, 13, 14, 15). Although IL-33 is a member of the IL-1 cytokine family, its role in renal infections remains underexplored; investigating its expression in pyelonephritis may uncover novel insights into its immunomodulatory and tissue-repair functions within the renal microenvironment. This gap underscores the need for further investigation into the diagnostic and prognostic utility of these cytokines.

The objective of this study was to assess the serum levels of TNF-α, IL-1β, and IL-33 in patients with pyelonephritis compared to healthy controls, examine differences between acute and chronic presentations, and evaluate the sensitivity and specificity of these markers using ROC curve analysis. We hypothesised that TNF-α and IL-1β would show significantly elevated levels in pyelonephritis patients compared to controls and could serve as reliable diagnostic biomarkers, whereas IL-33 might have limited predictive value due to its dual roles in inflammation and tissue repair.

While previous studies have explored inflammatory cytokines in pyelonephritis, this study provides a novel comparative analysis of TNF-α, IL-1β, and IL-33 across acute and chronic disease presentations

Materials and Methods

Study design and participants

A case-control study was conducted at Al-Sadder Teaching Hospital between September 2024 and January 2025. The study population included 120 participants: 60 healthy controls and 60 patients clinically diagnosed with pyelonephritis, subdivided into 30 with acute pyelonephritis (APN) and 30 with chronic pyelonephritis (CPN). All participants were between 13 and 70 years old. The sample size was determined based on effect sizes reported in prior studies evaluating cytokine levels in renal infections, ensuring sufficient statistical power (≥80%) to detect significant differences between groups.

Eligibility Criteria

Patients were eligible for inclusion if they were between 13 and 70 years of age, had a clinical diagnosis of pyelonephritis based on symptoms (e.g., fever, flank pain, dysuria), and had supporting laboratory findings such as positive urine culture and pyuria. Acute pyelonephritis (APN) was defined as the first episode of pyelonephritis with acute onset of symptoms and no prior renal scarring or structural abnormalities on imaging. Chronic pyelonephritis (CPN) was diagnosed based on a history of recurrent urinary tract infections, radiological evidence of renal scarring or calyceal deformity, and/or reduced renal function. Exclusion criteria included current immunosuppressive therapy, autoimmune disease, diabetes mellitus, recent antibiotic use within 10 days, pregnancy, and other active systemic infections

Cytokine Quantification

Serum samples were analysed using a commercial ELISA kit to determine the concentrations of TNF-α, IL-1β, and IL-33. All cytokine measurements were conducted using commercial ELISA kits according to manufacturer instructions: TNF-α (Elabscience, Cat. No. E-EL-H0109), IL-1β

(Elabscience, Cat. No. E-EL-H0149), and IL-33 (Elabscience, Cat. No. E-EL-H1565).

Principle of the ELISA Kit
The ELISA kit employed in this study utilises the sandwich ELISA principle. Microplate wells are pre-coated with antibodies specific to the cytokines of interest. When standards and patient samples are added to the wells, target antigens bind to the immobilised antibodies. A horseradish peroxidase (HRP)-conjugated detection antibody is then added to form a cytokine-antibody-HRP complex. Following incubation and washing, a substrate solution is added that reacts with HRP to produce a colour change. The intensity of the colour, measured at 450 nm, is directly proportional to the concentration of the cytokine.

Procedure of the ELISA Kit
All reagents were prepared and equilibrated to room temperature before use. Standards and diluted serum samples were pipetted into the wells in duplicate. After incubation at 37°C for 30 minutes, wells were washed thoroughly to remove unbound substances. HRP-conjugated detection antibody was added, followed by a second incubation and washing step. Substrate solution was then applied, and the reaction was stopped with a stop solution, changing the colour from blue to yellow. Absorbance was read at 450 nm using a microplate reader, and cytokine concentrations were calculated using a standard curve.

Statistical Analysis
Data were analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). All quantitative variables were expressed as mean ± standard deviation (SD). Due to the large standard deviations observed in TNF-α and IL-33 levels, data distribution was assessed using the Shapiro-Wilk test and visual inspection of histograms and boxplots. Mild skewness was detected, though no extreme outliers were found. Therefore, parametric tests were retained, and this variability was acknowledged as a limitation.
Group comparisons were performed using independent samples t-tests for normally distributed data, and the Mann-Whitney U test for non-parametric variables. Correlations among cytokines were examined using Pearson's correlation coefficient. Receiver Operating Characteristic (ROC) analysis was used to evaluate diagnostic performance, reporting area under the curve (AUC), sensitivity, specificity, and statistical significance. A p-value < 0.05 was considered statistically significant

Results
This study showed the difference in TNF-α, IL-1β and IL-33 levels between patients and the healthy group, as well as between ACP and CPN. The distribution of TNF-α and IL-33 values revealed considerable variability, as indicated by their high standard deviations. Normality assessment confirmed mild skewness but no extreme outliers, allowing for continued use of parametric statistical methods with appropriate caution.
Table 1 presents the number and percentage of all participants in the research according to age group and sex.

Table 1: Study groups according to age groups and sex.

Characteristic	Patient group n = 60	Healthy group n = 60	p-value
Age group, n (%)			
13-19 years	5 (8.3%)	9 (15%)	0.247
20-29 years	8 (13.3%)	11 (18.3%)	
30-39 years	15 (25%)	16 (26.7%)	
40-49 years	16 (26.7%)	13(21.7%)	
50-59 years	7 (11.7%)	9 (15%)	
60-70 years	9(15%)	2(3.3%)	
Sex			
Male, n (%)	30 (50%)	28(46.7%)	0.855
Female, n (%)	30 (50%)	32 (53.3%)	

Chi-Square test used at a significant level ≤0.05

The correlation between the healthy and patient groups with age and sex in P-value shows there was no significant difference (patients and healthy) with age (P-value>0.05) and gender (P-value>0.05).

Table 2 presents the comparative analysis of serum cytokine concentrations between pyelonephritis patients and healthy controls. TNF-α levels were significantly higher in the patient group (36.23 ± 64.12 pg/ml) compared to the control group (21.68 ± 18.52 pg/ml; p = 0.023), indicating increased inflammatory response in infected individuals. IL-1β also demonstrated a significant elevation in patients (15.17 ± 27.82 pg/ml) compared to controls (8.04 ± 7.00 pg/ml; p = 0.001), further supporting its role as a key mediator of renal inflammation. IL-33 levels showed a significant rise in patients (23.19 ± 36.88 pg/ml) relative to healthy individuals (12.52 ± 8.96 pg/ml; p = 0.001), though variability was higher.

Table 2: Immunological study in correlation with the patient group and healthy individuals.

Characteristic	Total patient N=60	Control group N=60	p-value
TNF-α			
Mean ± SD	36.23 ± 64.12	21.68 ± 18.52	0.023*
IL-1β			
Mean ± SD	15.17 ± 27.82	8.04 ± 7.00	0.001***
IL-33			
Mean ± SD	23.19 ± 36.88	12.52 ± 8.96	0.001***

Independent t-test used at a significance level of 0.05
* Show the significant (p≤0.05) difference between the total patients and the total controls
***Show the significant (p≤0.001) difference between the total patients and the total controls

Table 3 compares cytokine levels between acute and chronic pyelonephritis cases. Chronic cases had significantly elevated TNF-α (48.71 ± 87.62 pg/ml) and IL-1β (19.69 ± 34.77 pg/ml) levels compared to acute cases (TNF-α: 23.75 ± 19.12 pg/ml; IL-1β: 10.65 ± 17.98 pg/ml), with p-values of 0.013 and 0.007, respectively. IL-33 was also significantly higher in chronic cases (28.02 ± 46.53 pg/ml) than in acute cases (18.36 ± 23.54 pg/ml; p = 0.044), suggesting a potential association with disease duration or severity.

Table 3: Immunological study in correlation with the type of pyelonephritis patients

Characteristic	APN (N=30)	CPN (N=30)	p-value
TNF-α (mean ± SD)	23.75 ± 19.12	48.71 ± 87.62	0.013*
IL-1β (mean ±SD)	10.65 ± 17.98	19.69 ± 34.77	0.007**
IL-33 (mean ± SD)	18.36 ± 23.54	28.02 ± 46.53	0.044*

Independent t-test used at significant level 0.05
* Show the significant (p≤0.05) between acute and CPN

Table 4 presents the correlation coefficients between the measured cytokines in pyelonephritis patients. TNF-α showed a strong positive correlation with IL-1β (r = 0.839, p ≤ 0.01) and IL-33 (r = 0.810, p ≤ 0.01), indicating a co-regulated inflammatory response among these cytokines. Additionally, IL-1β and IL-33 exhibited a moderate but significant correlation (r = 0.788, p ≤ 0.01). These findings suggest that while all three cytokines are elevated in pyelonephritis, TNF-α may act as a central mediator influencing the expression of IL-1β and IL-33.

Table 4: The correlation coefficient between immunological parameters

Characteristics		Total patient n = 60		
		TNF-α	IL-1β	IL-33
TNF-α	Correlation Coefficient (r)	1		
IL-1β	Correlation Coefficient (r)	0.839**	1	
IL-33	Correlation Coefficient (r)	0.810**	0.788**	1

Correlation is significant at the 0.01 level (2-tailed)

The sensitivity and specificity of immunological parameters

Figure 1 illustrates the Receiver Operating Characteristic (ROC) curve for TNF-α. The X-axis represents the false positive rate (1 - specificity), while the Y-axis represents the true positive rate (sensitivity). The ROC curve analysis for TNF-α showed an area under the curve (AUC) of 0.618,

indicating a poor to fair discriminatory power to distinguish between pyelonephritis patients and healthy controls. The test was statistically significant, with a p-value of 0.026, suggesting that the observed difference is not due to chance. The 95% confidence interval ranged from 0.516 to 0.719, which does not include 0.5, further supporting the test's reliability in distinguishing between the two groups.

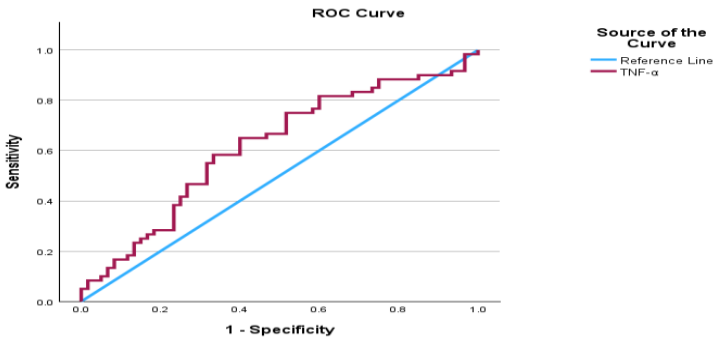

Figure 1: The ROC curve of TNF-α

Figure 2 presents the Receiver Operating Characteristic (ROC) curve for IL-1β. The X-axis shows the false positive rate (1 - specificity), and the Y-axis shows the true positive rate (sensitivity). The ROC curve analysis for IL-1β revealed an AUC of 0.618, indicating a weak to fair diagnostic accuracy in distinguishing pyelonephritis cases from healthy individuals. The result was statistically significant (p= 0.036), suggesting that IL-1β may have potential as a modest diagnostic biomarker for pyelonephritis. The 95% confidence interval ranged from 0.516-0.719.

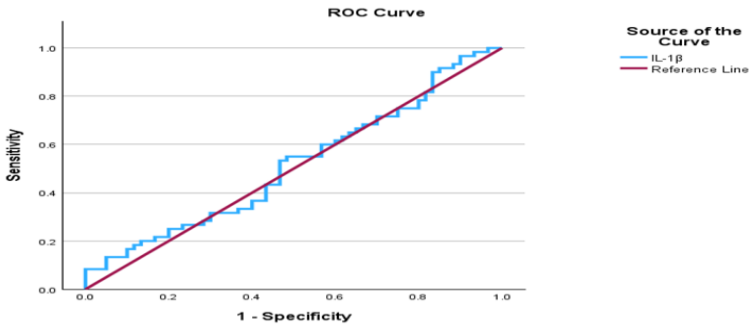

Figure 2: The ROC curve of IL-1β

As seen in Figure 3, The ROC curve of IL-33 figure explain that the AUC for IL-33 was approximately 0.594, indicating a poor to fair diagnostic ability. However, this result was not statistically significant (p = 0.076), suggesting that IL-33 may have limited discriminative power in distinguishing pyelonephritis cases from controls. The 95% confidence interval ranged from 0.492-0.695.

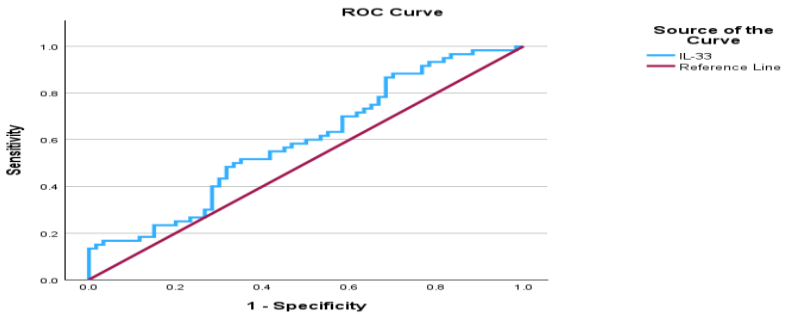

Figure 3: The ROC curve of IL-33

Discussion

The findings of this study are consistent with previous research highlighting the pivotal role of pro-inflammatory cytokines in urinary tract infections, particularly in the context of ascending pyelonephritis. The observed significant elevation of TNF-α and IL-1β in patients compared to controls supports their roles as immune response mediators during infection and renal inflammation. TNF-α, known for its ability to regulate immune cell recruitment and activation (16, 17), has previously been implicated in the pathogenesis of pyelonephritis and other forms of renal inflammation (18, 19). This study's finding of higher TNF-α levels in chronic pyelonephritis patients aligns with the hypothesis that TNF-α levels may reflect disease severity and duration (20).

Similarly, IL-1β plays an integral role in initiating and propagating the inflammatory cascade during infection. Its elevated levels in chronic compared to acute cases underscore its potential as both a diagnostic and prognostic biomarker. Prior studies have shown that IL-1β is critical for activating further cytokine production and immune cell recruitment in response to bacterial invasion (21). Its involvement in both innate and adaptive immune responses in renal infections has been well established (22, 23).

The study also assessed IL-33, a less-characterised member of the IL-1 cytokine family in pyelonephritis. Although IL-33 levels were significantly elevated in patients, particularly in chronic cases, their diagnostic performance was comparatively weaker. This observation aligns with existing literature suggesting that IL-33, while capable of inducing Th2 responses and contributing to tissue repair, may not serve as a direct inflammatory marker like TNF-α or IL-1β (24, 25). Nevertheless, its significant correlations with both TNF-α and IL-1β ($r = 0.810$ and $r = 0.788$, respectively) suggest a regulatory interplay, potentially mediated through shared upstream signalling mechanisms (26). Previous studies have suggested that TNF-α can induce IL-33 expression in keratinocytes and other cell types (27).

Moreover, there is a lack of specific studies linking IL-1β and IL-33 in the context of pyelonephritis. However, findings from diabetic nephropathy and periodontal disease research imply a possible cross-regulatory role where IL-1β and IL-33 together modulate inflammation and tissue remodelling (28, 29). The absence of IL-33's predictive value in ROC analysis in this study might be attributable to its broader function in homeostasis rather than acute-phase immune activation.

Given their significant elevation and strong diagnostic performance, TNF-α and IL-1β could potentially be used in clinical settings to identify patients at higher risk for severe or chronic pyelonephritis. Elevated TNF-α levels may support earlier therapeutic intervention in high-risk patients or serve as a marker for monitoring response to treatment. Although IL-33 showed limited diagnostic accuracy in ROC analysis, its significant elevation in chronic pyelonephritis cases suggests a role in ongoing immune regulation or tissue remodelling rather than acute inflammatory response. This aligns with prior literature indicating IL-33's involvement in fibrosis and repair mechanisms, particularly in chronic renal inflammation. In clinical practice, TNF-α and IL-1β could serve as supplementary biomarkers to traditional diagnostic tools, helping to stratify patients based on severity and guide early therapeutic decisions. For example, elevated TNF-α may indicate a more aggressive inflammatory response, prompting closer monitoring or early antibiotic escalation, while persistently high IL-1β levels may suggest progression toward chronicity

In summary, this study confirms TNF-α and IL-1β as robust markers of inflammation in pyelonephritis and suggests a supplementary, though limited, role for IL-33 in reflecting disease chronicity. These cytokines not only aid in understanding the disease process but could also be harnessed for future diagnostic or therapeutic purposes.

Study limitations

Several limitations must be acknowledged. The sample size, though balanced between groups, remains relatively small, limiting the generalizability of the findings. Additionally, potential confounding factors such as prior antibiotic use, co-existing infections, and comorbidities (e.g., diabetes mellitus, autoimmune disorders) were not controlled for in the analysis. These factors may have influenced cytokine expression and could introduce bias in the interpretation of our findings. Also, the cross-sectional design does not allow for causal inference or the assessment of cytokine trends over time. The large standard deviations observed in TNF-α and IL-33 levels suggest potential biological variability or mild skewness, which, although addressed analytically, may limit the precision of some estimates.

Conclusion

This study provides compelling evidence that TNF-α and IL-1β are significantly elevated in patients with ascending pyelonephritis compared to healthy individuals. These cytokines also demonstrated

superior diagnostic performance, as confirmed by ROC analysis. Their strong correlations with each other and with IL-33 indicate an interconnected inflammatory response. TNF-α plays a central role in immune cell recruitment [16–20], and IL-1β's function in initiating inflammation [21–23] reinforces their utility as reliable biomarkers for identifying and differentiating between acute and chronic forms of the disease.

Although IL-33 was significantly elevated in pyelonephritis, its diagnostic value was limited, consistent with its known dual role in both inflammation and tissue repair [24–27]. The moderate but significant correlation of IL-33 with TNF-α and IL-1β suggests that it may be indirectly influenced by these more potent pro-inflammatory mediators.

In conclusion, TNF-α and IL-1β emerge as promising diagnostic and potentially prognostic biomarkers for ascending pyelonephritis. IL-33 may reflect disease chronicity, but it appears to lack the specificity required for standalone diagnostic use. Further research with larger, longitudinal cohorts is essential to confirm these findings and to clarify the mechanistic relationships among these cytokines, especially IL-33's modulatory role in renal inflammation. Future studies should adopt a longitudinal design to monitor cytokine dynamics throughout treatment, enabling a better understanding of their temporal patterns and prognostic value. Mechanistic investigations are also warranted to elucidate the regulatory role of IL-33 in chronic renal inflammation and its potential contribution to tissue remodelling or fibrosis in pyelonephritis.

List of Abbreviations

APN: Acute Pyelonephritis
CPN: Chronic Pyelonephritis
CKD: Chronic Kidney Disease
ELISA: Enzyme-Linked Immunosorbent Assay
HRP: Horseradish Peroxidase
IL-1β: Interleukin-1 Beta
IL-33: Interleukin-33
OD: Optical Density
ROC: Receiver Operating Characteristic
SD: Standard Deviation
ST2: Suppression of Tumorigenicity 2 (IL-33 receptor)
TNF-α: Tumour Necrosis Factor Alpha
TPR: True Positive Rate
FPR: False Positive Rate
Th1 T: Helper Type 1
Th2 T: Helper Type 2
UTI: Urinary Tract Infection

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Medical Ethics Committee at the University of Kufa (Reference Number: MEC-172). All procedures involving human participants were conducted following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study, and for minors under the age of 18, consent was additionally obtained from their parents or legal guardians.

Consent for Publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license.

Availability of Data

Data for this work is available from the authors and may be provided upon reasonable request.

Conflicts of Interest

None.

Funding

None.

Authors' contributions

AMAA conceptualised the study and led the writing. SKA performed data collection and analysis. Both authors reviewed and approved the final manuscript.

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