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Proenkephalin plasma levels as a predictor of acute kidney injury in adult septic subjects

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Abstract

***Background*: Sepsis is a leading cause of increased morbidity and mortality rates in hospitalized patients and is the most common cause of acute kidney injury (AKI). A potential biomarker that can predict the occurrence of AKI in septic patients is proenkephalin (PENK), an endogenous precursor of opioids.**

***Methods*: This prospective cohort study included 40 septic patients at Wahidin Sudirohusodo Hospital, Makassar, from March to May 2024. Plasma levels of PENK were measured using the enzyme-linked immunosorbent assay (ELISA) method. Data were analyzed statistically using the Shapiro-Wilk, Mann-Whitney, Wilcoxon, and Spearman correlation tests.**

***Results*: The study included 23 men (57.5%) and 17 women (42.5%). Patients predominantly required ventilators as respiratory aids (35%). The average length of stay was 23.5 days. The mean Sequential Organ Failure Assessment (SOFA) score was 5.03±2.6. The mean procalcitonin level was 38.6±56.2, with a range of 0.12-249.26. The mean PENK level on day 7 was lower (294.67 pg/ml) than the initial level (402.02 pg/ml) in septic patients who did not experience AKI. In septic patients who experienced AKI, the mean PENK level on day 7 was higher (421.56 pg/ml) than the initial level (191.78 pg/ml). A plasma PENK level >194.65 pg/ml can indicate AKI in adult septic patients with a sensitivity of 62.5% and a specificity of 82.25%, with a positive likelihood ratio of 3.33.**

***Conclusion*: There was a significant difference between the initial PENK levels and the PENK levels on day 7 in septic patients who did not experience AKI and those who did. Plasma PENK levels in septic patients could be used as a predictive marker for the likelihood of acute kidney injury.**

Key words: Proenkephalin (PENK), sepsis, acute kidney injury (AKI).

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Background

Sepsis is a potentially life-threatening organ dysfunction syndrome caused by the dysregulation of the body's immune response to infection. It is a major cause of high morbidity and mortality rates in hospitalized patients, particularly in intensive care units (ICUs). It is the most common cause of acute kidney injury (AKI), with an incidence of 45-70%. (1) Sepsis is the leading cause of death among ICU patients in the United States, with an estimated 31.5 million cases globally each year. Of these, 19.4 million are categorized as severe sepsis, resulting in 5.3 million deaths annually. (2) According to the World Health Organization (WHO), sepsis affects an estimated 58 out of every 100,000 ICU patients per year, with a mortality rate exceeding one-third of the total cases (42%). A 2012 meta-analysis by

Jawad et al. reported an incidence of sepsis of 240 cases per 100,000 people, with severe sepsis at 56 cases per 100,000 people and septic shock at 11 cases per 100,000 people. The mortality rate for sepsis was 30%, 50% for severe sepsis, and 80% for septic shock. (3)

Research by Rhee et al. in 2017 recorded over 170,000 cases of sepsis in the United States, with 55% requiring ICU care. (4) In Asia, a 2009 study of 150 ICUs across 16 countries, including Indonesia, found that severe sepsis and septic shock accounted for 10.9% of ICU diagnoses, with a mortality rate of 44.5%. (5) Data on sepsis prevalence in Indonesia are limited, but Tambajong et al. reported in 2016 that 82.8% of ICU patients at Prof. Dr. RD Kandou Hospital Manado were diagnosed with sepsis. (6) In 2020, Wahidin Sudirohusodo Hospital Makassar recorded 494 sepsis cases, with the ICU reporting 139 cases and a mortality rate of 88%. (7) AKI frequently occurs in critically ill patients, significantly impacting short- and long-term morbidity and mortality. However, early detection of AKI remains challenging due to the low sensitivity and specificity of current standard biomarkers, such as serum creatinine and urine output (UO). AKI continues to be a major cause of morbidity and mortality among ICU patients. (8) The primary risk factors for AKI in critically ill patients are sepsis and septic shock. Despite resuscitation efforts or renal replacement therapy (RRT), AKI often results in high mortality rates. (9) Sepsis, with a prevalence of 45-75%, is the dominant cause of AKI. (10-12)

Reported AKI rates vary globally, from 0.5-0.9% in the general population, 0.7-18% in outpatients, and up to 20% in ICU patients. The global mortality rate ranges from 25% to 80%. Using new biomarkers that can efficiently stratify AKI risk in ICU patients could lead to developing early management strategies that positively impact patient outcomes. Several kidney injury biomarkers have been proposed as alternatives, but results often vary due to specificity issues and the distinction between kidney damage and loss of kidney function. Some of these biomarkers include kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), liver fatty acid binding protein (L-FABP), insulin-like growth factor binding protein 7 (IGFBP-7), and tissue inhibitor of metalloproteinases-2 (TIMP-2). (13)

One potential biomarker for predicting AKI in septic patients is proenkephalin (PENK), an endogenous precursor of opioids from the enkephalin family with a molecular weight of 4.5 kDa. PENK is considered a stable surrogate marker compared to unstable enkephalins. Research indicates that PENK is not bound to plasma proteins, and its concentrations in plasma are negatively correlated with glomerular filtration rate (GFR). In acute kidney failure, PENK increases more rapidly than creatinine and elevated plasma PENK levels are highly specific for kidney dysfunction and are unaffected by non-renal variables such as systemic inflammation. (14) However, further research is needed to confirm these findings. This study aimed to determine the role of plasma PENK in predicting the occurrence of acute kidney injury in adult patients with sepsis.

Method

Study design, study population, and sampling method

This study was an observational study with a prospective cohort approach. The researchers first determined the PENK levels of septic subjects without AKI. The subjects were then observed until the 7th day to see if acute kidney injury occurred. The study population consisted of septic subjects who did not initially experience AKI upon hospital admission, were over 18 years old, and were hospitalized in the treatment room at Dr. Wahidin Sudirohusodo General Hospital, Makassar. The research sample included the entire accessible population that met the inclusion and exclusion criteria. The inclusion criteria were subjects over 18 years of age who had been diagnosed with sepsis without acute kidney disorders upon hospital admission and were willing to participate in the study. Exclusion criteria were subjects with a history of kidney disease. The sample selection method used was consecutive sampling.

Data collection

Research subjects were enrolled based on the order of hospital admission. Patients meeting the inclusion criteria were included in the study sample. After informed consent was obtained, venous blood samples were collected from the subjects for PENK examination. During treatment, subjects were observed using Kidney Disease: Improving Global Outcomes (KDIGO) parameters until the 7th day. Blood samples were then taken to examine PENK levels to determine whether the septic patients experienced AKI. The study involved 40 samples, split into two groups: those with AKI and those without AKI. PENK level examination was conducted at the Hasanuddin University Medical Research Center using the enzyme-linked immunosorbent assay (ELISA) method.

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 24.0. Data were presented as numbers and frequencies for categorical variables. Statistical tests used in this research included the Mann-Whitney test, Wilcoxon test, and Spearman Correlation test, adjusted according to the results of the basic normality test. The significance level (p-value) used was $p<0.05$.

Ethical consideration

All procedures were carried out after providing information and obtaining permission through informed consent. The study was approved by the Health Research Ethics Commission of the Faculty of Medicine, Hasanuddin University, and the Hasanuddin University State University Hospital (approval number 176/UN4.6.4.5.31/PP36/2024). A research permit was also obtained from Wahidin Sudirohusodo Hospital, Makassar (permit number DP.04.03/D.XIX.2/7964/2024).

Results

Characteristics of research subjects

The total number of research subjects met the inclusion criteria was 40 septic patients: 16 (40%) patients with AKI and 24 (60%) patients without AKI. **Table 1** shows the characteristics of the research subjects. The subjects comprised 23 (57.5%) males and 17 (42.5%) females aged 19-80. Patients predominantly used ventilators as respiratory support (35%). Comorbidities among the subjects included cardiovascular disease (7.5%), respiratory disease (30%), liver disease (10%), malignancy (30%), and post-surgery (20%). One patient (2.5%) had other conditions. The average length of stay was 23.5 days, ranging from 7 to 74 days. The average Sequential Organ Failure Assessment (SOFA) score was 5.03±2.6, ranging from 2 to 10. The average procalcitonin level was 38.6±56.2, ranging from 0.12 to 249.26.

PENK I and PENK II levels in research subjects

Table 2 illustrates the PENK levels on days 0 (PENK I) and 7 (PENK II). PENK I levels ranged from 34.67 to 1377.41 pg/ml, with a mean of 317.92±328.8. PENK II levels ranged from 22.91 to 1225.65 pg/ml, with a mean of 345.42±306.9. Based on the data normality test, the distribution of PENK I ($p<0.001$) and PENK II ($p=0.013$) was not normally distributed.

Differences in PENK I and PENK II levels in research subjects

Table 3 shows the differences between initial PENK I on admission and PENK II on day 7 in non-AKI septic patients. The mean PENK II level on the 7th day was lower (294.67 pg/ml) compared to initial PENK I on admission (402.02 pg/ml) and was statistically significant ($p=0.024$). This result indicated a significant difference between initial PENK levels on admission and day 7 in septic patients who did not experience AKI. **Table 4** shows the differences between initial PENK I on admission and PENK II on the 7th day in septic patients who experienced AKI. The mean level of PENK II on day 7 was higher (421.56 pg/ml) compared to PENK I on admission (191.78 pg/ml) and was statistically significant ($p=0.001$). This result indicated a significant difference between the level of PENK on admission and the level of PENK on day 7 in septic patients with AKI. **Table 5** shows the differences between PENK I on admission and PENK II on day 7 in survived septic patients. The mean level of PENK II on day 7 was slightly lower (416.70 pg/ml) compared to PENK I on admission (454.12 pg/ml), and this difference was not statistically significant ($p=0.569$). This result indicated no significant difference between the level of PENK on admission and the PENK on day 7 in septic patients who survived. **Table 6** shows the differences between initial PENK I on admission and PENK II on the 7th day in septic patients who died. The mean level of PENK II on the 7th day was higher (297.89 pg/ml) compared to initial PENK I on admission (227.12 pg/ml), but this difference was not statistically significant ($p=0.209$). This result indicated no significant difference between initial PENK levels on admission and PENK levels on the 7th day in septic patients who died.

Correlation of PENK I levels with AKI

Table 7 shows the correlation between PENK I levels and AKI. This study found a weak correlation between PENK I levels and the incidence of AKI in septic patients, which was not statistically significant ($p=0.06$).

ROC curve of PENK I based on AKI incidence

Figure 1 shows the receiver operating characteristic (ROC) curve of PENK I levels based on AKI incidence. The AUC value of PENK I was 0.673 and was statistically significant ($p=0.016$), indicating that PENK I levels could distinguish between septic patients with and without AKI. Based on the coordinate value of the PENK I ROC curve, the cut-off value was >194.65 pg/ml for septic patients who experienced AKI and ≤194.65 pg/ml for septic patients who did not experience AKI.

Sensitivity and specificity of plasma PENK as a predictor of AKI in septic patients

Table 8 shows the sensitivity and specificity of PENK I. The PENK marker's sensitivity was 62.5%, and its specificity was 82.25%. The PENK marker's likelihood ratio for AKI occurrence was 3.33, meaning that septic patients with PENK levels >194.65 pg/ml were 3.33 times more likely to experience AKI.

Discussion

The study included 40 septic patients, with 16 (40%) experiencing AKI and 24 (60%) not experiencing AKI. Most patients were male (23 men, 57.5%), with an average age of 54 years. Male gender is an independent risk factor for sepsis, partly due to the effects of sex hormones. Estrogen has a protective effect by suppressing the hyperinflammatory state of sepsis through reduced levels of circulating proinflammatory cytokines like interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Conversely, testosterone and androgen hormones in men have immunosuppressive effects on innate and adaptive immunity, reducing the production of immunoglobulins, cytokines, and lymphocyte proliferation during infection. Old age is also a risk factor due to immunosenescence, characterized by functional disorders in cell-mediated immunity and humoral responses, chronic hyperstimulation of the immune system, and thymus atrophy with age. (15,16) Patients in the study predominantly required ventilator support (35%), which is often necessary for severe sepsis and septic shock due to acute respiratory distress syndrome (ARDS). ARDS is marked by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to lung injury. The use of ventilators also raises the risk of ventilator-associated pneumonia (VAP) and subsequent sepsis. (17,18)

The most common comorbidities were respiratory diseases (30%) and malignancies (30%). Chronic obstructive pulmonary disease and malignancy are independent risk factors for death in septic patients. Cancer patients are particularly vulnerable to severe infections due to immune suppression from the malignancy itself or cancer therapy. (19,20)

The average length of stay was 23.5 days, with a range of 7-74 days. This result aligns with a 2018 retrospective study by Paoli et al., which reported that the length of stay for septic patients in the U.S. increased with disease severity. (21,22) Sepsis is generally caused by bacterial infections, necessitating rapid therapeutic markers like procalcitonin. In this study, the average procalcitonin level was 38.6±56.2 ng/ml, indicating bacterial infection in most subjects. Procalcitonin is produced by parafollicular cells of the thyroid and neuroendocrine cells of the lungs and intestines, and its levels rise significantly during bacterial infections, making it helpful in guiding antibiotic therapy. (23,24) Plasma levels of PENK I and II varied considerably among the study samples. PENK I levels ranged from 34.67 to 1377.41 pg/ml, with a mean of 317.92±328.8. PENK II levels ranged from 22.91 to 1225.65 pg/ml, with a mean of 345.42±306.9. Both distributions were not normally distributed. The average PENK level on day 7 was significantly lower (294.67 pg/ml) compared to initial levels (402.02 pg/ml) in patients without AKI. Conversely, in patients with AKI, the average PENK level on day 7 was significantly higher (421.56 pg/ml) than initial levels (191.78 pg/ml). The study by Saleh et al. in 2022 found that PENK levels increased with AKI severity. The cohort study by Kim H et al. in 2017 established a cut-off plasma PENK level of 154.5 pmol/l for diagnosing AKI sepsis. (25,26) Marino et al. (2015) found that PENK levels were higher in AKI patients with severe sepsis or shock compared to those with sepsis alone. (27) No significant differences in PENK levels on day 7 compared to initial levels in septic patients who survived or died. However, high PENK concentrations on admission were associated with worse outcomes in the multicenter cohort study by Hollinger et al. (2018). A weak, non-significant correlation was found between PENK I levels and AKI incidence. (28) This finding contrasts with Beunders et al. in 2020, who reported a strong correlation between plasma PENK concentrations and GFR measured using iohexol's gold standard plasma clearance. (29) The area under the curve (AUC) value of PENK on admission was 0.673, indicating its potential as a predictor for AKI in septic patients. The cut-off value was >194.65 pg/ml for septic patients with AKI. This result aligns with Hollinger et al. in 2018, who found PENK on admission to be an independent indicator of AKI. The systematic review by Lin et al. in 2023 reported an optimal cut-off value of 57.3 pmol/L for early AKI detection. (30) The sensitivity of the PENK marker was 62.5%, and its specificity was 82.25%, with a positive likelihood ratio of 3.33. This result is consistent with Lim et al. 2023, who found similar sensitivity and specificity values.

Conclusion

There was a significant difference between initial PENK levels on admission and day 7 levels in septic patients with and without AKI. However, the correlation between initial PENK levels and AKI incidence was weak. Plasma PENK levels >194.65

pg/ml can indicate AKI in adult septic patients, with a sensitivity of 62.5% and a specificity of 82.25%.

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Competing interests
The authors declare no potential conflicts of interest.

Table 1. Characteristics research subject (n=40)

Characteristics	n (%)	Mean±SD	Median (min-max)
Gender - Male - Female	 23 (57.5%) 17 (42.5%)		
Age (years)		54.2±15.1	54 (19-80)
Acute kidney injury - Non-AKI - AKI	 24 (60%) 16 (40%)		
Breathing aids - None - NRM - Ventilator	 13 (32.5%) 13 (32.5%) 14 (35%)		
Outcome - Life - Death	 16 (40%) 24 (60%)		
Comorbid - Cerebrovascular disease - Respiratory disease - Liver disease - Malignancy - Surgery - Other	 3 (7.5%) 12 (30%) 4 (10%) 12 (30%) 8 (20%) 1 (2.5%)		
Length of stay (days)		23.5±17.5	17.50 (7-74)
SOFA score		5.03±2.6	5 (2-10)
Procalcitonin levels, ng/ml		38.6±56.2	16.29 (0.12-249.26)
Initial proenkephalin levels (day 0), pg/ml		317.92±328.8	228.13 (34.67-1377.41)
Proenkephalin levels on day 7, pg/ml		345.42±306.9	239.49 (22.91-1225.65)

Legend: SD=standard deviation; AKI=acute kidney injury; NRM=non-rebreathing mask; SOFA=Sequential Organ Failure Assessment.

Table 2. Description of proenkephalin I and proenkephalin II levels in research subjects

Variable	Minimum	Maximum	Mean	SD	p-value*
Proenkephalin I (day 0) (pg/ml)	34.67	1377.41	317.92	328.8	<0.001
Proenkephalin II (day 7) (pg/ml)	22.91	1225.65	345.42	306.9	0.013

Legend: SD=standard deviation.
*Shapiro-Wilk test.

Table 3. Comparison of proenkephalin I with proenkephalin II levels in non-AKI group

Group	n	Mean±SD	Medium (min-max)	p-value
Initial proenkephalin levels (day 0)	24	402.02±376.1	265.36 (38.02-1377.41)	0.024*
Proenkephalin levels (day 7)	24	294.67±293.9	226.67 (22.91-995.35)	

Legend: AKI=acute kidney injury; SD=standard deviation.
*Wilcoxon test.

Table 4. Comparison of proenkephalin I with proenkephalin II levels in AKI group

Group	n	Mean±SD	Medium (min-max)	p-value
Initial proenkephalin levels (day 0)	16	191.78±189.4	113.36 (34.67-678.28)	0.001*
Proenkephalin levels (day 7)	16	421.56±319.5	370.86 (29.38-1225.62)	

Legend: AKI=acute kidney injury; SD=standard deviation.
*Wilcoxon test.

Table 5. Comparison of proenkephalin I with proenkephalin II levels in living patients

Group	n	Mean±SD	Medium (min-max)	p-value
Initial proenkephalin levels (day 0)	16	454.12±367.4	315.74 (38.02-1377.41)	0.569*
Proenkephalin levels (day 7)	16	416.70±376.19	251.78 (49.70-1225.62)	

Legend: SD=standard deviation.
*Wilcoxon test.

Table 6. Comparison of proenkephalin I with proenkephalin II levels in death patients

Group	n	Mean±SD	Medium (min-max)	p-value
Initial proenkephalin levels (day 0)	24	227.12±271.6	126.69 (34.67-1167.50)	0.209*
Proenkephalin levels (day 7)	24	297.89±248.1	237.53 (22.91-847.47)	

Legend: SD=standard deviation.
*Wilcoxon test.

Table 7. Correlation of proenkephalin I levels with AKI

Variable	Statistics	AKI incident
Proenkaphalin I	r p-value n	0.294 0.06 40

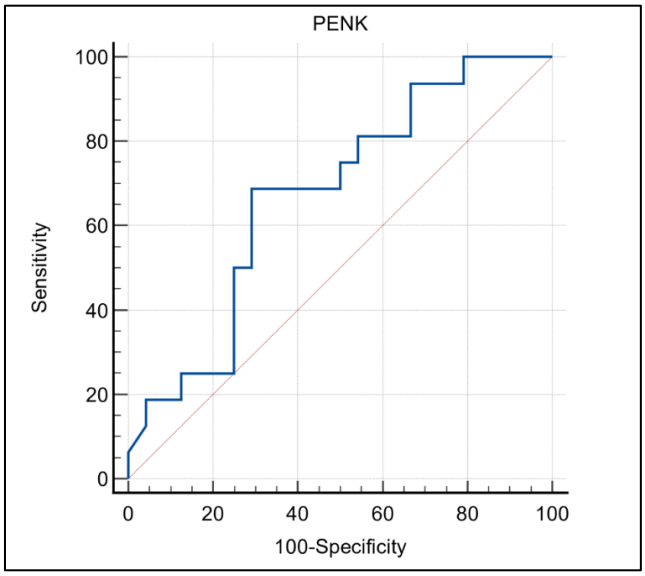
Legend: AKI=acute kidney injury.
*Spearman's correlation test.

Table 8. Sensitivity and specificity of proenkephalin I

Proenkaphalin I	AKI incident		Total	p-value	Sensitivity	Specificity	PPV	NPV	AUC
	Non-AKI	AKI							
≤194.65	3	15	18	0.016	62.50	81.25	83.33	59.09	0.673
>194.65	13	9	22						
Total	16	24	40						

Legend: AKI=acute kidney injury; PPV=positive predictive value; NPV=negative predictive value; AUC=area under the curve.

Figure 1. ROC curve of proenkephalin I levels based on AKI incident



Legend: ROC=receiver operating characteristic; AKI=acute kidney injury; PENK=proenkephalin.

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