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Original Article

The role of plasma angiotensin-converting enzyme and interleukin-6 levels on the prognosis of non-dialysis chronic kidney disease patients

[Papel de los niveles plasmáticos de la enzima convertidora de angiotensina e interleucina-6 en el pronóstico de los pacientes con enfermedad renal crónica no sometidos a diálisis]

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Abstract

Context: Inflammatory factors and oxidative stress were discovered to play significant roles in the progression of chronic kidney disease (CKD). There is, however, no research on the direct impact of high plasma angiotensin converting enzyme (ACE) and interleukin (IL)-6 levels on CKD prognosis, particularly in non-hemodialysis patients.

Aims: To investigate the potential role of plasma ACE and IL-6 levels in CKD prognosis.

Methods: A total of 75 non-dialysis CKD patients participated in this cross-sectional study. The estimated glomerular filtration rate (e-GFR) and albuminuria were used to determine the prognosis of CKD. The plasma ACE and IL-6 levels were measured using an enzyme-linked immunoassay (ELISA). Spearman's rank correlational analysis was used to examine the relationship between ACE and IL-6 plasma levels with the prognosis of CKD.

Results: The result showed a statistically significant correlation between age and plasma ACE ($p = 0.038$, $r = 0.241$), serum creatinine, and urine albumin-creatinine ratio with CKD prognosis ($p<0.0001$). A negative significant correlation was found between the e-GFR and CKD prognosis ($p<0.0001$). Additionally, there were also significant correlations between plasma ACE and IL-6 with CKD prognosis ($p = 0.021$, $r = 0.266$ and $p = 0.04$, $r = 0.238$, respectively). A significant positive correlation was also found between plasma ACE and IL-6 ($p = 0.024$, $r = 0.260$).

Conclusions: There was a significant correlation between plasma ACE and IL-6 levels with CKD prognosis. Further investigation revealed a statistically significant positive relationship between plasma ACE and IL-6 levels.

Keywords: angiotensin converting enzyme; chronic kidney disease; interleukin-6; non-hemodialysis; prognosis.

Resumen

Contexto: Se ha descubierto que los factores inflamatorios y el estrés oxidativo desempeñan un papel importante en la progresión de la enfermedad renal crónica (ERC). Sin embargo, no existen investigaciones sobre la repercusión directa de los niveles elevados de la enzima convertidora de angiotensina (ECA) e interleucina (IL)-6 en plasma sobre el pronóstico de la ERC, en particular en los pacientes que no están en hemodiálisis.

Objetivos: Investigar el papel potencial de los niveles plasmáticos de ECA e IL-6 en el pronóstico de la ERC.

Métodos: Un total de 75 pacientes con ERC no en diálisis participaron en este estudio transversal. Se utilizaron la tasa de filtración glomerular estimada (TFGe) y la albuminuria para determinar el pronóstico de la ERC. Los niveles plasmáticos de ECA e IL-6 se midieron mediante un inmunoensayo enzimático (ELISA). Se utilizó el análisis correlacional por rangos de Spearman para examinar la relación entre los niveles plasmáticos de ECA e IL-6 y el pronóstico de la ERC.

Resultados: El resultado mostró una correlación estadísticamente significativa entre la edad y la ECA plasmática ($p = 0,038$, $r = 0,241$), la creatinina sérica y el cociente albúmina-creatinina en orina con el pronóstico de la ERC ($p<0,0001$). Se encontró una correlación negativa significativa entre el e-GFR y el pronóstico de la ERC ($p<0,0001$). Además, también hubo correlaciones significativas entre la ECA y la IL-6 plasmáticas con el pronóstico de la ERC ($p = 0,021$, $r = 0,266$ y $p = 0,04$, $r = 0,238$, respectivamente). También se halló una correlación positiva significativa entre la ECA plasmática y la IL-6 ($p = 0,024$, $r = 0,260$).

Conclusiones: Existe una correlación significativa entre los niveles plasmáticos de ECA e IL-6 con el pronóstico de la ERC. Investigaciones posteriores revelaron una relación positiva estadísticamente significativa entre los niveles plasmáticos de ECA e IL-6.

Palabras Clave: enfermedad renal crónica; enzima convertidora de angiotensina; interleucina-6; no hemodiálisis; pronóstico.

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Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CVD: cardiovascular disease; CKD: chronic kidney disease; CKD-EPI: chronic kidney disease epidemiology collaboration; eNOS: endothelial nitric oxide synthase; ELISA: enzyme-linked immunoassay; ESRD: end-stage renal disease; e-GFR: estimated glomerular filtration rate; IL-6: interleukin-6; KDOQI: Kidney Disease Outcomes Quality Initiative; RAAS: renin-angiotensin-aldosterone system; UACR: Urine Albumin-Creatinine Ratio.

INTRODUCTION

Chronic kidney disease (CKD) is a life-threatening condition that has long been a worldwide health problem with substantial care and economic burden, affecting 8–16% of the global population (Chen et al., 2019). CKD is defined as a progressive and irreversible decline in renal function indicated by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 that persists for longer than three months (Levin et al., 2013). It is recognized that decreased GFR in CKD increases the risk of cardiovascular events, hospitalization, and mortality (Bikbov et al., 2020). In CKD, the decline in kidney function has reached the "point of no return," indicating that the decline in renal function is unavoidable and irreversible over time (Yan et al., 2021).

Several heterogeneous factors, such as lifestyle and systemic and metabolic disorders, including diabetes, hypertension, and cardiovascular disease, influence the progression of CKD (Lee et al., 2021). Evidence revealed that inflammatory factors and oxidative stress both play a significant role in the course of CKD (Duni et al., 2019; Su et al., 2017). This process is intimately associated with the renin-angiotensin-aldosterone system (RAAS). Angiotensinogen is degraded by renin to produce angiotensin (Ang) I, which is subsequently converted by the angiotensin-converting enzyme (ACE) to Ang II, which stimulates the inflammatory response by releasing interleukin-6 (IL-6) (Dai et al., 2019). Furthermore, IL-6 promotes the progression of the disease by worsening renal injury, such as by promoting renal fibrosis and commencing its consequences. IL-6 causes renal endothelium damage via decreased production of endothelial nitric oxide synthase (eNOS) and adiponectin (anti-atherogenic adipokine) (Amador-Martínez et al., 2019; Magno et al., 2019).

Past studies reported that IL-6 increased the 5-year risk of all-cause death in non-hemodialysis CKD patients (Kamińska et al., 2019); meanwhile, studies on hemodialysis patients showed consistent results in which an increase in IL-6 was associated with coronary artery calcification and mortality risk (Roy and Rosas, 2021). On the other hand, it has been observed that ACE inhibition reduces proteinuria in renal disease (Perna et al., 2000), an essential indication of CKD development (Zhong et al., 2017). However, research on the direct impact of high plasma IL-6 and ACE levels on the prognosis of CKD, particularly in non-hemodialysis patients, is sparse. Therefore, this study aimed to determine the potential role of plasma ACE and IL-6 levels on the prognosis of CKD, which needs to be investigated further to gain a comprehensive understanding of renal disease and determine the optimal treatment.

MATERIAL AND METHODS

Subjects and ethics

This study analyzed the role of plasma ACE and IL-6 levels on the prognosis of non-dialysis CKD patients. This study enrolled 75 CKD patients from Universitas Airlangga Hospital, Surabaya, Indonesia. The inclusion criteria were non-dialysis CKD patients aged 30–80 years. The exclusion criteria were CKD patients with unstable conditions. This study had been approved by the local ethics committee (ethical clearance number: 146/KEP/2021), and all involved participants had agreed to sign written informed consent.

Sample collection

Plasma was isolated from the peripheral blood (5 mL) of all patients. The prognosis of CKD was determined by the estimated glomerular filtration rate (e-GFR) and albuminuria. The risk outcome of CKD was grouped based on low, moderate, high, and very high risk (International Society of Nephrology, 2013).

Measurements

The plasma ACE levels were analyzed via enzyme-linked immunoassay (ELISA) procedure using human ACE (angiotensin I-converting enzyme) ELISA kit (Elabscience, USA) and IL-6 ELISA kit (Elabscience, USA) according to the manufacturer's instructions.

Data analysis

The baseline characteristics of the samples were analyzed descriptively. The mean and standard deviation (SD) were used to analyze numerical data, and the percentage was used to determine the frequency. To determine the correlation between ACE and IL-6 plasma levels with the progression of CKD, Spearman's rank correlational analysis was used. A p-value <0.05 was considered as statistical significance. SPSS version 26 was used as the software for the analysis.

Table 1. Sample characteristics in this study.

Variable	Value (n = 75)
Gender, male (%)	38 (50.7)
Age (years)	58.03 ± 7.092
No Diabetes, n (%)	17 (22.7)
Diabetes < 10 years, n (%)	41 (54.7)
Diabetes 10-20 years, n (%)	12 (16.0)
Diabetes > 20 years, n (%)	5 (6.7)
No hypertension, n (%)	10 (13.3)
Hypertension <10 years, n (%)	56 (74.7)
Hypertension 10-20 years, n (%)	7 (9.3)
Hypertension >20 years, n (%)	2 (2.7)
Non-smoker, n (%)	53 (70.7)
Current Smoker, n (%)	4 (5.3)
Former Smoker, n (%)	18 (24.0)
CKD stage 2, n (%)	3 (4.0)
CKD stage 3, n (%)	38 (50.7)
CKD stage 4, n (%)	21 (28.0)
CKD stage 5, n (%)	13 (17.3)
Body mass index (kg/m^2)	25.96 ± 5.163
Systolic blood pressure (mm Hg)	143.51 ± 23.464
Diastolic blood pressure (mm Hg)	80.80 ± 12.218
Total cholesterol (mg/dL)	183.92 ± 51.547
High-density lipoprotein (mg/dL)	39.55 ± 12.249
Serum creatinine (mg/dL)	2.67 ± 1.680
e-GFR (mL/min/1.73 m^2)	31.44 ± 15.005
Urine albumin-creatinine ratio (mg/g)	649.09 ± 969.775
Plasma ACE (pg/mL)	4076.52 ± 1200.495
Plasma IL-6 (pg/mL)	9.64 ± 28.002
Prognosis of CKD	
Low risk	2 (2.7)
Moderate risk	5 (6.7)
High risk	15 (20)
Very high risk	53 (70.7)

RESULTS

The mean age of all the seventy-five non-dialysis CKD participants in this study was 58.03 ± 7.092 years, with mostly male (50.7%). The medical history showed that 77.3% of the patients had diabetes, 87.7% had hypertension, and 70.7% were non-smokers (Table 1). Most patients had a very high-risk prognosis of CKD (70.7%).

Correlational analyses between plasma ACE and IL-6 levels with several variables were conducted in this study, as shown in Table 2. The results revealed a statistically significant correlation between age and plasma ACE ($p = 0.038$, $r = 0.241$). There was a positive significant correlation between serum creatinine and urine albumin-creatinine ratio with CKD prognosis ($p<0.0001$). A negative significant correlation was found between the estimated glomerular filtration rate (e-GFR) and CKD prognosis ($p<0.0001$).

Table 2. Correlational analysis for variables in this study with plasma ACE, IL-6, and prognosis of CKD.

Variable	Plasma ACE		Plasma IL-6		Prognosis of CKD	
	r	p	r	p	r	p
Age	0.241*	0.038*	0.100	0.393	-0.128	0.273
Body Mass Index (kg/m^2)	-0.201	0.084	-0.170	0.144	-0.093	0.426
Systolic blood pressure (mm Hg)	-0.035	0.765	-0.144	0.217	0.107	0.361
Diastolic blood pressure (mm Hg)	0.045	0.702	-0.144	0.217	-0.091	0.437
Total Cholesterol (mg/dL)	0.020	0.864	-0.004	0.975	0.150	0.199
High Density Lipoprotein (mg/dL)	-0.217	0.061	-0.139	0.235	-0.223	0.054
Serum creatinine (mg/dL)	0.104	0.376	0.188	0.106	0.630*	0.000*
e-GFR (mL/min/1.73m2)	-0.11	0.348	-0.200	0.085	-0.661*	0.000*
Urine Albumin-Creatinine Ratio (mg/gram)	0.132	0.26	0.150	0.199	0.582*	0.000*

*Significant if p<0.05.

Table 3. Correlation between plasma ACE and IL-6 with the prognosis of CKD.

Variable	Plasma ACE		Plasma IL-6	
	r	p	r	p
Prognosis of CKD	0.266*	0.021*	0.238*	0.04*

*Significant if p<0.05.

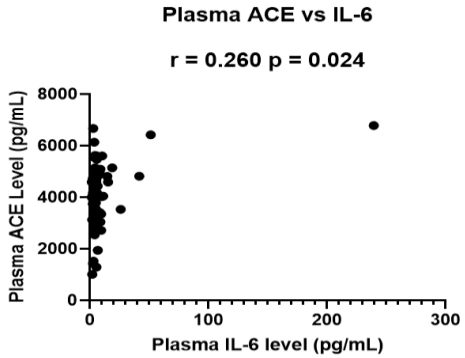

Figure 1. Correlations between ACE levels and IL-6 levels with Spearman analysis.

The dots show a linear relationship between plasma ACE and IL-6 levels, meaning that an increase in plasma ACE levels will result in an increase in plasma IL-6 levels as well.

Correlational analyses between plasma ACE and IL-6 with the prognosis of CKD were conducted in this study (Table 3). There were significant correlations between plasma ACE and IL-6 with CKD prognosis (p = 0.021, r = 0.266 and p = 0.04, r = 0.238, respectively).

A correlation analysis between the two variables was performed to robustly analyze the correlation between plasma ACE and IL-6 levels, as shown in Fig. 1. Intriguingly, there was a significant positive correlation between plasma ACE and IL-6 (p = 0.024, r = 0.260).

DISCUSSION

Chronic kidney disease (CKD), a growing worldwide health problem, can progress to a serious end-stage renal disease requiring dialysis or a kidney transplant (Imig and Ryan, 2013). However, the underlying basis for its severity and progression to the more serious end-stage renal disease remains poorly understood. As the inevitable side effects and limitations in treatment with ACE inhibitor (ACEI)/ angiotensin II receptor blockers (ARB) resulted in the lack of available medicine in some situations, it is important to excavate potential targets to supplement the defects of a classical axis. Therefore, this study investigated the role of plasma ACE and IL-6 levels

on the prognosis of CKD among non-hemodialyzed patients to provide evidence regarding the novel treatment of CKD. Results indicated that the correlations between plasma ACE and IL-6 to CKD prognosis were weak but statistically significant. In addition, plasma ACE also significantly correlates to IL-6 levels, yet the correlation also seems weak.

ACE, a key enzyme of the classical axis within the RAAS, converts Ang I to Ang II, which promotes water-sodium retention, vasoconstriction, induction of reactive oxygen species (ROS), apoptosis, and stimulation of extracellular matrix synthesis (Shi et al., 2020). Several previous investigations have revealed an increase in plasma ACE levels in CKD patients (Anguiano et al., 2015; Yang et al., 2017). In accordance with this study's findings, the result of another study by Miura et al. (1984) showed that higher ACE levels in CKD patients are possibly the result of vascular endothelial injury. Subsequently, the increased ACE in CKD patients and the consequent elevation of Ang II can promote the progression of cardiovascular disease (CVD) and renal disease. Even though this proposition is still limited, the expanding knowledge of the complex nature of RAAS implies its implications on CKD progression, particularly in CKD patients with a history of CVD, as demonstrated in this study populations. In addition, this study found a minor positive correlation between advanced age and higher plasma ACE levels that was statistically significant. In contrast, Anguiano et al. (2015) found an inverse correlation between advanced age and ACE activity in stage 3-5 CKD patients. Other research, however, has not shown a correlation between circulating ACE activity and age (Miura et al., 1984; Soler et al., 2012; Yang et al., 2017). Aside from the evidence that ACE I/D polymorphism can directly affect higher ACE concentrations in plasma (Dai et al., 2019; Susilo et al., 2022), we surmise that the incongruences seen in this study may be attributable to the effect of RAAS inhibition on circulating ACE levels. In addition, different sample characteristics may potentially contribute to this discrepancy, as the majority of CKD patients in the present study have diabetes and hypertension.

The KDOQI guidelines recommend screening high-risk patients with a urinalysis, a urine albumin-creatinine ratio (UACR), measurement of serum creatinine, and estimation of GFR preferably by chronic kidney disease epidemiology collaboration (CKD-EPI) equation (Vaidya and Aeddula, 2022). In this study, there was a statistically significant positive correlation between serum creatinine and UACR to CKD prognosis. In contrast, a negative correlation was found between eGFR and CKD prognosis. The result is consistent with the study by Chang et al. (2019), which reported that every increase of 1 mg/dL of serum creatinine would significantly increase the risk of ESRD (HR 1.24, 95%CI [1.22–1.27]). Higher UACR was also associated with a significantly higher cumulative incidence of CKD progression in both male and female patients, as reported by Tang et al. (2022). According to the 2012 KDIGO guideline, the prediction of CKD prognosis is based on the assessment of the eGFR and urinary albumin excretion (UAE) (Levin et al., 2013). UACR is recommended by national guidelines to assess albuminuria as the ratio of urinary albumin to creatinine owing to its steady excretion pattern, which corrects for urine volume (Christofides and Desai, 2021; Lambers Heerspink et al., 2010). Notably, albumin excretion is highly varied between individuals, and more importantly, the prevalence of pathological albuminuria increases with decreasing eGFR (Miller et al., 2009; Rodríguez-Ortiz et al., 2018). Consequently, these parameters may not be precise enough to predict CKD prognosis at early CKD stages.

Intriguingly, the analysis revealed a significant correlation between plasma ACE and IL-6 levels to CKD prognosis. Similar to the present study, Shi et al. (2020) discovered that serum ACE progressively increased with the deterioration of renal function. Several prior investigations revealed that elevated plasma IL-6 levels are frequently detected in CKD patients as a result of increased synthesis due to oxidative stress, chronic inflammation, and fluid overload (Su et al., 2017; Zhang et al., 2012). Likewise, a previous cross-sectional study evaluating plasma IL-6 levels in patients at earlier CKD stages (3–5) reported that this interleukin was considerably higher in CKD patients compared to healthy controls, but had no association with the eGFR (Oberg et al., 2004). Although the correlations in this study demonstrated statistical significance, it is notable that both correlations were weak. Prior research demonstrated that Ang II, the primary biological component of the classical axis, played a central mediator in numerous pathophysiological processes, including hypertension, oxidative stress, renal inflammation, and fibrosis (Kagami, 2012). Further, excessive oxidative stress might also be a significant contributor to hypertension, renal ischemia, glomerular damage, inflammation, and endothelial dysfunction (Krata et al., 2018). A study by Zhang et al. (2012) offered evidence for potential mechanisms underlying Ang II-induced renal fibrosis. Their study specifically demonstrated that elevated IL-6 contributed to Ang II-mediated induction of multiple fibrotic genes and endothelin-1 synthesis in the kidneys, which may lead to renal injury and renal fibrosis. Considering these findings, it is surmised that additional parameters, such as Ang II and oxidative stress, may correlate to CKD progres-

sion more strongly than plasma ACE and IL-6 levels, as they can directly affect the kidney's signaling pathway. However, further study is required to corroborate these findings.

The elevated inflammatory response associated with CKD is considered to have contributed to the pathogenesis of the disease. According to a previous study, increasing IL-6 production may result in mesangial cell proliferation, leukocyte proliferation and infiltration, epithelial cell apoptosis, and endothelial cell damage (Carrero and Stenvinkel, 2010). As the RAAS is elevated in CKD patients (Khosla et al., 2009; Zhang et al., 2012), further analysis in this study revealed that plasma ACE levels exhibited a statistically positive correlation to IL-6 levels, albeit a weak one. Findings provided in the previous in vivo study may elaborate on the weak correlation found in the analysis. Instead of ACE, Ang II can directly promote IL-6 expression in human endothelial cells and is regarded as a mediator of Ang II-induced kidney damage (Zhang et al., 2012). Additionally, the elevated IL-6 contributed to the enhanced expression of particular genes in the kidney that contribute directly to the advancement of renal fibrosis and damage (Lee et al., 2006). Indeed, IL-6 may potentially hasten the progression of CKD not only by aggravating kidney injury as previously described but also by initiating its complications, especially CVD (Su et al., 2017). An earlier clinical investigation has confirmed that Ang II can induce IL-6 and oxidative stress in humans via a mineralocorticoid receptor-dependent and mineralocorticoid receptor-independent pathway, respectively (Luther et al., 2006). In light of the findings, this study supports a central role for ACE and IL-6 in Ang II-induced kidney damage and highlights a potential direct contribution to the subsequent development of renal fibrosis. These findings complement prior studies regarding the implications of therapeutic possibilities of targeting these signaling pathways to attenuate the progression of CKD.

Inevitably, this study contains limitations that should be addressed when assessing the significance of the data. This cross-sectional study had a relatively small sample size, which may have limited its statistical power. Due to the lack of research examining the effect of plasma ACE and IL-6 levels on the development of non-dialysis CKD patients, this sample size is still suitable to generate correlation analysis. Nevertheless, a larger sample would possibly have strengthened this study's findings. Additionally, a longitudinal study design would have likely resulted in additional data.

CONCLUSION

This study demonstrates a substantial correlation between plasma ACE and IL-6 levels and the prognosis of CKD, highlighting its role in monitoring disease progression. Further analysis demonstrated a statistically significant positive correlation between plasma ACE and IL-6 levels. These findings corroborate previous studies regarding the therapeutic potential of targeting these signaling pathways to slow the progression of CKD. However, more prospective investigations and follow-ups are warranted to validate these findings and elucidate the role of ACE and IL-6 as predictors of CKD progression in non-hemodialysis patients.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Susilo H	Thaha M	Pikir BS	Alsagaff MY	Suryantoro SD	Wafa IA	Pratama NR	Budi DS	Wiratama BS	Wungu CDK
Concepts or ideas	x	x	x							
Design	x									
Definition of intellectual content		x	x							
Literature search				x	x	x	x	x		
Experimental studies										x
Data acquisition										x
Data analysis									x	
Statistical analysis									x	
Manuscript preparation				x	x	x	x	x		x
Manuscript editing	x									x
Manuscript review	x	x	x	x	x	x	x	x	x	x

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