

Interleukin-6 and Procalcitonin as Potential Predictors of Acute Kidney Injury Occurrence in Patients with Sepsis

Liliriawati Ananta Kahar^{*1}

Abstract

Background: Timely treatment actions are critical for the early detection of sepsis in patients at high risk of acute kidney injury (AKI). This study aimed to investigate inflammatory biomarkers as potential predictors of AKI in patients with sepsis.

Methods: This prospective observational cohort study included 300 patients who received treatment in the Intensive Care Unit (ICU) of hospitals located in Padang, Indonesia. We obtained blood samples to evaluate inflammatory biomarkers, such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and procalcitonin (PCT). AKI development was predicted using multivariate logistic regression analysis to identify independent inflammatory biomarkers.

Results: IL-6, TNF- α , and PCT levels were markedly elevated in patients who developed AKI compared with those who did not ($p < 0.001$). The multivariable logistic regression analysis showed that IL-6 (OR = 1.82; 95% CI = 1.25-2.66; $p = 0.002$) and PCT (OR = 2.45; 95% CI = 1.58-3.80; $p < 0.001$) can both predict the development of AKI in patients with sepsis. The area under the curve (AUC) for IL-6 was 0.70, whereas the AUC for PCT was 0.81. These findings demonstrate that IL-6 and PCT exhibit strong predictive abilities for the onset of AKI in patients with sepsis. The ideal threshold values for IL-6 and PCT were 12.91 pg/mL and 1.79 ng/mL, respectively.

Conclusion: IL-6 and PCT can serve as inflammatory biomarkers for predicting the occurrence of AKI in patients with sepsis.

Keywords: Acute Kidney Injury, Biomarkers, Intensive Care Units, Interleukin-6, Sepsis.

Introduction

Sepsis, a disease characterized by organ dysfunction due to the body's uncontrolled response to infection, continues to be a pressing global health issue (1,2). Despite advancements in critical care techniques and our understanding of the pathophysiology of sepsis, the fatality rates associated with sepsis remain elevated, ranging from 20% to 50% (3). Sepsis is a complicated condition that can causes many problems, such as acute kidney injury (AKI) (4). AKI, or acute kidney injury, in sepsis patients greatly increases the likelihood of mortality, extends the duration of intensive care unit admission, and places a considerable strain on the healthcare system

(4,5). The complex relationship between sepsis and AKI involves different pathophysiological pathways, such as low blood flow to the kidneys, inflammation, injury from reperfusion, and medication toxicity. Renal hypoperfusion, a common occurrence in sepsis caused by low blood pressure, low blood volume, and impaired heart function, can lead to renal ischemia and tubular cell damage. Sepsis induces an unregulated systemic inflammatory response that leads to the secretion of many inflammatory agents, including cytokines, chemokines, and reactive oxygen species (5). Drug toxicity, particularly caused by the use of nephrotoxic antibiotics

1: Department of Anesthesiology and Intensive Care, Faculty of Medicine, Andalas University, Dr. M. Djamil General Hospital.

*Corresponding author: Liliriawati Ananta Kahar; Tel: +62 81363279385; E-mail: liliriawati@med.unand.ac.id.

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and vasopressor drugs, is an additional risk factor for AKI in patients with sepsis (6). Vasopressor drugs can lower blood flow to the kidneys and increase the risk of renal ischemia, whereas aminoglycoside antibiotics can cause acute tubular necrosis (4-6).

Timely and vigorous treatment is crucial for the early detection of sepsis in patients at high risk of developing AKI (6,7). Traditional methods for diagnosing AKI, such as blood creatinine monitoring and urine output measurement, are frequently slow and may not effectively identify early kidney injury. Hence, novel biomarkers that can precisely and expeditiously forecast the occurrence of AKI in sepsis patients are urgently required (8). Several inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and procalcitonin (PCT), have been shown to predict AKI in sepsis (9-11). Multiple studies have examined the significance of inflammatory biomarkers in predicting the occurrence of AKI in individuals with sepsis (9-12). Although these inflammatory biomarkers can predict acute kidney injury (AKI) in sepsis, they still face several obstacles and restrictions. First, it is crucial to acknowledge that these inflammatory indicators do not exclusively target AKI, as they can also increase in other inflammatory conditions. Furthermore, the ideal threshold values for predicting AKI can vary among different patient groups. Moreover, further research is necessary to determine the optimal timeframe for evaluating these inflammatory biomarkers to predict AKI. This study aimed to fill this knowledge gap by examining the role of inflammatory biomarkers in forecasting the occurrence of AKI in patients in Indonesia's intensive care unit setting. Additionally, we aimed to identify inflammatory biomarkers that can independently predict the development of AKI while considering probable factors that could influence the results. This study aimed to investigate inflammatory biomarkers as potential predictors of AKI in patients with sepsis

Materials and Methods

Patients

This prospective observational cohort study was conducted at three referral hospitals in Padang City, Indonesia: Dr. M. Djamil General Hospital, Dr. Rasidin General Hospital, and Siti Rahmah Islamic Hospital. These hospitals were chosen due to their status as the primary referral centers for sepsis patients in the region. The study included adult patients (aged 18 years or older) who met the Sepsis-3 require the presence of a suspected or confirmed infection and an increase in the Sequential Organ Failure Assessment (SOFA) score by at least two points (13). The exclusion criteria were pregnancy, chronic kidney disease stage 5 (CKD-5), kidney transplantation, recent occurrence of acute renal illness within the past 3 months, and incapacity or unwillingness to provide informed consent. A total of 300 participants were enrolled in the study.

Demographic, clinical, and laboratory data were obtained from the patient's medical records. Demographic data included age, gender, and the presence of comorbidities such as hypertension, diabetes mellitus, and coronary heart disease. Clinical data encompassed essential physiological measurements, such as vital signs and illness severity as determined by the Sequential Organ Failure Assessment (SOFA) score. In addition, the data included information regarding the origin of the infection and the specific treatments delivered.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2012 defined AKI (14,15). The KDIGO criteria were established by evaluating alterations in serum creatinine levels and/or urine output over a span of 48 hours. The KDIGO criteria for acute kidney injury are as follows: an increase in serum creatinine of at least 0.3 mg/dL (equivalent to 26.5 μ mol/L) over a 48-h period; an increase in serum creatinine of at least 1.5 times the baseline value within the last seven days; or a urine output of less than 0.5 mL/kg/hour for a

duration of six hours. Patients are diagnosed with AKI if they meet any of the aforementioned criteria. Assessing the extent of increase in blood creatinine levels or decrease in urine output determines the stage of AKI.

Biochemical analysis

Inflammatory biomarkers; IL-6, TNF- α , and PCT were assessed using the enzyme-linked immunoassay (ELISA) (CloudClone, Hangzhou, China). We collected peripheral venous blood samples at two specific points in time: Time point 1 (T1) was the patient's initial admission to the ICU (baseline), and Time point 2 (T2) was the third day of treatment in the ICU. We collected blood samples in ethylenediaminetetraacetic acid (EDTA) tubes (Sunway Co., Jakarta, Indonesia) and centrifuged them to separate the plasma. The plasma was held at -80 °C until analysis.

Different cells generate IL-6 as a type of proinflammatory cytokine in response to infection and injury. IL-6 is crucial in stimulating and increasing the number of immune cells, as well as in generating acute-phase proteins. TNF- α is a proinflammatory cytokine that is synthesized by macrophages and monocytes in response to infection and damage. TNF- α exerts many effects on various cells and tissues, such as triggering programmed cell death, enhancing blood vessel permeability, and promoting the synthesis of other cytokines. The C cells of the thyroid gland synthesize PCT, a hormone precursor that is eventually converted into calcitonin. However, in the context of bacterial infections, it is worth noting that cells located outside the thyroid gland can also produce PCT. Compared with other inflammatory biomarkers, PCT is considered a more precise biomarker for bacterial infections.

Statistical analysis

Data analysis were conducted using SPSS software version 26.0 (IBM, New York, USA). The data are reported as the mean $\pm$

standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and as number (%) for categorical variables. The continuous variables between two groups was compared using an independent t-test or a Mann-Whitney U test. The chi-square test or Fisher's exact test was used to compare categorical variables between two groups. Using multivariate logistic regression analysis, we identified inflammatory biomarkers that could autonomously predict the occurrence of AKI. This was performed while accounting for other potential risk variables, including age, gender, comorbidities, and SOFA score. A p value of less than 0.05 was considered statistically significant.

Results

This study included a group of 300 patients with sepsis who received treatment in hospital ICUs in Padang City, Indonesia, from January 2023 to December 2023. Table 1 shows a comparison of the characteristics of sepsis patients in two groups: those who experienced acute kidney injury (AKI) and those who did not (non-AKI) in hospitals in Padang City, Indonesia. The ages of patients in both groups were relatively comparable. This implies that age does not play a significant role in determining the risk of AKI in sepsis. While older age often correlates with reduced kidney function, it appears that other factors exert a more significant influence in sepsis. The gender distribution was comparable in both groups. Men and women have an equal likelihood of developing AKI when they have sepsis. Patients with history of hypertension are more likely to get AKI when they have sepsis ($p < 0.05$). Patients with diabetes mellitus exhibited a higher susceptibility to acute kidney injury (AKI) during sepsis, as indicated by a statistically significant p-value of 0.049. However, the observed difference was not substantial. Additionally, there was an inclination for those with heart disease to have a higher vulnerability to AKI during sepsis ($p = 0.052$), although this disparity did not reach statistical significance. There was no significant

difference in the source of infection between the two groups. These findings indicate that the site of the original infection does not have a direct

impact on the likelihood of developing acute kidney injury (AKI).

Table 1. Demographic and clinical characteristics of sepsis patients.

Characteristics	AKI	Non-AKI	p-value
Age (Mean±SD)	54.6 ± 14.01	56.91 ± 14.7	0.098
Gender			
Men	64 (53.0%)	92 (51.0%)	0.121
Women	56 (47.0%)	88 (49.0%)	
History of hypertension			
Yes	61 (51.0%)	132 (73.0%)	0.034*
No	59 (49.0%)	48 (27.0%)	
History of diabetes mellitus			
Yes	84 (70.0%)	135 (75.0%)	0.049*
No	36 (30.0%)	45 (25.0%)	
History of heart disease			
Yes	85 (71.0%)	146 (81.0%)	0.052
No	35 (29.0%)	34 (19.0%)	
SOFA Score			
Mean ± SD	8.3±1.1	8.5±1.2	0.813
Median (IQR)	8 (6-10)	7 (5-9)	
Infection sources			
Pneumonia	60 (50.0%)	98 (54.0%)	0.765
Urinary tract infection	30 (25.0%)	41 (23.0%)	
Intraabdominal infection	15 (12.0%)	21 (12.0%)	
Others	15 (12.0%)	20 (11.0%)	

Notes: *p-value <0.05; SD: standard deviation; IQR: interquartile range; SOFA=sequential organ failure assessment.

The levels of the inflammatory biomarkers IL-6, TNF- α , and PCT were compared between the two groups of sepsis patients: those who developed acute kidney injury (AKI) and those who did not (non-AKI) (Fig. 1). The findings revealed substantial disparities between the two groups. The AKI group had a median IL-6 level of 13.1 pg/mL (IQR 11.1–15.6 pg/mL), whereas the non-AKI group had a lower median IL-6 level of 7.2 pg/mL (IQR 5.8–8.8 pg/mL) (Fig. 1A). The TNF- α biomarker exhibited a comparable pattern. The AKI group had a median TNF- α level of 7.0 pg/mL (with an IQR of 6.1–8.5 pg/mL), whereas the non-AKI group exhibited a lower median

TNF- α level of 5.5 pg/mL (IQR 4.7–6.3 pg/mL) (Fig. 1B). The PCT biomarker was associated with the most notable disparities. In the AKI group, the median PCT level was 2.7 ng/mL and the IQR 2.3–3.2 ng/mL (Fig. 1C). This was significantly higher than the non-AKI group, which had a median level of 1.3 ng/mL with an IQR of 1.1–1.5 ng/mL. The levels of inflammatory biomarkers (IL-6, TNF- α , and PCT) are much higher in sepsis patients who develop AKI than in sepsis patients who do not develop AKI. This suggests that this inflammatory biomarker can serve as an indicator of the risk of AKI in individuals with sepsis.

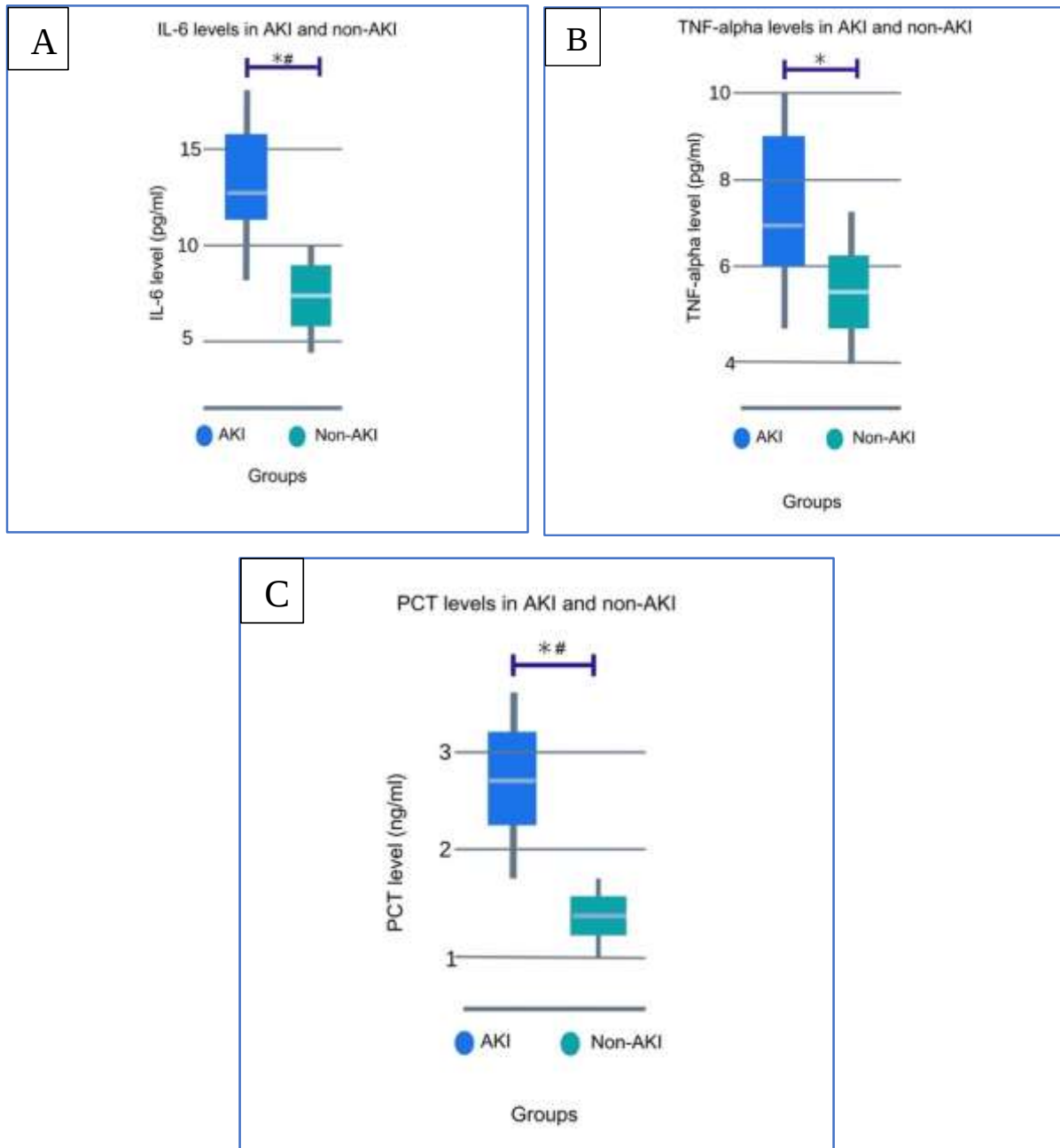


Fig. 1. Comparison of IL-6 (A), TNF- α (B) and PCT (C) levels between groups. Note: *bivariate analysis, p-value <0.05; #multivariate analysis, p-value <0.05; IL-6: Interleukin-6; TNF- α : Tumor necrosis factor- α ; PCT: procalcitonin.

A multivariate logistic regression analysis (Table 2) was conducted to identify inflammatory biomarkers that can predict the development of AKI in individuals with sepsis. The multivariate logistic regression model was modified to account for age, gender, coexisting medical conditions (hypertension, diabetes mellitus, heart disease), and SOFA score. Based on the multivariable logistic regression analysis, IL-6 (OR 1.82; 95% CI 1.25-2.66; p

= 0.002) and PCT (OR 2.45; 95% CI 1.58-3.80; p < 0.001) were found to be independent predictors of AKI in patients with sepsis. Specifically, for every one-unit increase in IL-6 levels equivalent to one standard deviation, there was an 82% increase in the risk of AKI. Similarly, for every one-unit increase in PCT levels equivalent to one standard deviation, there was a 145% increase in the risk of AKI, considering other parameters in the model.

Table 2. Multivariate logistic regression analysis for predicting AKI.

Predictor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Interleukin-6	1.82	1.25-2.66	0.002*
Procalcitonin	2.45	1.58-3.80	0.001*
Age	1.03	0.99-1.07	0.128
Gender (men)	1.15	0.72-1.83	0.551
Hypertension	1.38	0.86-2.21	0.185
Diabetes mellitus	1.52	0.94-2.46	0.089
Heart disease	1.27	0.75-2.14	0.372
SOFA score	1.18	1.08-1.29	0.076

Note: *p-value<0.05 (statistically significant).

The ROC (Receiver Operating Characteristic) curve is a statistical tool used to assess the effectiveness of a diagnostic tests. The area under ROC curve (AUC) quantifies the diagnostic test precision. A diagnostic test with a high AUC value is

more accurate. The study's results indicate that AUC for IL-6 was 0.70, whereas the AUC for PCT was 0.81 (Fig. 2). These findings demonstrate that IL-6 and PCT exhibit strong predictive abilities for developing AKI in patients with sepsis.

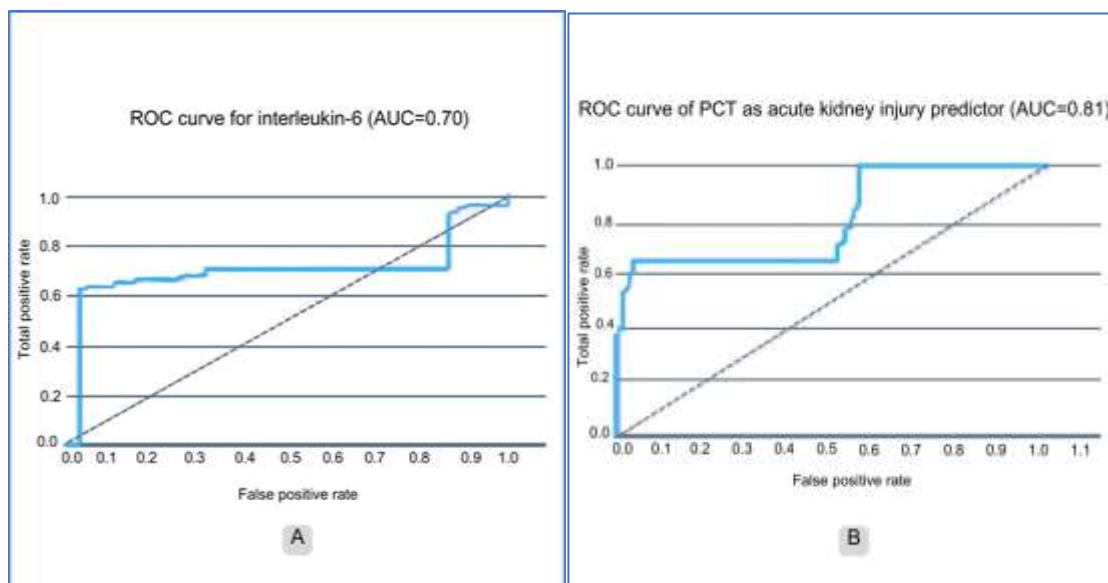


Fig. 2. ROC curves of inflammation biomarkers. (a) IL-6 ROC curve; (b) PCT ROC curve. Notes: IL-6: Interleukin-6; PCT: procalcitonin; ROC: Receiver operating characteristic.

The optimal cutoff value for IL-6 was 12.91 pg/mL and PCT cutoff value was 1.79 ng/mL (table 3). The cutoff value was established by ROC curve analysis using the Youden's index with the objective of optimizing the sensitivity and specificity of predictions. IL-6 is a cytokine with proinflammatory properties that has a significant impact on the overall inflammatory response in sepsis. Procalcitonin (PCT) is an

indicator of both bacterial infection and widespread inflammation in the body. Increased IL-6 levels can suggest increased inflammation and greater damage to tissues, including the kidneys. Elevated PCT levels indicate an increased susceptibility to AKI in sepsis patients. This cutoff value can serve as a clinical tool for identifying patients with sepsis who are at increased risk for AKI.

Table 3. Optimal cutoff of inflammation biomarkers.

Biomarkers	Optimal cutoff	Interpretations
IL-6	12.91 pg/mL	Values exceeding this threshold indicate an elevated risk of acute kidney injury.
PCT	1.79 ng/mL	Values exceeding this threshold indicate an elevated risk of acute kidney injury.

Discussion

Our research demonstrated that IL-6 and PCT exhibit strong predictive abilities for the onset of AKI in patients with sepsis. These findings align with other prior studies that found IL-6 and PCT to be separate indicators of AKI in patients with sepsis (12,16). IL-6 is a prominent proinflammatory cytokine that plays a crucial role in the immunological response to infection. Sepsis leads to the overproduction of IL-6 as a result of a cytokine storm, which causes malfunction in several organs, including AKI. IL-6 causes the production of more proinflammatory cytokines, such as TNF- α and interleukin 1 β (IL-1 β), which enhance the overall inflammatory response stronger. This unregulated inflammation can directly harm renal cells and interfere with the functioning of glomeruli and tubules. IL-6 induces vascular permeability, leading to the flow of fluid and proteins into the renal interstitial tissue. This can lead to the development of renal edema, impaired renal blood flow, and decreased the glomerular filtration rate (GFR). IL-6 has the potential to harm the cells that line the blood vessels in the kidneys, causing them to malfunction and affecting the regulation of blood flow in the kidneys. This can lead to the narrowing of blood vessels in the kidneys, decrease the amount of blood flowing to the kidneys, and contribute to a lack of oxygen in the kidneys. IL-6 has the ability to stimulate the overproduction of reactive oxygen species (ROS), leading to oxidative stress and subsequent damage to kidney cells. Oxidative stress can disturb the functioning of mitochondria, trigger the death of renal cells, and intensify AKI. It is possible that IL-6 directly causes kidney cells to die through programmed cell death and help tubulointerstitial fibrosis, a type of scar tissue,

in the kidneys. Apoptosis and fibrosis can lead to permanent kidney damage and contribute to the progression of prolonged AKI or possibly chronic kidney disease.

This study demonstrated that elevated IL-6 levels upon admission to the intensive care unit (ICU) were a robust indicator of the risk of developing AKI in sepsis patients. The results are in line with earlier study that showed IL-6 to be a very sensitive and reliable indicator of inflammation (17). Therefore, it can be a useful biomarker for predicting AKI in some clinical situations, such as sepsis. Increased IL-6 levels in sepsis may indicate the extent of widespread inflammation and organ malfunction (18). As a result, assessing IL-6 levels can provide valuable insights into the likelihood of developing AKI and help physicians identify patients who require prompt intervention and more intensive treatment. Our research revealed a strong link between higher IL-6 levels in patients with sepsis admitted to the ICU and a higher risk of developing AKI. In line with other studies, ours results confirmed that IL-6 is a sensitive and reliable indicator of inflammation. Therefore it can be a useful biomarker for predicting AKI in a number of clinical situations, such as sepsis.

The precise processes that explain the link between IL-6 and AKI in sepsis remain incompletely understood. However, researchers have proposed numerous plausible processes. It is possible for IL-6 to initiate the inflammatory cascade, which includes the production of more proinflammatory cytokines like TNF- α and IL-1 β . These cytokines can cause damage to kidney cells and tissues. Furthermore, IL-6 has the ability to increase blood vessel permeability and disrupt blood circulation in the kidneys,

resulting in a condition of reduced blood flow and oxygen supply known as renal ischemia and hypoxia. IL-6 can directly cause renal cell death and the formation of scar tissue in the kidney, leading to acute kidney injury (AKI) (19-21).

The thyroid gland C cells synthesize procalcitonin (PCT), a peptide, as a precursor to the hormone calcitonin. Nevertheless, diverse cell types throughout the body, including immune and endothelial cells, also produce and discharge PCT during bacterial infections and sepsis. This study adds to the growing body of evidence that PCT is not only a biomarker for bacterial infection but also a key indicator of inflammatory response and organ failure in sepsis. Our study found a strong correlation between elevated PCT levels upon admission to the ICU and a high risk of developing AKI. Although the precise processes connecting PCT to AKI in sepsis are not well known, numerous putative pathways have been recognized. PCT can cause an uncontrolled start of the inflammatory cascade, which includes the release of proinflammatory cytokines like IL-6, TNF- α , and IL-1 β (22). Cytokines have the ability to directly harm kidney cells and interfere with the functions of the glomerulus and kidney tubules. PCT has the potential to disrupt the function of the vascular endothelium, which is the cellular layer that coats the interior of blood vessels (23). Endothelial dysfunction can cause blood vessels to narrow, activate blood platelets, and leak more blood vessels, all of which can lead to decreased blood flow to the kidneys and the development of AKI. PCT has the potential to disrupt the kidney microcirculation, which is a complex system of tiny blood vessels that play a crucial role in filtering blood and generating urine. Microcirculatory disturbances can lead to renal hypoxia and ischemia, resulting in additional damage to kidney cells and the development of AKI. PCT can more easily produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress in renal cells. Oxidative stress has the potential to harm DNA, proteins, and cellular lipids,

resulting in cell death and AKI (23,24). PCT has the ability to induce apoptosis, often known as programmed cell death, in renal cells. Excessive apoptosis can deplete functioning kidney cells and contribute to the onset of acute kidney injury (AKI).

The results of this study have significant implications for clinical practice. IL-6 and PCT can serve as biomarkers for identifying patients with sepsis who are at increased risk of AKI. By recognizing these patients immediately, physicians can start more aggressive and immediate treatments, like giving vasopressors, increasing fluid resuscitation, and renal replacement therapy, to stop or lessen the severity of AKI. In addition, IL-6 and PCT can serve as monitoring measures to assess patient response to treatment and predict prognosis. If IL-6 and PCT levels increase throughout treatment, thus may suggest that the patient's condition is worsening or that the medication is not effective. In such cases, the treatment plan may need to be adjusted (25-27).

There are several limitations in this study. First, it is crucial to acknowledge that this study occurred at several hospitals in one region. Therefore, caution must be exercised when applying to apply these findings to different groups because generalization may not be appropriate. Furthermore, as an observational study, this research cannot definitively establish a cause-and-effect association between inflammatory biomarkers and AKI. Additional empirical investigation is required to validate this cause-and-effect relationship. Furthermore, this study only assessed IL-6 and PCT levels at two specific time intervals: upon admission to the intensive care unit and on the third day. Consecutive assessments of these indicators may provide a more comprehensive understanding of changes in inflammation and the risk of AKI in individuals with sepsis. An additional factor that might affect the likelihood of acute kidney injury (AKI) in sepsis patients was not considered in this study. These factors include the use of nephrotoxic medications and history of renal disease. In order to obtain a more

thorough understanding of the pathophysiology of AKI in sepsis, future research should consider these aspects. Furthermore, this study did not assess the influence of incorporating inflammatory biomarkers into clinical decision-making on the outcomes of patients with sepsis. Further investigation is required to determine whether the use of inflammatory biomarkers can improve the clinical outcomes of patients with sepsis, including decreasing mortality rates, reducing the duration of stay in intensive care unit, and lowering healthcare expenses.

Further research is needed to confirm these results in a larger and more diverse group of people and to investigate how these inflammation biomarkers could be used to help doctors treat sepsis patients. Further research should also focus on the development of prediction algorithms that combine inflammation biomarkers with other clinical variables to enhance the accuracy of predicting AKI in patients with sepsis. Interventional research is needed to determine whether targeted therapeutic interventions based on inflammatory biomarkers can improve the health outcomes of people with sepsis and AKI. Overall, this study provides new evidence supporting the use of IL-6 and PCT as inflammatory biomarkers for predicting AKI development in patients with sepsis. These findings have the potential to improve the clinical management of sepsis patients and

ultimately reduce the AKI burden in this population.

In conclusion, IL-6 and PCT are useful biomarkers for predicting the development of AKI in patients with sepsis. Further research is necessary to validate these findings in a larger and more diverse population, as well as to explore the potential use of these inflammation biomarkers in clinical management strategies for sepsis patients.

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Ethics statement

We conducted this study in accordance with the Declaration of Helsinki's ethical guidelines for human clinical research. The Ethics Committee of Dr. M. Djamil Hospital in Padang, Indonesia approved the research protocol (permission no. LB.03.02/6.8/408/2023). Furthermore, we informed the participants or their legal guardians about the study's purpose and obtained their informed consent to participate.

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Conflict of interest

The author declares no conflict of interest.

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