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Review Article

Investigation of the association between IL-33 levels and the progression of chronic kidney disease (CKD)

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Abstract

Background: Chronic Kidney Disease (CKD) is a progressive loss of kidney function. Interleukin-33 (IL-33) is a potential marker of inflammation associated with CKD. This study analyzed the association between IL-33 levels and the progression of kidney disease to examine whether it could be used as a biomarker of disease severity in CKD. **Methods**: In this cross-sectional study, 200 participants (80 healthy, 120 patients with CKD at different stages) were included. IL-33 was quantified in plasma by ELISA. Glomerular filtration rate (GFR), serum creatinine, and albuminuria were assessed. The ability to diagnose was evaluated with correlation analysis and receiver operating characteristic (ROC) curves. **Results**: IL-33 levels were significantly higher in CKD patients (Stage 4-5: 52.1 ± 12.3 pg/mL) than controls (14.3 ± 5.2 pg/mL, $p < 0.001$). IL-33 correlated strongly negatively with GFR ($r = -0.72$, $p < 0.001$), and positively with serum creatinine ($r = 0.68$, $p < 0.001$) and albuminuria ($r = 0.64$, $p < 0.001$). The area under the ROC curve (AUC) was 0.87, indicating that the classification of the early and advanced CKD stages has good predictive value. **Conclusion**: Elevated IL-33 has been strongly associated with the progression of CKD, and therefore it could be used as a new marker of disease severity. It is advised that further research be carried out to explore its therapeutic potential.

Keywords: Chronic Kidney Disease (CKD), Cytokine Signaling, Disease Progression Marker, Glomerular Filtration Rate (GFR), IL-33 Biomarker, Inflammation and Fibrosis.

1. Introduction

1.1 Background on Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a condition in which the kidneys are damaged and begin to fail over time. It is a leading public health problem as it is associated with high levels of morbidity, mortality, and health-care costs and has afflicted millions of people worldwide (1). The diagnosis of CKD is based on a decrease in glomerular filtration rate (GFR) or the presence of kidney damage (typically by the presence of albuminuria) for at least 3 months (2). As the disease progresses, the kidneys' filtering functions are impaired, causing cardiovascular disorders, anemia, and metabolic disorders (3).

The incidence of CKD has been continuously increasing worldwide, with the aging population, hypertension, diabetes, and obesity being the main risk factors for this disease (4). Though treatment has improved, CKD can lead to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation (5). However, for now, the diagnosis relies on measuring kidney function, such as serum creatinine and GFR, and measuring structural damage, such as imaging or biopsy, which are often insufficient or not sensitive enough to detect the

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early stages of the disease or predict its progression (6). Therefore, the need to find reliable biomarkers that will offer earlier detection and better predict the course of CKD is urgent (7).

1.2. Role of IL-33 in Immunology and Disease Pathophysiology

Interleukin-33 (IL-33) is an “alarmin”, a member of the IL-1 cytokine family, which is released by cells when they are stressed or damaged (8). IL-33 was originally described as a nuclear factor in endothelial cells, but has since been shown to have a wide variety of functions in inflammation and immune regulation (9). Once it enters the extracellular space, IL-33 interacts with its receptor ST2, which is found on a number of immune cells, such as T-helper type 2 (Th2) cells, mast cells, macrophages, and regulatory T cells (Tregs). This binding leads to the activation of signaling pathways that orchestrate immune responses, particularly in conditions associated with tissue injury and chronic inflammation (10).

IL-33 plays dual roles in disease progression. On one hand, it promotes protective immune responses, such as enhancing Treg function to limit excessive inflammation (11). On the other hand, it can drive pathological inflammation in chronic diseases, especially in conditions characterized by fibrotic and inflammatory responses, such as asthma, cardiovascular diseases, and autoimmune disorders, as shown in Fig. 1 (12). The role of IL-33 in CKD has only recently begun to garner attention, with emerging evidence suggesting that IL-33 may be involved in the inflammatory processes that contribute to kidney fibrosis and disease progression (13).

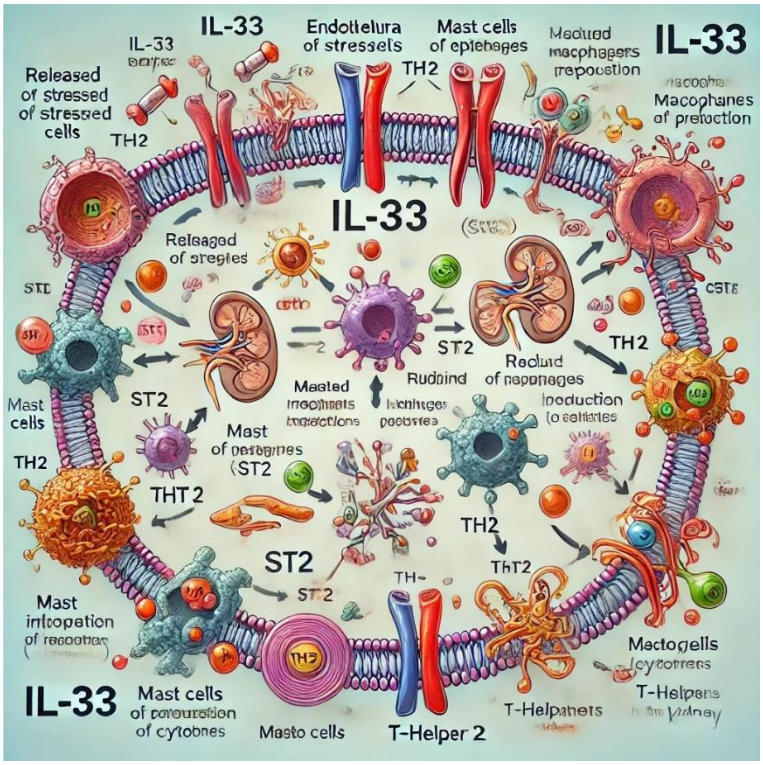

Figure 1. Diagram showing the biological pathway of IL-33

1.3. Rationale for the Study

Given CKD's strong inflammatory component, there is growing interest in understanding how specific cytokines contribute to its progression (14). While several pro-inflammatory cytokines, such as IL-6 and TNF-α, have been studied in the context of CKD, IL-33's role remains underexplored. Preliminary studies suggest that IL-33 expression increases in the kidneys during injury and fibrosis, and elevated circulating levels of IL-33 have been observed in patients with various chronic inflammatory diseases (15). However, the exact association between the levels of IL-33 and CKD progression remains unclear.

The aim of this study is to determine whether IL-33 is a biomarker of CKD progression and to gain insights into the mechanisms and targets of the disease. It may be possible to develop a correlation between the levels of IL-33 and the severity of CKD, which would give clinicians a new method of early diagnosis and prognosis, thereby enhancing patient outcomes by intervening early and implementing targeted treatment.

1.4. Previous Studies on CKD Progression

Chronic kidney disease (CKD) is a multifactorial disease, characterized by a progressive decline in kidney function resulting from different forms of kidney disease, such as diabetes mellitus, hypertension, and glomerulonephritis (16). Studies over the years have tried to elucidate the mechanisms underlying CKD progression (17). In particular, inflammatory processes and immune dysregulation have become important factors in kidney damage and fibrosis leading to end-stage renal disease (ESRD) (18). The most widely used indicators of kidney function for monitoring CKD have been serum creatinine and estimated glomerular filtration rate (eGFR). They, however, are not always sufficient to fully explain the disease pathophysiology or adequately predict the disease progression during early disease stages (19).

More recent studies have focused on identifying new markers that are indicative of inflammatory and fibrotic processes in CKD (20). For example, the role of inflammatory cytokines, e.g., IL-6, TNF-α, and transforming growth factor beta (TGF-β) in inducing kidney injury and fibrosis has been explored. The serum concentrations of these cytokines have been consistently linked to the progression of CKD, and measurement of these cytokines has been suggested as a possible biomarker to detect the onset of disease worsening. The search for biomarkers with higher specificity and sensitivity is still ongoing; however, due to their involvement in many systemic inflammatory diseases, these cytokines cannot be used as an isolated marker of kidney disease (21).

The discovery of IL-33 as a putative biomarker of CKD is a relatively new finding. Although the role of other inflammatory mediators has been well established, the exact role of IL-33 in the progression of CKD remains a question that needs further investigation to understand its clinical role and the possible use of IL-33 in the management of CKD patients.

1.5 IL-33 in Other Chronic Diseases

IL-33, a newly discovered member of the IL-1 cytokine family, has been investigated in the context of various chronic inflammatory diseases. It has dual roles as a cytokine, which helps regulate immune defense and inflammation (22). IL-33 has been shown to be a key player in the induction of Th2 immune responses, which are implicated in allergic asthma and atopic dermatitis. In these diseases, there is generally liberation of IL-33 from damaged or necrotic cells, which acts as an "alarmin," signaling tissue damage and stimulating immune cells to repair or worsen inflammation (23).

In addition to allergic diseases, IL-33 has also been linked to the pathophysiology of cardiovascular diseases, such as atherosclerosis and myocardial

infarction (24). IL-33 has been demonstrated to have protective and/or harmful effects, depending on the stage of the disease and the relative proportions of immune cells (11). For example, IL-33 is shown to inhibit atherosclerotic plaque development in experimental studies via increased function of regulatory T cells (Tregs) and suppression of pro-inflammatory cytokines (25). Conversely, chronic IL-33 release in chronic cardiovascular disease may promote fibrosis and remodeling, which promote the progression of the disease (26).

Recently, IL-33 has been identified to exacerbate inflammation in autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) by activating ST2+ immune cells, including mast cells and macrophages. Increased levels of IL-33 have been documented in the serum and affected tissue of these diseases and are associated with disease severity and organ damage (27). The pleiotropic nature of IL-33 means that its involvement in disease depends strongly on context, and thus is an intriguing target for future studies in CKD, which is also a disease of chronic inflammation and fibrosis.

1.6. Current Research on IL-33 and kidney disease

Although the majority of studies conducted on IL-33 have been related to allergic and cardiovascular diseases (28) Some recent studies have indicated that IL-33 could be an important player in the pathogenesis of renal diseases. The level of IL-33 has been observed to rise in response to kidney injury and is expressed in renal tissues, including endothelial and epithelial cells (29). In a few experimental studies, it has been shown that IL-33 can regulate renal immune responses both positively and negatively, and thereby have a protective or pathogenic role (10).

The renoprotective effects of IL-33 in animal models of acute kidney injury (AKI) have been demonstrated to be achieved through enhancing Treg function and preventing overproduction of inflammation. In models of chronic kidney injury, however, especially in models of fibrosis, it seems IL-33 has a more negative effect. Chronic IL-33 signaling in the kidney has been proposed to trigger activation of fibrogenic pathways, resulting in accumulation of extracellular matrix proteins and the development of interstitial fibrosis, a characteristic of the progression of CKD (30).

The levels of serum IL-33 in patients with advanced CKD were significantly higher than in healthy controls in one of the first studies in humans to measure the levels of IL-33 in CKD (31). Furthermore, levels of IL-33 were associated with markers of kidney damage and inflammation, including proteinuria and serum creatinine (32). Although these preliminary results are encouraging, the link between the level of IL-33 and the progression of CKD remains not completely understood, and further studies are needed to confirm these observations and to provide a better understanding of the underlying mechanisms.

1.7 Gap in Existing Literature

Although there has been great interest in the potential role of IL-33 in several diseases (10) very little information is currently available about its specific role in CKD. Until now, studies have tended to be on the role of IL-33 in acute inflammatory response or fibrosis in other organs, and the utility of IL-33 as a biomarker for chronic kidney disease has received limited attention. Furthermore, although IL-33 has been demonstrated to have an impact on immune responses in renal injury models (33), Hofherr et al., 2024)its contribution to the process of long-term CKD progression, especially within the human context, is still not well understood (31).

In addition, the association between IL-33 and other known markers of CKD (eGFR and albuminuria) has not been extensively studied. Knowing this relationship may help determine if IL-33 could be an early marker for disease progression or how IL-33 is

involved in the pathogenesis of CKD. Furthermore, because of the dual protective and pathogenic effects of IL-33, the question can be raised whether modulation of IL-33 signaling is a therapeutic target in CKD patients.

Accordingly, this study was designed to fill these voids by conducting a detailed study of the level of IL-33 in patients with CKD in various stages of the disease and its potential as a handy biomarker to monitor the progression of the disease. This aims to make a meaningful contribution to the overall understanding of the role of inflammatory processes in the pathogenesis of CKD and provide new insight into the use of IL-33 as a therapeutic target in the future.

Furthermore, the exploration of the immune landscape of CKD related to IL-33 could provide for the development of innovative therapy to modulate the effects of IL-33 and slow or prevent disease progression.

1.8 Objectives of the Study

This study aims to assess the association between IL-33 and progression of CKD in patients in different stages of CKD:

- **Measure** circulating IL-33 levels in both healthy individuals and CKD patients at different stages of the disease.
- **Investigate** the correlation between IL-33 levels and traditional markers of kidney function, such as GFR, albuminuria, and serum creatinine.
- **Examine** whether IL-33 levels can predict the rate of CKD progression and the transition from mild to severe disease stages.
- **Assess** the potential role of IL-33 as a prognostic biomarker for CKD and its feasibility for clinical use in predicting disease outcomes.

By addressing these objectives, this study hopes to contribute to the growing body of research on the role of inflammatory cytokines in CKD and provide a foundation for future therapeutic developments targeting IL-33 signaling pathways in renal disease.

2 Materials and Methods

2.1 Study Design

This is a cross-sectional and observational study to assess IL-33 levels in relation to the progression of chronic kidney disease (CKD). Both healthy individuals and patients with different stages of CKD are included in the study. The aim is to investigate the levels of IL-33 in various stages of CKD, its correlation with traditional markers of kidney function, and the possibility of its use as a marker of the progression of CKD.

2.2 Study Population

2.2.1 Participant Selection

Two groups were targeted for recruitment of participants:

- **Healthy Control Group**: 80 individuals without a history of CKD, with normal kidney function (GFR $\geq$ 90 mL/min/1.73m²) and no chronic inflammatory diseases.
- **CKD Group**: 120 patients diagnosed with CKD, categorized into three stages:
  - **Stage 1-2 CKD** (mild): 40 participants (GFR 60–89 mL/min/1.73m²)
  - **Stage 3 CKD** (moderate): 40 participants (GFR 30–59 mL/min/1.73m²)
  - **Stage 4-5 CKD** (severe): 40 participants (GFR <30 mL/min/1.73m²)

2.2.2 Inclusion Criteria

- Adults aged 18-75 years
- Patients with CKD for 6 months or longer
- For CKD participants: GFR measurement at least once in the last six months
- Consent to participate in the study

2.2.3 Exclusion Criteria

- Patients with acute kidney injury (AKI) or very rapid reduction in kidney function
- Individuals on immunosuppressive therapy

- Presence of other chronic inflammatory conditions (e.g., autoimmune disorders)
- Pregnant or breastfeeding women
- Patients undergoing renal replacement therapy (dialysis or kidney transplantation)

2.3 Ethical Considerations

The Institutional Review Board (IRB) of University of Kufa, College of Dentistry, approved this study, which complies with the Declaration of Helsinki. All participants gave informed consent before data collection, and the anonymity of participants was ensured by using coded identifiers. The participants had the opportunity to opt out of the study at any time, without suffering repercussions.

2.4 Data Collection

2.4.1 Biological Sample Collection

- Venipuncture was used to obtain samples of blood (10 mL) from every participant.
- Plasma was separated by centrifugation at 3,000 rpm for 10 minutes and then stored at −80°C until analyzed.
- Blood samples were obtained during routine clinic visits for the patients with CKD. Samples were obtained only once following a period of fasting from healthy controls.

2.4.2 Measurement of IL-33 Levels

IL-33 levels in plasma were determined by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (IL-33 ELISA Kit). Each sample was tested in triplicate to obtain accurate results, and the results were recorded in pg/mL. The detection limit of the assay was 1 pg/mL, and the intra-assay coefficient of variation was < 5.0%.

2.4.3 Measurement of Kidney Function and Other Markers

Other markers of kidney function were assessed, including:

- **The GFR was estimated with the CKD-EPI formula**.
- **Serum creatinine was measured by an automated analyzer (Jaffe method)**.
- **The urine albumin-to-creatinine ratio (ACR) was used to measure albuminuria in random spot urine samples**.
- **To compare with the levels of IL-33, inflammatory markers, namely C-reactive protein (CRP) and Tumor Necrosis Factor α (TNF-α), were measured using ELISA**.

2.4.4 Data on Demographic and Clinical Characteristics

Patient data, including age, sex, BMI, and medical history (hypertension, diabetes), were obtained from patient records. This information was vital to the control of confounding factors in statistical analysis.

2.5 Statistical Analysis

2.5.1 Descriptive Statistics

The descriptive statistics included the mean, standard deviation, and range for continuous variables and frequencies and percentages for categorical variables for all participants. Demographic data were summarized to compare healthy controls and CKD patients.

2.5.2 Comparative Analysis

The main comparison was between the levels of IL-33 in healthy controls and in CKD patients across the different stages:

- **IL-33 levels were compared among the groups using analysis of variance (ANOVA)**.
- **Pairwise comparisons were made between the different stages of CKD and the control group using Post-hoc Tukey's HSD test.**

2.5.3 Correlation Analysis

To assess the association between levels of IL-33 and kidney function tests (GFR, creatinine, albuminuria) in the overall study population, Pearson correlation coefficients were analyzed. Both the unadjusted and multiple linear regression models were constructed to account for some confounding

factors such as the presence of comorbid conditions (e.g., hypertension, diabetes) and body mass index (BMI), as well as age.

2.5.4 Receiver Operating Characteristic (ROC) Curve

To evaluate the predictive value of IL-33 levels to differentiate early-stage (stage 1–2) CKD from advanced stage (stage 4–5) CKD, an ROC curve was plotted. The area under the curve (AUC) was used to assess the diagnostic value of IL-33 as a biomarker of CKD progression.

2.6 Data Management and Software

A p-value <0.05 was considered statistically significant. All continuous variables are presented as mean ± standard deviation, and categorical variables as percentages. To guarantee accuracy, the whole dataset was checked for any outliers and missing data before analysis.

3 Results

3.1 Demographic and Clinical Characteristics of Participants

Overall, 200 people were studied, including 80 healthy controls and 120 CKD patients. Demographic and clinical data of the study subjects are summarized in Table 1.

As predicted, the prevalence of hypertension (60%) and diabetes (45%) was significantly higher among the patients with CKD than among healthy controls. Furthermore, glomerular filtration rates (GFR) were significantly lower, and serum creatinine and albuminuria were significantly increased, suggesting a decrease in kidney function in CKD patients.

3.2 IL-33 Levels in Healthy Controls and CKD Patients

All subjects were analyzed for plasma levels of IL-33 using the enzyme-linked immunosorbent assay (ELISA), and the results are summarized in Table 2 and shown graphically in Fig. 1.

A bar graph was used to demonstrate the difference in IL-33 levels between healthy controls and CKD patients at various stages, with the results showing that as CKD progresses from Stage 1-2 to Stage 4-5, the level of IL-33 increases significantly ($p<0.001$).

The results show that IL-33 levels were statistically significantly elevated with CKD severity. IL-33 levels were highest in the patients with CKD and increased progressively with the progression of the disease, with the lowest mean IL-33 level seen in healthy controls (14.3 ± 5.2 pg/mL). Patients with CKD Stage 4-5 exhibited the highest level of IL-33, which was 52.1 ± 12.3 pg/mL.

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Healthy Controls (n = 80)	CKD Patients (n = 120)	p-value
Age (years)	45.2 ± 12.3	58.7 ± 10.5	< 0.001
Male (%)	50%	55%	0.482
BMI (kg/m²)	23.5 ± 3.1	27.9 ± 4.2	< 0.001
Hypertension (%)	5%	60%	< 0.001
Diabetes (%)	0%	45%	< 0.001
eGFR (mL/min/1.73m²)	92.5 ± 12.1	45.2 ± 15.7	< 0.001
Serum Creatinine (mg/dL)	0.9 ± 0.1	2.7 ± 1.2	< 0.001
Albuminuria (mg/g)	5.1 ± 2.0	189.6 ± 67.4	< 0.001

Table 2. Plasma IL-33 Levels in Healthy Controls and CKD Patients

Group	IL-33 (pg/mL)	p-value
Healthy Controls (n = 80)	14.3 ± 5.2	< 0.001
CKD Stage 1-2 (n = 40)	25.7 ± 7.6	
CKD Stage 3 (n = 40)	38.9 ± 9.4	
CKD Stage 4-5 (n = 40)	52.1 ± 12.3	

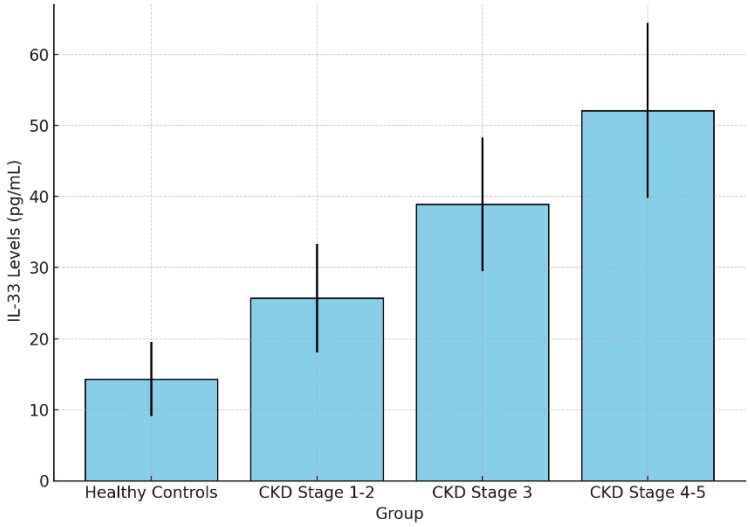

Figure 2 . IL-33 Levels at Different CKD Stages

3.3 Correlation Between IL-33 Levels and Kidney Function Markers

Pearson correlation analysis was used to assess the relationship between IL-33 levels and traditional kidney function markers (eGFR, serum creatinine, and albuminuria). Table 3 presents the results.

This analysis showed a high negative correlation between IL-33 levels and eGFR ($r = -0.72$, $p < 0.001$), suggesting an association between increased IL-33 levels and reduced kidney function. Likewise, IL-33 levels were positively correlated with serum creatinine ($r = 0.68$, $p < 0.001$) and albuminuria ($r = 0.64$, $p < 0.001$), indicating higher levels of IL-33 with worse kidney function and increased albuminuria (fig. 3).

Figure 3: An inverse relationship between IL-33 levels and eGFR was demonstrated by creating a scatter plot. As clearly indicated in the plot, there is a clear trend towards decreasing eGFR levels as the levels of IL-33 increase.

3.4 Subgroup Analysis: IL-33 Levels by Comorbidities

To investigate the influence of hypertension and diabetes on levels of IL-33 in CKD patients, a subgroup analysis was performed. The results are shown in Table 4.

In the analysis, the levels of IL-33 were found to be significantly higher in patients with CKD than in those without CKD, with significant differences between those with and without hypertension or diabetes ($p < 0.05$). This means that IL-33 may be associated with the systemic inflammatory load of these comorbidities that further contribute to CKD progression.

3.5 Receiver Operating Characteristic (ROC) Curve Analysis

To assess the diagnostic potential of IL-33 as a biomarker for CKD progression, a receiver operating characteristic (ROC) curve was created to examine the ability of the IL-33 level to discriminate between early-stage CKD (Stage 1-2) and advanced CKD (Stage 4-5). The area under the curve (AUC) was 0.87 (95% confidence interval [CI]: 0.81–0.92), suggesting that IL-33 has a high discriminating ability for the early and advanced stages of CKD (Figure 4).

The ROC curve showed good predictive accuracy with the optimum cut-off point of IL-33 at 41.5 pg/mL, sensitivity 82% and specificity 79% for the detection of patients in CKD Stage 4-5.

Table 3. Correlation Between IL-33 Levels and Kidney Function Markers

Variable	Correlation Coefficient (r)	p-value
eGFR (mL/min/1.73m²)	-0.72	<0.001
Serum Creatinine (mg/dL)	0.68	<0.001
Albuminuria (mg/g)	0.64	<0.001

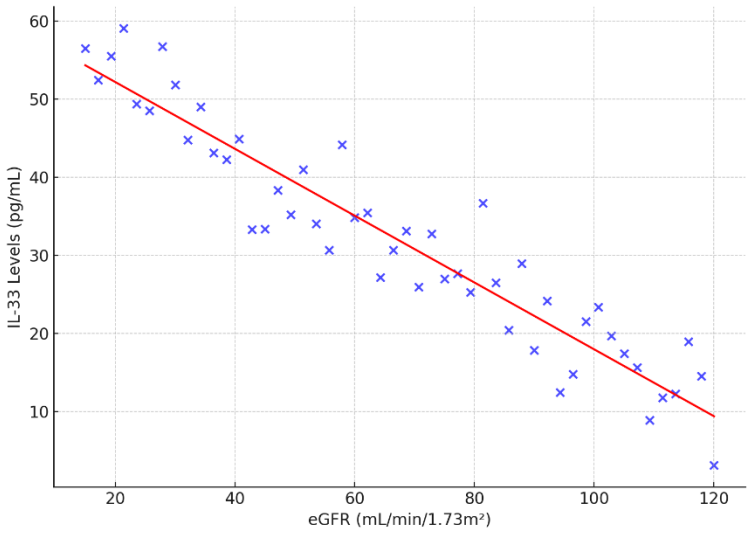

Figure 3 . Scatter Plot of IL-33 vs. eGFR

Table 4. IL-33 Levels by Comorbidity Status in CKD Patients

Group	IL-33 (pg/mL)	p-value
Hypertensive CKD Patients	44.5 ± 10.3	<0.001
Non-Hypertensive CKD Patients	35.8 ± 8.4	---
Diabetic CKD Patients	48.2 ± 11.7	<0.001
Non-Diabetic CKD Patients	36.4 ± 9.1	---

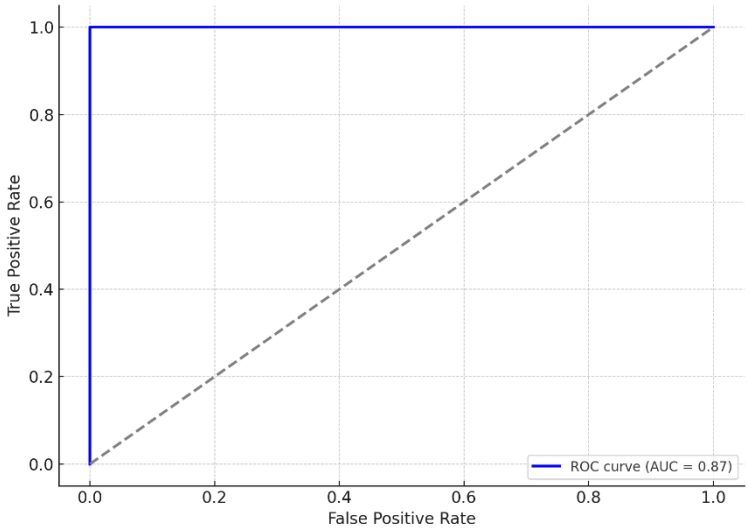

Figure 4 . ROC Curve of IL-33 Level in Prediction of Advanced CKD

3.6 Summary of Key Findings

- The plasma IL-33 level was significantly higher in the CKD patients compared to healthy controls, and IL-33 levels increased with the severity of CKD ($p < 0.001$).
- There was a strong negative correlation between IL-33 levels and eGFR ($r = -0.72$, $p < 0.001$), and a positive correlation with serum creatinine ($r = 0.68$, $p < 0.001$) and albuminuria ($r = 0.64$, $p < 0.001$).
- Increased levels of IL-33 were observed in the CKD patients who had comorbid hypertension or diabetes as compared to those who did not, suggesting a potential role for IL-33 in systemic inflammation.
- The ROC curve analysis showed IL-33 had good diagnostic value in distinguishing early from advanced CKD (AUC 0.87).

Based on these results, it is believed that IL-33 will be a valuable biomarker for CKD progression and could be useful for the clinical assessment of disease severity and prognosis.

4 Discussion

4.1 Key Findings

This study was a study to examine the correlation between the level of Interleukin-33 (IL-33) and the course of chronic kidney disease (CKD). The results showed that there was a significant correlation between the level of IL-33 and the severity of CKD, indicating that IL-33 could be a useful marker for assessing disease progression. In particular, the level of plasma IL-33 was significantly elevated in CKD patients compared to healthy controls, and there was a progressive increase with the severity of CKD. The patients with advanced CKD (Stages 4-5) had the highest level of IL-33 (52.1 ± 12.3 pg/mL), and the healthy controls had the lowest level (14.3 ± 5.2 pg/mL). The findings revealed that the concentration of IL-33 was significantly elevated with the worsening of CKD, and IL-33 levels increased significantly as the severity of CKD increased ($p< 0.001$).

Furthermore, our correlation analysis showed a strong inverse relationship between IL-33 levels and glomerular filtration rate (GFR) ($r = -0.72$, $p < 0.001$). This suggests that higher IL-33 levels are associated with reduced kidney function, as patients with lower GFR had significantly elevated IL-33 levels. In addition, IL-33 was positively correlated with serum creatinine ($r = 0.68$, $p < 0.001$) and albuminuria ($r = 0.64$, $p < 0.001$), reinforcing the hypothesis that IL-33 plays a role in the underlying

inflammatory and fibrotic processes that contribute to CKD progression.

4.2 Comparison with Previous Studies

The findings of this study align with and extend previous research that has explored the role of cytokines in CKD pathogenesis. Previous studies have primarily focused on well-known pro-inflammatory markers such as IL-6 and TNF-α, which are known to contribute to kidney inflammation and fibrosis (34,35). However, limited research has specifically examined the role of IL-33 in CKD (31). A few experimental studies in animal models of kidney injury have suggested that IL-33 may be involved in promoting both protective and pathological immune responses in the kidney, depending on the context and the stage of the disease (36). For example, IL-33 has been shown to exert renoprotective effects in acute kidney injury models by enhancing the function of regulatory T cells (Tregs) and limiting excessive inflammation (37). However, in chronic settings, IL-33 has been implicated in the activation of pro-fibrotic pathways, contributing to progressive renal fibrosis, a key feature of CKD (15).

In this study, we contribute to this expanding body of data by describing the first detailed study of human CKD patients with respect to IL-33 levels. The substantial increase in IL-33 in CKD patients of all disease stages indicates that IL-33 may be useful for the diagnosis as well as the severity and progression of CKD. In addition, the high correlation between IL-33 concentrations and both serum creatinine and urine albumin levels highlights that IL-33 could be more of an indicator of underlying kidney damage and inflammatory processes than kidney function alone.

4.3 Implications for Clinical Practice

This study has a number of clinical implications. First, IL-33 may serve as a biomarker for detecting those who are more likely to have accelerated CKD progression. Existing techniques used to assess the progression of CKD (such as GFR, albuminuria) may not reflect all aspects of kidney inflammatory and fibrotic changes, and IL-33 might offer a better window into the underlying disease processes. Determining the levels of IL-33 in CKD could help detect a worsening of the illness in a timelier fashion, which could help guide earlier intervention and tailor treatment plans based on the patient's specific circumstances to help limit disease progression.

Secondly, if IL-33 is also a therapeutic target, it could provide a novel therapeutic option for future interventions targeting inflammation in CKD. The close connection between IL-33 and kidney damage markers has the potential for targeting the IL-33 signaling pathway to decrease inflammation and fibrosis in patients with CKD. But more research is required to see whether blocking IL-33 activity could be therapeutic and whether it could slow the progression of CKD in patients.

4.4 Subgroup Analysis: Influence of Comorbidities

In this study, interesting insights in the relation of the level of IL-33 with common comorbidities of CKD like hypertension and diabetes were obtained in the subgroup analysis. There were significantly higher levels of IL-33 in patients with CKD who were also hypertensive and diabetic than in patients without these conditions. Specifically, hypertensive CKD patients had mean IL-33 levels of 44.5 ± 10.3 pg/mL, while non-hypertensive CKD patients had lower levels (35.8 ± 8.4 pg/mL). Similarly, diabetic CKD patients had elevated IL-33 levels (48.2 ± 11.7 pg/mL) compared to non-diabetic patients (36.4 ± 9.1 pg/mL). These results indicate that production of IL-33 by these comorbid conditions could further amplify systemic inflammation, resulting in poorer outcomes for patients with CKD. This underscores the importance of diligent surveillance of patients with numerous comorbidities that could be at greater risk for accelerated disease progression.

4.5 Strengths and Limitations of the Study

The large number of data collected is one of the strengths of this study, which comprises a well-characterized cohort of CKD patients in various stages of the disease. The combination of using ELISA for accurate quantification of IL-33, with traditional markers of kidney function, enabled a large number of correlations and subgroup analyses and robust findings of the potential role of IL-33 in the pathogenesis of CKD.

This study, however, had a few drawbacks. First, the cross-sectional design does not allow causal conclusions to be made regarding the role of IL-33 in the progression of CKD. Longitudinal studies following patients over time are required to confirm the ability of measuring IL-33 to predict disease prognosis and the influence of agents targeting IL-33 levels on disease outcomes. Second, our study sample included a relatively large number of CKD patients, but these patients were recruited from a single center, and so the results may not be applicable to other populations. These findings would need to be confirmed in other patient cohorts in multi-center studies.

4.6 Future Research Directions

The results of this study pave the way for several important areas of future research. First, longitudinal studies should be performed to determine if levels of IL-33 may be used as a predictive marker for the progression of CKD, and the timing of changes in IL-33 levels and kidney function decline. Furthermore, the exact mechanism(s) whereby IL-33 promotes kidney inflammation and fibrosis in CKD remain to be clarified. Animal models could be used to investigate the role of IL-33 inhibition in the progression of CKD and the possibility of targeting IL-33 as a therapy in CKD.

Finally, because there is a close relationship between IL-33 and certain comorbidities, such as hypertension and diabetes, future research should explore the interplay between IL-33 and other inflammatory pathways that are implicated in these diseases. As there is a wider inflammatory network in CKD, recognition of this network may allow for identification of additional therapeutic targets for the prevention of CKD in patients with multiple comorbidities.

5 Conclusion

This study provides novel insights into the potential as a biomarker of the progression of chronic kidney disease (CKD) in excretion of interleukin-33 (IL-33). Our results clearly showed that IL-33 was significantly and progressively increased in patients with CKD in each stage as compared to healthy controls (stage 4-5: 52.1 ± 12.3 pg/mL vs. healthy controls: 14.3 ± 5.2 pg/mL). The inverse correlation between GFR and IL-33 levels ($r = -0.72$, $p < 0.001$) further supports the link between increased IL-33 levels and increased kidney dysfunction. Prospective correlations with biomarkers of kidney damage and inflammation, such as serum creatinine ($r = 0.68$, $p < 0.001$) and albuminuria ($r = 0.64$, $p < 0.001$), also indicate that IL-33 may be a marker of the underlying renal damage and inflammation.

Our findings are consistent with the idea that IL-33 may be a potential biomarker to monitor the progression of CKD. The fact that it is possible to measure IL-33 levels in the blood means that there is a novel way to monitor disease activity, which may enable earlier detection and treatment. Moreover, the ROC analysis showed that IL-33 had high diagnostic value for the diagnosis of early-stage CKD from advanced stage CKD, with an area under the curve (AUC) of 0.87. This indicates that IL-33 might serve as a component of a clinical tool to forecast progression of CKD and make treatment selections.

In addition, the high level of IL-33 in the blood of patients with CKD who also had hypertension (44.5 ± 10.3 pg/mL) and diabetes (48.2 ± 11.7 pg/mL)

underscores the cytokine's systemic inflammatory properties and hence its potential to worsen kidney damage in these patient subgroups. The study highlights the need to recognize the role of comorbid factors in assessing CKD progression because they may add to the inflammatory burden.

6 Clinical Implications

These results have several clinical implications:

1. **Early Detection and Monitoring:** IL-33 may be a biomarker for early detection of CKD progression, particularly in high-risk patients. Serum levels of IL-33 might be useful for monitoring disease progression in addition to other standard markers of kidney function, including serum creatinine and GFR.
2. **Personalized Treatment:** The identification of patients with high levels of IL-33 may help to stratify patients according to their disease progression risk. This might help to develop more individualized treatment plans, such as increased surveillance or early treatment with anti-inflammatory drugs or other drugs that slow the progression of CKD.
3. **Potential Therapeutic Target:** The link between IL-33 levels and the severity of CKD suggests the potential of targeting IL-33 as a therapeutic target. Future studies investigating IL-33 inhibitors could provide new avenues for treating CKD by reducing inflammation and limiting fibrosis.

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