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ORIGINAL PAPER

Clinical significance of serum interleukin-6 levels in patients with chronic kidney disease

Renuka Charan Chokkavarapu [1], Parimala Bachireddy [1], Vaibhavi Reddy Billa [1], Yethindra Vityala [2]

[1] Maheshwara Medical College and Hospital, Hyderabad, Telangana, India
[2] Honorary International Faculty, AJ Research Centre, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

ABSTRACT

Introduction and aim. Elevated levels of interleukin-6 (IL-6) in serum and kidney tissues are associated with the development and progression of chronic kidney disease (CKD). Although the role of pro-inflammatory cytokines, such as IL-6, in the development of cardiovascular complications is well studied, the relationship between serum IL-6 levels and CKD markers remains unclear. This study investigated the clinical significance of serum IL-6 levels in patients with CKD.

Material and methods. Participants were divided into two groups based on estimated glomerular filtration rate (eGFR): group 1 (n=86) with eGFR >60 mL/min and group 2 (n=74) with eGFR <60 mL/min. The CKD Epidemiology Collaboration equation was used to calculate eGFR from serum creatinine and cystatin C levels to assess CKD severity.

Results. Systolic blood pressure was higher in Group 2 than in Group 1 (138±22 mmHg vs. 129±19 mmHg; p<0.05). Serum IL-6 levels were also higher in group 2 (3.095 [interquartile range: 1.528–6.547] pg/mL) than in group 1 (1.711 [interquartile range: 0.920–3.342] pg/mL; p <0.05). Serum IL-6 levels were strongly correlated with eGFR in multivariable-adjusted linear regression analysis.

Conclusion. IL-6 levels increased in patients with CKD with an eGFR <60 mL/min, and this increase was associated with eGFR and diastolic blood pressure.

Keywords. blood pressure, body mass index, chronic kidney disease, estimated glomerular filtration rate, interleukin, obesity

Introduction

The severity of chronic kidney disease (CKD) and occurrence of cardiovascular and cerebral complications should be assessed in a timely manner for primary and secondary prevention. Changes in interleukin (IL)-6 levels in both serum and kidney tissues are associated with the development and progression of CKD.[1-3] IL-6 is absent in healthy kidneys, and its normal level in blood plasma is 1–2 pg/mL.[3] Furthermore, it is produced by activated monocytes, macrophages, fibroblasts, endothelial cells, and mesangial and epithelial cells of the renal tubules.[4,5] It is a major mediator of acute inflammation.[6-8] Its secretion increases in acute inflammatory diseases, with serum concentrations reaching up to 1,000 pg/mL. In muscle and adipose tissues, it stimulates energy mobilization and increases body temperature. It is the main stimulator of the acute-phase protein synthesis in the liver.

Additionally, IL-6 stimulates the proliferation and differentiation of B and T cells as well as leukopoiesis. Patients with CKD frequently have high levels of IL-6 in their blood,[9] which occur mostly through increased production as a result of oxidative stress, chron-

Corresponding author: Yethindra Vityala, e-mail: yethindravityala10@gmail.com

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ic inflammation, and excess fluid in the body. Decreased IL-6 clearance, due to compromised renal function, leads to its accumulation. Cardiovascular events are associated with elevated IL-6.[10,11] Similarly, cardiovascular disease (CVD) is associated with CKD.[12] The relationship between CKD and CVD remains unclear; however, inflammation can be associated with it.[12] Inflammatory activity, as measured by biomarkers, may affect cardiovascular outcomes across renal function. Although the role of proinflammatory cytokines in the development of cardiovascular complications has been extensively studied, the relationship between serum IL-6 levels and CKD markers is not completely understood.

Aim

This study aimed to evaluate the clinical significance of serum IL-6 levels in patients with CKD.

Material and methods

Study design and participants

We enrolled 150 patients with CKD, of whom 64 (42.7%) were men and 86 (57.3%) were women, aged 18–80 years, with a mean age of 55.2±11.9 years at the time of diagnosis. Based on the estimated glomerular filtration rate (eGFR), the participants were divided into two groups: group 1 (n=82) included patients with eGFR >60 mL/min (50 women and 30 men), and group 2 (n=68) included those with eGFR <60 mL/min (32 women and 36 men). CKD was diagnosed based on the presence of signs of damage and/or decreased renal function.[13] The level of IL-6 was classified as <2 ng/L or ≥2 ng/L for categorical analysis, as the study median was 2.1 ng/L. To assess the severity of CKD, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI$_{cr\text{-}cys}$) equation was used to calculate the estimated glomerular filtration rate (eGFR) from serum creatinine and cystatin C, which were obtained prior to dialysis initiation.[14]

Inclusion and exclusion criteria

The inclusion criteria were the presence of signs of CKD and the exclusion criteria were the presence of thyroid pathology, fever, or stage 5G CKD; treatment with tocilizumab, itolizumab, sarilumab, satralizumab, siltuximab, and other drugs directed against the IL-6 receptor; diseases characterized by an increase in IL-6 in the blood regardless of kidney function, such as rheumatoid arthritis and systemic lupus erythematosus; and a history of treatment with corticosteroids and immunosuppressants. Body mass index (BMI) was calculated as follows: BMI (kg/m^2) = mass (kg)/height (m)^2. Systolic and diastolic blood pressure levels (SBP and DBP, respectively; mmHg) and heart rate (beats/min) were measured following the standard guidelines.[15] Participants with a history of any of the following conditions were considered to have CVD: hypertension, myocardial infarction, stroke, heart failure, angina pectoris, or angina/peripheral artery disease surgery.

Data collection and process

All the patients were tested for serum cystatin C (mg/L) and creatinine (μmol/L) levels. Low-weight proteinuria (mg/day) was evaluated by high-performance liquid chromatography (Thermo Fisher Scientific, Waltham, MA, United States). Serum IL-6 samples were obtained and analyzed using a human IL-6 enzyme-linked immunosorbent assay kit (Sigma–Aldrich, Burlington, MA, USA). The results were recorded using a chromate Microplate Reader (Awareness Technology Inc., Palm City, FL, USA). The normal upper limit for IL-6 level was set to 10 pg/mL.

Ethical approval

Confidentiality of patient data was maintained, and participants provided their informed consent. This study was approved by the Institutional Ethics Committee of Maheshwara Medical College and Hospital, Hyderabad on June 26, 2023 and was performed in accordance with the Declaration of Helsinki.

Statistical analysis

Data are expressed as n (%) or the mean±standard deviation. Student's t-test (parametric data) and Mann–Whitney U test (nonparametric data) was used to assess the significance of differences between the groups. Nonparametric data are expressed as the interquartile range (IQR; 25th–75th quartile). Pearson or Spearman correlation coefficients were used to measure the linear relationship between variables depending on the type of distribution. The adjusted odds ratios (ORs) between the highest and lowest tertiles of IL-6 levels in patients with CKD and controls were obtained using multivariate logistic regression. When comparing the groups based on the tertile of IL-6, our study was intended to have 80% statistical power to detect an odds ratio of 1.77 at a 2-sided $p<0.05$. Furthermore, at a 2-sided $p<0.05$, we have 80% statistical power to identify a mean difference of 0.3 standard deviations in IL-6 between the groups. In categorical analyses, IL-6 levels <2 ng/L were used as a reference to obtain Cox proportional hazard ratios (HRs) with 95% confidence intervals. Statistical significance was set at two-sided $p<0.05$. Statistical analyses were performed using Statistica 8.0 software package (TIBCO Software Inc., Palo Alto, CA, USA).

Results

All patients with CKD had comorbidities, including coronary heart disease, overweight or obesity, hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease, chronic pyelonephritis, and chronic glomerulonephritis. The number of patients with primary kidney pathologies did not differ significantly between

the two groups. Stages G1, G2, G3a, G3b, and G4 were observed in 25 (16.7%), 72 (48.0%), 28 (18.7%), 14 (9.3%), and 11 (7.3%) patients, respectively (Table 1).

Table 1. Number of patients with CKD at different stages*

Stages of CKD	GFR categories (ml/min/1.73 m²), description and range	n (%)
G1	Normal and high (≥90)	25 (16.7%)
G2	Mild reduction related to normal range (60–89)	72 (48.0%)
G3a	Mild-moderate reduction (45–59)	28 (18.7%)
G3b	Moderate-severe reduction (30–44)	14 (9.3%)
G4	Severe reduction (15–29)	11 (7.3%)

* CKD – chronic kidney disease, KDOQI – kidney disease outcomes quality initiative, GFR – glomerular filtration rate

The mean patient age differed significantly between the two groups ($p < 0.05$). The sex distribution differed significantly between the two groups, with a higher female predilection in group 1 than in group 2. BMI, DBP, and heart rate did not differ significantly between the two groups (Table 2). SBP was significantly higher in group 2 than in group 1 (138±22 mmHg vs. 129±19 mmHg; $p<0.05$). Serum IL-6 levels were significantly higher in group 2 (3.095 [IQR: 1.528–6.547] pg/mL) than in group 1 (1.711 [IQR: 0.920–3.342] pg/mL; $p < 0.05$). Thus, serum IL-6 levels were negatively correlated with eGFR ($r = -0.152$; $p=0.022$). Additionally, serum IL-6 levels were strongly associated with DBP ($r=0.125$, $p=0.048$).

Table 2. Clinical and laboratory parameters in groups 1 and 2[a]

Parameters	Group 1	Group 2
Age, years	54.6±13.8*	55.2±11.9*
Sex, female:male	61%:39%	47.1%:52.9%
SBP, mmHg	128 ±18	139±23*
DBP, mmHg	92±16	91±17
Heart rate, beats/min	81±15	81±14
Presence of CVD, n (%)	42 (28%)	39 (26%)
BMI, kg/m²2	29.3±5.1	29.2±4.6
IL-6, pg/mL	1.703 (IQR: 0.905–3.232)	3.082 (IQR: 1.510–6.458)*
Serum creatinine, µmol/L	75.8 (IQR: 61.1–91.3)	196 (IQR: 91.4–296.6)*
Serum cystatin C, mg/L	1.022 (IQR: 0.844–1.192)	2.242 (IQR: 1.436–2.964)*
Proteinuria, mg/d	79.4 (IQR: 70.2–94.1)	85.8 (IQR: 69.4–99.6)
eGFR, mL/min	80.2 (IQR: 73.6–87.9)	33.2 (IQR: 22.3–48.3)*

[a] data are expressed as mean±standard deviation or number (frequency) for binary variables, * – $p<0.05$. SBP – systolic blood pressure, DBP – diastolic blood pressure, CVD – cardiovascular disease, BMI – body mass index, IL-6 – interleukin-6, eGFR – estimated glomerular filtration rate, IQR – interquartile range

Multivariate-adjusted logistic regression analysis was used to calculate the ORs (with 95% confidence intervals) for CKD when comparing the two higher tertiles of serum IL-6 levels with the lower tertiles (Table 3). After adjusting for possible confounders, higher IL-6 levels were associated with the odds of developing CKD. Serum IL-6 levels were strongly correlated with eGFR in multivariable-adjusted linear regression analysis (Table 4).

Table 3. Odds ratios of CKD associated with the higher compared to the lowest tertiles of IL-6*

	Multivariable-adjusted[a]	
	OR (95 % CI)	p
IL-6 (µg/mL)		
≤1.2	1.0 (ref)	0.03
>1.2–2.6	1.2 (0.5–2.3)	
>2.6	2.5 (1.1–5.5)	

* CI – confidence interval; IL-6 – interleukin 6, [a] – adjusted for age, sex, systolic blood pressure, diastolic blood pressure, heart rate, presence of cardiovascular disease, body mass index, serum creatinine, serum cystatin C, and estimated glomerular filtration rate

Table 4. Multivariable-adjusted regression coefficients (95% CI) of eGFR associated with a SD difference in IL-6*

SD	eGFR, mL/min/1.73 m²2	
	β (95 % CI)	p
IL-6 (Log, 0.8 ng/mL)	−3.95 (−6.56 to −1.22)	0.0015

* SD – standard deviation, eGFR – estimated glomerular filtration rate, CI – confidence interval, IL-6 – interleukin-6

The event rates for major adverse CV events, such as CV death, myocardial infarction, and stroke, associated with the concentration of IL-6 in the CKD strata (eGFR >60 mL/min and <60 mL/min) are shown in Figure 1.

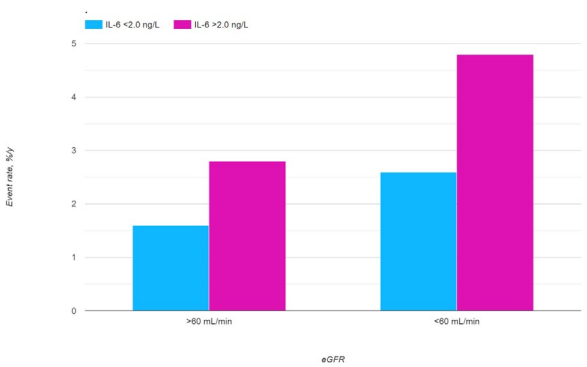

Fig. 1. Event Rates for major adverse CV events by CKD Strata

Discussion

In this study, we considered serum cystatin C in the eGFR assessment as the serum cystatin C level is a better indicator of renal function (GFR) than the serum creatinine level.[16,17] The prognoses of both CVD and CKD are associated with proinflammatory cytokines.[7,8] CKD is worsened by pro-inflammatory cytokines including IL-6.[18] Our study demonstrated a notable increase in IL-6 levels in patients with CKD. Furthermore, CKD severity directly correlated with IL-6 levels. These findings align with the results of prior extensive epidemiological investigations.[19,20] All kid-

ney cell types, such as podocytes, mesangial cells, endothelial cells, and epithelial cells, generate IL-6.[21] Podocytes, the central cell type involved in IL-6 signaling, express the IL-6 receptor. However, all kidney cells are susceptible to the harmful effects of IL-6 trans-signalling because they express Glycoprotein 130. Studies have shown that podocytes produce IL-6 in response to high glucose levels, and inhibiting IL-6 in rats prevents podocyte damage and death. Mesangial cells also recruit monocytes in response to high IL-6 levels by secreting chemoattractant protein 1. Although the IL-6 signaling pathway appears to be involved in only one type of kidney cell, both this pathway and the trans-signaling pathways are active in the development of diabetic nephropathy.[22] Renal abnormalities associated with high IL-6 expression and CKD include increased fibronectin expression in the mesangium, IL-6 mRNA levels, podocyte damage, glomerular hypertrophy, and endometrial alterations.

Elevated IL-6 levels are often linked to CKD because of their harmful effects on kidney cells. Research indicates that IL-6 levels increase in the early stages of CKD and are associated with higher mortality rates in late-stage CKD.[21,23] Moreover, reduced renal clearance of IL-6 suggests that it may be a symptom of impaired kidney function rather than a cause of the disease.

IL-6 secretion is moderately increased in chronic, mild inflammatory processes, which are characteristic of CKD.[6-8] Accordingly, in this study, patients with CKD showed significantly elevated IL-6 levels, and eGFR was significantly associated with serum IL-6 levels. eGFR is also significantly associated with tumor necrosis factor-alpha levels.[24]

Table 5. Correlation between interleukin-6 levels and clinical and laboratory parameters*

Parameters	IL-6, pg/mL	
	r	p
SBP, mmHg	0.071	0.297
DBP, mmHg	0.125	0.048
BMI, kg/m^2	0.013	0.843
Serum creatinine, mmol/L	0.019	0.695
Serum cystatin C, mg/L	0.041	0.516
Proteinuria, mg/d	0.017	0.604
eGFR, mL/min	0.152	0.022

* SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, eGFR – estimated glomerular filtration rate, IL-6 – interleukin-6

In the present study, the number of overweight or obese patients with T2DM was high. In an Egyptian study, IL-6 levels were elevated in patients with obesity and T2DM.[25] IL-6 elevation is accompanied by the proliferation of vascular smooth muscle cells and increased production of platelet growth factor.[26,27] In this study, proinflammatory cytokines were involved in the occurrence of cardiovascular complications in patients with CKD. IL-6 levels were not correlated with SBP; however, in group 2, the levels of proinflammatory cytokines and SBP were significantly higher. Furthermore, IL-6 levels were strongly associated with DBP (Table 5). The correlations between serum IL-6 levels and hemodynamic parameters are attributable to the induction of vasoconstriction and increased activity of the sympathetic nervous system caused by IL-6 and the association of elevated tumor necrosis factor-alpha levels with increased vascular stiffness.[28] Thus, the pathogenetic mechanisms of CKD progression involving proinflammatory cytokines, particularly IL-6, are extremely complex and diverse and require further research.

Conclusion

The mean patient age differed significantly between the two groups, with a higher female predilection in group 1 than in group 2. The study found that IL-6 levels were significantly higher in patients with CKD than in healthy individuals, and the levels were positively correlated with CKD severity. This study also found that IL-6 levels were significantly associated with cardiovascular events, and the odds of cardiovascular events were higher in patients with higher IL-6 levels.

Declarations

Funding

No funding was received for the study.

Author contributions

Conceptualization, R.C.C., P.B., V.R.B. and Y.V.; Formal Analysis, P.B., V.R.B., and Y.V.; Writing – Review & Editing, R.C.C., P.B., V.R.B. and Y.V.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Data are available from the corresponding author upon reasonable request.

Ethics approval

This study was approved by the Institutional Ethics Committee of Maheshwara Medical College and Hospital, Hyderabad on June 26, 2023.

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