Original Article

Diagnostic Value of Proenkephalin A 119–159 Serum in Early Detection of Sepsis-Associated Acute Kidney Injury

Adefri Wahyudi[1], Drajad Priyono[2], Deka Viotra[2], Harnavi Harun[2], Najirman[3], Roza Kurniati[4], Rohayat Bilmahdi Simajuntak[5], Arina Widya Murni[6]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas / Dr. M. Djamil Central General Hospital, Padang, Indonesia
[2]Department of Internal Medicine, Division of Nephrology and Hypertension, Faculty of Medicine, Universitas Andalas/ Dr. M. Djamil Central General Hospital, Padang, Indonesia
[3]Department of Internal Medicine, Division of Rheumatology, Faculty of Medicine, Universitas Andalas/ Dr. M. Djamil Central General Hospital, Padang, Indonesia
[4]Department of Internal Medicine, Division of Pulmonology, Faculty of Medicine, Universitas Andalas /Dr. M. Djamil Central General Hospital, Padang, Indonesia
[5]Department of Internal Medicine, Division of Tropical Medicine and Infection, Faculty of Medicine, Universitas Andalas/ Dr. M. Djamil Central General Hospital, Padang, Indonesia
[6]Department of Internal Medicine, Division of Psychosomatics and Rehabilitation, Faculty of Medicine, Universitas Andalas/ Dr. M. Djamil Central General Hospital, Padang, Indonesia

ARTICLE INFO

Article history:
Received: March 6, 2026
Accepted: April 13, 2026
Published Online: April 24, 2026

Corresponding Author:
Adefri Wahyudi, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas / Dr. M. Djamil Central General Hospital, Padang, Indonesia,
dr.adefriwahyudi@gmail.com

ABSTRACT

Background: Sepsis-associated acute kidney injury (SA-AKI) is a common condition found in sepsis. Due to the lack of creatinine serum, this condition may delay therapy. Proenkephalin A 119-159 (PENK) is a breakdown product of the prohormone proenkephalin A, which is freely filtered at the glomerulus. On the other hand, this prohormone and its receptor are predominantly expressed in proximal tubular epithelial cells (pTEC) of the kidney. Elevated serum PENK levels are an indicator of AKI. However, previous studies have shown various results.

Objective: This study aims to identify early-detection biomarkers for AKI in sepsis.

Methods: This diagnostic test was conducted at Dr. M. Djamil General Hospital, Padang, in sepsis patients. The diagnosis of AKI was established based on the 2012 KDIGO criteria.

Results: The study involved 98 sepsis patients, 58.16% (n=57) of them experienced AKI. Serum creatinine levels at admission and within 48 hours of hospitalization were 1.0 (IQR 0.8–1.5) mg/dl and 1.6 (IQR 0.9 – 2.1) mg/dl, respectively. A serum PENK level ≥82.6 pmol/L at admission had a sensitivity of 98.6%, a specificity of 95.1%, a positive predictive value of 96.1%, a negative predictive value of 97.5%, and an accuracy of 96.9% in the early detection of AKI in sepsis.

Conclusion: Serum PENK level has excellent diagnostic value in the early detection of AKI in sepsis.

Keywords: Sepsis, proenkephalin A 119–159, AKI.

Introduction

Acute kidney injury (AKI) is a part of the spectrum of acute kidney diseases and disorders characterized by a rapid and significant decline in kidney function due to various potential causes. Clinically, the Kidney Disease Improving Global Outcome (KDIGO) defines AKI as an increase in serum creatinine level ≥0.3 mg/dL within 48

Cite this as:
Wahyudi A, Priyono D, Viotra D, et al. Diagnostic Value of Proenkephalin A 119–159 Serum in Early Detection of Sepsis-Associated Acute Kidney Injury. InaKidney. 2026;3(1):169-177. doi:10.32867/inakidney.v3i1.239

hours or more than 1.5 times the baseline level. The global incidence of AKI varies from 114 to 174 cases per 10,000 population and occurs in almost all critical illnesses. Among them, sepsis is the main cause in 45–70% cases. A study suggests that AKI events increase the risk of progression to chronic kidney disease (CKD). Early detection and appropriate management could reduce the morbidity and mortality of AKI.[1–3]

Sepsis-associated AKI (S-AKI) is a condition characterized by a rapid decline of kidney function caused by tubular epithelial cell damage and the accumulation of inflammatory cytokines. Zou et al. (2022) reported the increase in creatinine serum level detected 24–36 hours after kidney injury. This limitation makes the creatinine serum unreliable and might be the cause of delayed therapy in unstable settings. Its level is influenced by factors such as age, gender, body fluid volume, and use of diuretics and antihypertensive medications. Finally, in 2023, the 28th Acute Disease Quality Initiative (ADQI) Consensus recommended the use of additional biomarkers to diagnose AKI. Until now, no single biomarker that could replace creatinine serum as the gold standard AKI diagnostic.[4,5]

Proenkephalin A 119-159 (PENK) serum is a potential biomarker to diagnose AKI. PENK has 4,5 kDa weight molecules, unbound with plasma protein, and its levels are not influenced by gender and age. Proenkephalin A is a precursor of PENK. Upon activation, proenkephalin A will be cleaved into active enkephalin peptides such as *met*-enkephalin and *leu*-enkephalin that would be degraded in several minutes. Another cleavage product is an inert peptide called PENK that flows in the vascular until 48 hours. In physiological conditions, active enkephalin binds to delta opioid receptors (DORs), which are found in proximal tubular epithelial cells (PTEC)as cell regulator functions such as diuresis, natriuresis, and inhibition of antidiuretic hormone (ADH). Under injury conditions, proenkephalin will be prepared in cells to adapt to ischemic conditions by reducing cell metabolism and modulating angiogenesis.[6–8]

The use of PENK serum as a diagnostic biomarker for AKI in sepsis has been approved by European Conformity (CE). Multicenter studies in Europe have reported various diagnostic thresholds. In the sepsis population, Rosengvist et al. (2019) reported PENK levels >100 pmol/L, while admission can predict an AKI event 3.5-fold in 48 hours. A study in Germany in 2024 reported that the elevated PENK serum level >89 pmol/L at the time of admission also had good early diagnostic performance. In Asia, similar purpose studies are still limited. Kim et al. (2017) in South Korea reported PENKserum levels linearly with the severity of AKI and sepsis and better diagnostic performance than neutrophil gelatinase-associated lipocalin (NGAL). One similar study was conducted in Indonesia in 2025 with a small population and unsatisfactory results.[5,9,10]

Methods

Design and participants

This study is a diagnostic test using a cross-sectional approach conducted in an inpatient setting in Dr. M. Djamil General Hospital, Padang. Samples were collected from June to December 2025. First, we conducted anamnesis to determine the inclusion and exclusion criteria, and then blood tests were performed. In this study, the sample selection was carried out using consecutive sampling. The sample size was determined by using a particular diagnostic formula, and an optimum sample of 98 people was obtained. The subjects taken as samples were subjects who met the inclusion criteria and were not excluded by the exclusion criteria. The inclusion criteria were sepsis patients with normal serum creatinine levels. While the exclusion criteria were patients with a history of chronic kidney disease (CKD), renal replacement therapy (RRT), acute stroke, acute coronary syndrome, acute heart failure, advanced chronic heart failure, malignancy, hypoalbuminemia, use of diuretics, ACEi or ARB, agonist and antagonist delta opioid receptors (DOR).

Testing of PENK serum was carried out using the Fluoroenzymeimmunoassay (FEIA) method using the AFIAS Penkid Boditech® reagent in the Central Laboratory of Dr. M. Djamil General Hospital, Padang. All samples were grouped into AKI and non-AKI based on KDIGO criteria. Elevated creatinine serum level ≥0.3 mg/dl in 48 hours is defined as AKI, and an elevated level <0.3 mg/dl is defined as non-AKI. The optimal *cut-off* PENK serum level was calculated by the Youden Index in ROC. After that, we conducted diagnostic performance by calculated sensitivy, specificity, negative predictive value, positive predictive value, and accuracy by using Table 2 x 2.

Results

Patient characteristic

This study involved 98% patients with a sepsis diagnosis while admitted. The average age of the sample is 60.5 (IQR 48.8 – 70.0) years old. The proportion of the subgroup geriatric and nongeriatric are relative similar, 53.1% and 46.9%. Then the proportion of females and males are relative similar too, 48% and 52%. Common comorbidities found in this study are diabetes mellitus 33.7%, hypertension 27.6%, chronic heart failure and chronic coronary syndrome 21.4%, and another medical condition 10.2%. Median of the SOFA score at admission is 7. The proportion of subgroups using vasopressor and not using vasopressor is 44.9% and 55.1%. Primary sources of infection are pneumonia 66.3%, skin and soft tissue infection (SSTI) 21.4%, urinary tract infection (UTI) 7.1%, and gastrointestinal hepatobiliary infection 3.1%. Almost 91.9% as a unifocal infection. Median of hemoglobin level at admission is 10.4 (IQR 8.9 – 12.3) gr/dl. The median of the lactate serum level is 1.8 (1.2 – 2.7) mmol/L. Median creatinine levels at admission and after 48 hours of hospitalization are 1.0 (IQR 0.8 – 1.5) mg/dl and 1.6 (IQR 0.9 – 2.1) mg/dl. Besides that, the median of PENK serum levels at admission and after 48 hours of hospitalization are 91.8 (71.1 – 105) pmol/L and 104.4 (71.8 – 245.3) pmol/L. (Table 1).

Table 1. Characteristic of Respondents

Characteristic	n = 98	Characteristic	n = 98
Age, median (IQR)	60,5 (48,8 – 70,0)	**Source infection**, n (%)	
Age Subgroup, n (%)		Pneumonia[1]	65 (66,3)
< 60 years old	46 (46,9)	Skin and soft tissue infection	21 (21,4)
≥ 60 years old	52 (53,1)	Urinary tract infection	7 (7,1)
Sex, n (%)		Gastrointestinal hepatobilliary	7 (7,1)
Males	51 (52,0)	Others[2]	3 (3,1)
Females	47 (48,0)	**Focal infection**, n (%)	
Hospitalization, n (%)		Unifocal	90 (91,9)
Intensive Care Unit	17 (17,3)	Multifocal[3]	8 (9,1)
High Care Unit	81 (82,7)	**Laboratory result**, median (IQR)	
Comorbidites, n (%)		Hb (g/dL)	10,4 (8,9 – 12,3)
Diabetes mellitus	33 (33,7)	Lactate (mmol/L)	1,8 (1,2 – 2,7)
Hypertension	27 (27,6)	Albumin serum (g/dL)	2,8 (2,6 – 3,1)
Chronic heart disease[4]	21 (21,4)	Creatinine serum H_1 (mg/dL)	1,0 (0,8 – 1,5)
Others[5]	10 (10,2)	Creatinine serum H_3 (mg/dL)	1,6 (0,9 – 2,1)
SOFA score, median (IQR)	7 (5 – 10)	PENK serum H_1 (pmol/L)	91,8 (71,1 – 140,5)
Using Vasopresor, n (%)		PENK serum H_3 (pmol/L)	104,4 (71,8 – 245,3)
No	54 (55,1)		
Yes	44 (44,9)		

Description: (1) Pneumonia: includes community-acquired pneumonia and hospitalized-acquired pneumonia, (2) Other sources of infection: includes central nervous system infections, malaria, and leptospirosis, (3) Multifocal: more than one focal infection, (4) Chronic heart disease: includes chronic heart failure and chronic coronary syndrome, and (5) Other comorbidities: includes stroke and chronic liver disease.

Diagnostic Value of Proenkephalin A 119–159 Serum

First, the value of the optimal cut-off of the PENK serum level is calculated by the Youden index. At admission (H_1), PENK serum level ≥82.60 pmol/L is the optimal value with AUC 0.981 (CI 95%; 0.956 – 1.000) and Youden Index 0.934. We also calculated the optimal cut-off after 48 hours of hospitalization (H_3). Its result is ≥85.3 pmol/L with AUC 0.923 (CI95%; 0.926 – 1.000) and Youden Index 0.023. In this study, we found 57 AKI and 41 non-AKI based on the KDIGO criteria. The ROC and diagnostic performances from this study can be found in Table 2 and Figure 1 below.

Table 2. Diagnostic Performance of PENK Serum to Diagnose Sepsis-Associated AKI

Day of Test	PENK (pmol/L)	AKI KDIGO Yes	AKI KDIGO No	Sensitivity	Specivity	NPV	PPV	Acuration
at Admission (H_1)	≥82.6	56	2	98.2%	95.1%	96.6%	97.5%	96.9%
	<82.6	1	39					
48 hours in hospitalization (H_3)	≥85.3	54	1	94.7%	97.6%	98.2%	93.0%	95.9%
	<85.3	3	40					

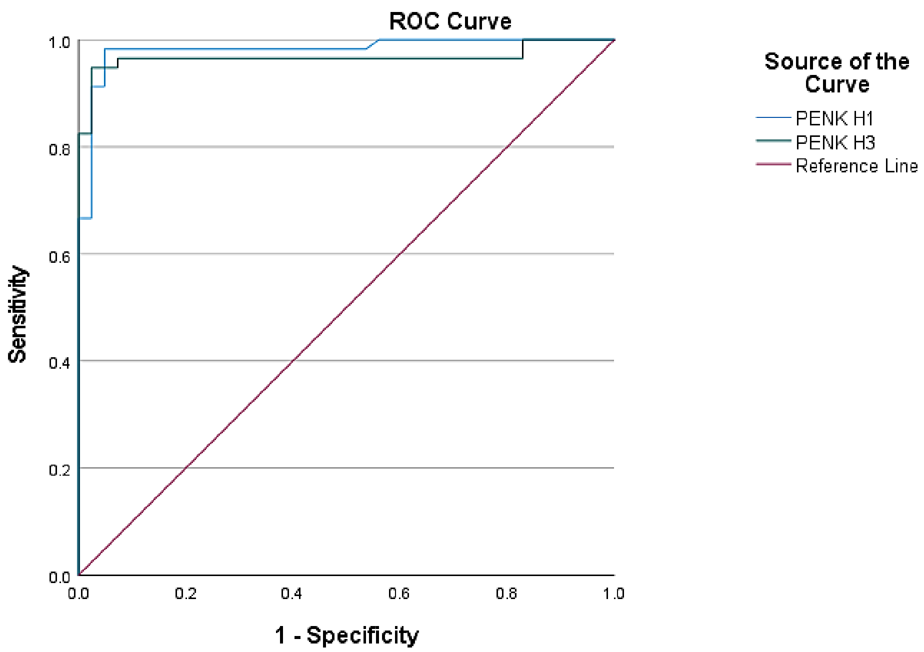

Figure 1. Receiver Operation Curve (ROC)

Discussion

In this study, we reported that PENK serum has excellent diagnostic performance for the early detection of AKI in sepsis patients. While creatinine serum was normal at admission, elevated PENK serum level more than 82.60 pmol/L resulted sensitiviy 98.2%, specivity 95.1%, negative prediction value 96.6%, positive prediction value 97.5%, and accuration 96.9% (AUC 0.981). This result is consistent with the multicenter study in Germany, 2020 – 2022. Martin et al. (2025) reported elevated PENK level more than 100 pmol/L in 910 critically ill patients, while creatinine serum was normal at admission, had better diagnostic performance than creatinine serum (AUC 0.880 vs 0.74). Another multicenter study in Germany was conducted by Schulte et al. (2024). Increased PENK serum level more than 89 pmol/L at admission in 529 sepsis patient result good diagnostic performance with sensitivity 72%, specificity 83%, positive predictive value 77%, and negative predictive value 79% (AUC 0.870).[11,12]

A Study in the Asian population reported similar results. Ji et al. (2025) documented 41% AKI in 161 septic patients in China. PENK serum level more than 241 pmol/L resulted in good performance with sensitivity 0.79 and specificity 0.83 (AUC 0.880). Another study in Bangladesh conducted by Hassan et al. (2025) reported elevated PENK serum level of more than 145 pmol/L resulted in fair performance with a sensitivity 67.9% and specivity 98.3% (AUC 0.796). Based on this result, we concluded elevated PENK serum level, while a normal creatinine serum level at admission, could be a tool for early diagnosis of AKI in sepsis patients. Compared with previous studies, we revealed a higher diagnostic value. It might have caused more exclusion criteria to be used. We have excluded conditions that might affect PENK level, such as an acute cardiac or stroke event. Meanwhile, in previous studies, they only excluded CKD, gravid, and palliative states.[13,14]

Determination of the threshold PENK serum level for detecting AKI in the general population is a challenge. In addition, until now, there is no reference normal PENK level in healthy people. These facts might be caused by the limitations of the studies about this topic. Since it started 2 decades ago, multicenter studies have focused in Europe population. Malmö Diet and Cancer Study (MDCS) in Sweden documented that the healthy PENK serum level is 46.34 (SD±14,6) pmol/L. Genomic analysis resulted in PENK serum level distinguished by polymorphism rs1012178 that located on chromosome 8. Every minor changed T allel would increase 0.057 pmol/L of PENK. But there is no global data reported on the variability of that polymorphism among populations.[15]

There are two studies that reported the association of PENK serum level with ethnicity and race. The Impact of Migration and Ethnicity on Diabetes in Malmö (MEDIM) in Sweden reported the determination of PENK level with deterioration of kidney function. Although by similar PENK level between the Swedish and Middle Eastern ethnic groups (71.1 and 70 pmol/L) and a significant traditional risk of CKD in the Middle Eastern ethnic group, deterioration of kidney function is greater in the Swedish ethnic group. The Reasons for Geographic and Racial Difference in Stroke (REGARDS) study in the USA reported insignificantly different PENK levels in the healthy kidney population of black and white races. The medians of PENK level are 62.6 (IQR 48.9 – 73.9) pmol/L and 56.2 (IQR 46.7 – 70.1) pmol/L. It is assumed that the effect of the genetic factor is the renal protective effect of PENK.[16,17]

Besides the genetic factor, another factor that might have affected the PENK level is heart condition. Historically, clinical studies about PENK were started in the 1980s in the heart failure population. Postmortem study reported the amount of DOR and vesicle proenkephalin A at postsynaptics of cardiac autonomous nerve (CAN) and tubulus transversalis of cardiomyocytes. Another study revealed that every release of a norepinephrine vesicle was accompanied by a proenkephalin A vesicle. Overactivation of the sympathetic nerve was well-known as characteristic of acute heart failure and advanced chronic heart failure. This emphasized the function of PENK as cardioprotective by the contraregulatory sympathetic effect. It is quite understandable that PENK levels was usual significanly increased in these diseases.[18]

Matsiras et al. (2025) described the reason for the increased PENK level in the heart failure population. It was still related to kidney dysfunction. In case of reduced ejection fraction (HfrEF), it was clearly understable and affected by hypoperfusion. In preserved EF, dyastolic dysfunction will increase central venous pressure (CVP) and concomitantly the vena cava. This condition will cause intraglomerular hypertension (renal tamponade) and ultimately affect kidney function. Because PENK freely filtrates in the glomerulus, increasing PENK level in the heart failure population is assumed to be caused by kidney dysfunction.[18]

Study of Emmen et al. (2019) emphasized that the main factor of increased PENK level in heart failure population is kidney dysfunction. Compared with cardiac biomarker (NT-pro BNP, troponin, LVEF) and renal biomarkers (eGFR, urine NGAL, urine KIM), increased PENK level is the strongest association with eGFR. Every increased PENK 40 pmol/L linearly associated with a 1.29-fold increased risk of AKI. Another Great Network Study reported that increased of PENK level of more than 97.2 pmol/L in the AHF population linearly associated with a 1.58-fold risk of AKI. However, in this study, we tried to exclude the heart failure factor by anamnesis without echocardiography findings.[19,20]

In a sepsis patient-based study, PENK levels might be affected by the severity of disease and inflammation, but it is still inconclusive. Verras et al. (2024) reported moderate correlation between PENK levels and creatinine serum (rho 0,327) and procalcitonin level (rho 0,527) and mild correlation with lactate serum (rho 0,369) and SOFA score (rho 0,391). On the other hand, a study by Frigyesi et al. (2021) reported that in 632 patients with sepsis, PENK levels are only correlated with renal and cardiovascular SOFA. There is no correlation with other SOFA components such as respiration, hepatic, neurological, and coagulation function. Another study in the sepsis population emphasized that the increased of PENK levels significantly occurred in AKI. Hassan et al. (2021) reported in a serial test (admission, 2nd, and 7th days of hospitalization) between AKI and non-AKI subgroups, PENK levels only significantly increased in the AKI population (159,4±78,7 pmol/L, 332,6±89,2 pmol/L, and 478,2±98,4 pmol/L). In non-AKI subgroups, serial test PENK level was relatively constant (69,4±32,9 pmol/L, 65,9±30,2 pmol/L, and 75,3±36,7 pmol/L).[14,21,22]

In addition to early diagnosis, the PENK serum level test could determine AKI severity. In critically ill patients, Martin et al. (2025) reported the mean of PENK serum level in AKI grade 1 is 56 (IQR 44 – 76) pmol/L and in AKI grade 2/3 is 88 (64 – 163) pmol/L. In the subgroup with renal replacement therapy, the PENK level was higher, 108 (55 – 142) pmol/L. Facts that lack of study in Indonesia and other potential of PENK in kidney dysfunction were expected to be the background to conduct further research.[11]

Conclusion

PENK serum level test has excellent diagnostic performance for early detection of sepsis-associated AKI.

Limitations of the Study

This study was conducted in a referral hospital. Most of the participants had already received vasopressor therapy or antibiotics, which may be nephrotoxic. Consequently, it is difficult to determine whether the tubular damage was a direct or indirect consequence of sepsis. Furthermore, advanced chronic heart failure, which could affect PENK levels, was only excluded from medical history without real-time echocardiography.

Declarations

Ethics approval and consent to participate

This study was conducted after obtaining ethical approval from the Health Research Ethics Committee of Dr. M. Djamil Padang General Hospital, Number: DP.04.03/D.XVI.10.1/201/2025.

Competing interests

There are no conflicts of interest in writing this article.

Funding source

Not applicable.

Acknowledgments

None.

Author's Contribution

Idea/concept: AW. Design: AW. Control/supervision: DP, DV, HH, NN, RK, RBS, AWM. Data collection/ processing: AW. Analysis/interpretation: AW, DP, DV, HH, NN, RK, RBS, AWM. Literature review: AW, DP, DV, HH, NN, RK, RBS, AWM. Writing the article: AW. Critical review: AW, DP, DV, HH, NN, RK, RBS, AWM. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Kidney Disease Improving Global Outcomes. Scope of work: KDIGO Clinical Practice Guideline for Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD. Update. 2023:1–20.
2. Peeraporratana S, Caballero CLM, Gomez H, A KJ. Acute kidney injury from sepsis: current concepts, epidemiology, pathopysiology, prevention and treatment. Kidney Int. 2019;96(5):1083–99. doi:10.1016/j.kint.2019.05.026
3. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systemic review and meta-analysis. Kidney Int. 2012;81(5):442–8. doi:10.1038/ki.2011.379
4. Zou C, Wang C, Lu L. Advances in the study of subclinical AKI biomarkers. Front Physiol. 2022;13:960059. doi:10.3389/fphys.2022.960059
5. Moledina DG, Parikh CR. Phenotyping of Acute Kidney Injury Beyond Serum Creatinine. Semin Nephrol. 2018;38(1):3–11. doi:10.1016/j.semnephrol.2017.09.002
6. Bhosale SJ, Kulkarni AP. Invited article: Biomarkers in acute kidney inury. Indian J Crit Care Med. 2020;24(Suppl 3):S90–3. doi:10.5005/jp-journals-10071-23398
7. Liu C, Liu X, He Z, Zhang J, Tan X, W Y. Proenkephalin a secreted by renal proximal tubules functions as a brake kidney regeneration. Nat Commun. 2023;14(1):7167. doi:10.1038/s41467-023-42929-5
8. Chen Y, He Y, Zhao S, He X, Xue D, Xia Y. Review: Hypoxic ischemic inflammation microRNAs and delta opioid receptors: hypoxia ischemia sensitive versus insensitive organs. Front Aging Neurosci. 2022;14:847374. doi:10.3389/fnagi.2022.847374
9. Rosenqvist M, Bronton K, Hartmann O, Bergmann A, Struck J, Melander O. Proenkephalin A 119-159 (penKid) a novel biomarker for acute kidney injury in sepsis: an observational study. BMC Emerg Med. 2019;19:75. doi:10.1186/s12873-019-0283-9
10. Kim H, Hur M, Lee S, Marino R, L M. Proenkephalin, Neutrophil Gelatinase-Associated Lipocalin, and eGFR in patient with sepsis. Ann Lab Med. 2017;37(5):388–97. doi:10.3343/alm.2017.37.5.388
11. Martin L, Martin C, Peine A, Imoohl M, Kersten A, R K. Implementation and one year evaluation of proenkephalin A in critical care. Int J Mol Sci. 2025;26(6):2602. doi:10.3390/ijms26062602
12. Schulte J, Depret F, Hartmann O, Pickkers P, F LP, F U. Clinical perfomance of proenkephalin A 119–159 for early diagnosis of acute kidney injury in patients with sepsis or septic shock. medRxiv. 2024;1–26. doi:10.1101/2024.10.11.24315291
13. Ji BK, Xie ZN, Pu XH, Gao N, Ye JL, Han YF. Proenkephalin A 119–159 as a biomarker for predicting sepsis associated acute kidney injury. Int Urol Nephrol. 2025;57(12):4285. doi:10.1007/s11255-025-04631-x
14. Hassan MM, Arnob AS, Ahmed AHH, Rahman AK. S, Akbar AAG, Jabin P, et al. Proenkephalin is an early biomarker to predict septic acute kidney injury among patients in intensive care unit. Arch Nephrol Urol. 2021;4(2):71–83. doi:10.26502/anu.2644-2833038
15. Schulz CA, Christensson A, Ericson U, Almgren P, Hindy G, Nilsson PM, et al. High level of fasting plasma proenkephalin A predicts deterioration of kidney function and incidence of CKD. J Am Soc Nephrol. 2017;28(1):291–303. doi:10.1681/asn.2015101177
16. Bullen AL, Katz R, Poursadrolah S, Short SAP, Long DL, Cheung KL, et al. Plasma proenkephalin A and incident chronic kidney disease and albuminuria in the Reasons for Geographic And Racial Difference in Stroke (REGARDS)

cohort. BMC Nephrol. 2025;25(1):16. doi:10.1186/s12882-023-03432-7

17. Nilsson C, Christensson A, Nilsson PM, Melander O, Bennet L. Proenkephalin and its association with renal function in Middle Eastern immigrants and native Swedes. Scand J Clin Lab Invest. 2021;81(7):573–8. doi:10.1080/00365513.2021.1979243

18. Matsiras D, Ventoulis I, Verras C, Bistola V, Bezati S, B F. Proenkephalin 119–159 in heart failure from pathophysiology. J Clin Med. 2025;14(8):2657. doi:10.3390/jcm14082657

19. Emmens JE, Maaten JM Ter, Damman K, Veldhuisen DJ van, Boer RA de, Struck J, et al. Proenkephalin, an opioid system surogate as a novel comprehensive renal marker in heart failure. Circ Hear Fail. 2019;12(5):e005544. doi:10.1161/circheartfailure.118.005544

20. Ng LL, Squire IB, Jones DJL, Cao TH, Chan DCS, Sandhu JK, et al. Proenkephalin, renal dysfunction and prognosis in patients with acute heart failure. J Am Coll Cardiol. 2017;69(1):56–69. doi:10.1016/j.jacc.2016.10.038.

21. Verras C, Bezati S, Bistola V, Ventoulis I, Matsiras D, S T. Point of care serum proenkephalin as an early predictor of mortality in patients presenting to the emergency departement with septic shock. Biomedicines. 2024;12(5):1004. doi:10.3390/biomedicines12051004

22. Frigyesi A, Bostroom L, Lengquist M, Johnson P, Lundberg OH, M S. Plasma proenkephalin A 119–159 in intensive care unit admission in a predictor of organ failure and 30 day mortality. Intensive Care Med Exp. 2021;9(1):36. doi:10.1186/s40635-021-00396-6