ORIGINAL ARTICLE

Prokineticin-2 and Procalcitonin's Diagnostic Accuracy for Sepsis in Critically Ill Patients: A Prospective Observational Study

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Received on: 29 December 2024; *Accepted on*: 10 February 2025; *Published on*: 28 February 2025

Abstract

Objective: Sepsis stands as a significant contributor to mortality in ICU settings worldwide. Early diagnosis and appropriate treatment are therefore essential to reduce mortality. We planned this study to investigate the diagnostic significance of prokineticin-2 (PK-2) in patients with sepsis.

Materials and methods: Adult patients with sepsis who were admitted to our intensive care unit (ICU) were included in this prospective observational study. On the day of admission and the 7th day of the ICU stay, the levels of procalcitonin (PCT) and PK-2 were assessed. Patients' mortality was observed for 28 days.

Results: This research involved 83 patients meeting the inclusion criteria. Prokineticin-2 showed a diagnostic sensitivity of 70.6% for sepsis, outperforming PCT with a sensitivity of 64.7%. In predicting mortality, PCT displayed a sensitivity of 95.5%, whereas Prokineticin-2 demonstrated an even higher sensitivity at 98.4%.

Conclusion: Prokinectin-2 can be used for screening adult patients with sepsis admitted to ICU.

Keywords: Procalcitonin, Prokineticin-2, Sepsis.

Indian Journal of Critical Care Medicine (2025): 10.5005/jp-journals-10071-24930

Highlights

- Rapid identification of sepsis is crucial for commencing early management.
- This study assessed Procalcitonin (PCT) and Prokinectin-2 (PK-2) levels upon admission and on the 7th day of ICU admission in patients suspected of sepsis.
- We found that PK-2 may reliably predict sepsis in adult patients admitted to the ICU.

Introduction

Sepsis is characterized as a condition encompassing physiological, pathological, and biochemical abnormalities brought on by infection.[1] Symptoms range from sepsis to septic shock and are described as a dysregulated host response to infection. Early diagnosis and treatment have contributed to reduced sepsis mortality.[2]

Various biomarkers have emerged for diagnosing sepsis, enhancing accuracy in detecting infection, and monitoring disease progression.[3] Procalcitonin (PCT) is used to diagnose sepsis in critically ill patients.[4] However, it may be raised in a variety of non-infectious conditions, such as major surgical procedures, major trauma without infection, and substantial burns.[5] According to Hoeboer et al.'s systematic review, PCT's sensitivity and specificity for sepsis are 76% and 69%, respectively.[6] It shows that there is plenty of potential for the identification of new sepsis markers.

Prokineticin-2 (PK-2) is considered a next-generation inflammatory marker of sepsis with superior prognostic value.[7] Unlike other biomarkers, PK-2 values are significantly decreased in patients diagnosed with sepsis compared with healthy controls. Additionally, lower concentrations of PK-2 were observed in patients who succumbed to sepsis compared with survivors, suggesting its potential for diagnosing sepsis and predicting mortality in adult patients.[7]

Prokinectin-2 may be a better option than traditional biomarkers for detecting sepsis, predicting patient prognosis, and guiding antibiotic therapy. In this investigation, the diagnostic accuracy of PK-2 was compared with that of PCT, a validated biomarker utilized in our hospital, and its relationship to patient outcomes was examined.

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How to cite this article: Bhat K, Kothari N, Sharma A, Goyal S, Meshram T, Paliwal B, *et al*. Prokineticin-2 and Procalcitonin's Diagnostic Accuracy for Sepsis In Critically Ill Patients: A Prospective Observational Study. Indian J Crit Care Med 2025;29(3):268–272.

Source of support: Nil

Conflict of interest: None

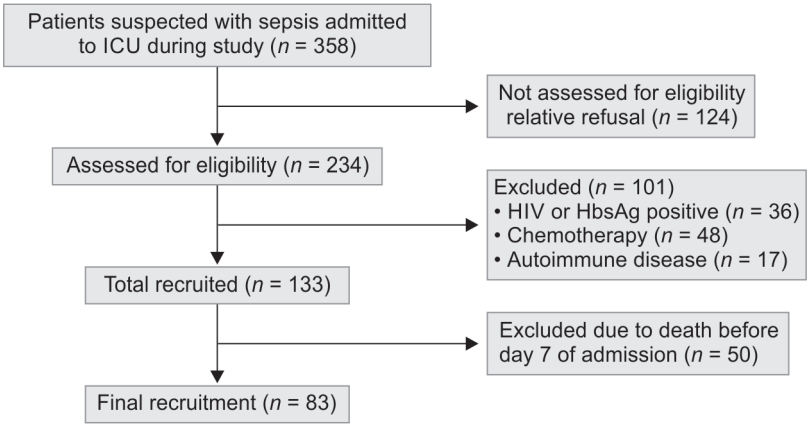

Fig. 1: Flow diagram

Materials and Methods

Study Design and Settings

This prospective observational investigation was conducted in the adult ICU of a tertiary care hospital. Subsequently, the Institutional Ethics Committee granted approval (IEC Reg No. - AIIMS/IEC/2022/3986, dated 22 March 2022) for this study. Patients enrolment began in April 2022 and concluded in September 2023.

Study Participants

After receiving informed written consent from the patient's family, patients who were 18 years of age or older and exhibited clinical signs of sepsis as indicated by the Sepsis-3 criteria at the time of ICU admission were included. Individuals with autoimmune diseases, HIV, HBsAg, HCV infections, on long-term steroids, immunosuppressants, chemotherapy, or with terminal illnesses (malignant cancer, end-stage liver or renal disease) were excluded.

As a part of blood sampling in ICU admission, the samples were collected for routine investigations, and from the same sample, 5 mL whole blood was drawn for Prokineticin-2 and Procalcitonin assessment (day 1). In our ICU, serum Procalcitonin is routinely done on admission as a biomarker of sepsis. The Prokineticin-2 and PCT tests were conducted again on the seventh day following the initial sample collection (day 7).

Whole blood was drawn from the participants using either gel separators or plain vacutainers. The sample was allowed to coagulate at ambient temperature for 2 hours or at 4°C for 15 minutes overnight. The serum was separated by centrifugation at 3000 rpm for 10 minutes at room temperature. The biochemistry lab kept the acquired serum at −80°C. The enzyme-linked immunosorbent assay (ELISA) kits were acquired because our institution does not routinely test for prokineticin-2. Following the manufacturer's instructions, an ELISA kit was used to estimate prokineticin-2 from the serum samples. Patients enrolled in the study did not bear any cost for participating in this study, and all tests were done with the help of our institute-funding source.

Upon ICU admission, blood, respiratory, urine, and any drain site cultures were collected to detect potential bacteremia. Subsequent analysis of all cultures was conducted, and the conclusive diagnosis of sepsis was established based on identifying organisms grown in these cultures. The patient's outcome regarding mortality or discharge was recorded 28 days after admission. The primary outcome was to assess PK-2 and PCT's diagnostic value in critically ill patients with sepsis. The secondary outcome was to establish PK-2's ability for predicting the outcome of sepsis in terms of 28-day mortality.

According to Tan et al.'s systematic review and meta-analysis, PCT has a sensitivity of 0.80 (95% confidence interval (CI): 0.69–0.87) for sepsis.[8] With a 95% confidence interval, 15% relative precision, and 10% dropout contingency, we calculated a sample size of 83 individuals, taking into account the lower bound CI of 0.69 to optimize the sample size computation.

Statistical Analysis

A Microsoft Excel spreadsheet was used for data entry in the investigation, and IBM's Statistical Package for the Social Sciences (SPSS) software, version 28.0, was used for evaluation. The mean and standard error (SE) were used to report the quantitative data, which were normally distributed. The paired *t*-test was used to compare the biomarker levels on days 1 and 7 to determine whether there was a significant difference. Discriminating abilities of the biomarkers were represented by areas under the receiver operating characteristic curve (ROC). For PK and PCT, ROC curve analysis was utilized to predict 28-day mortality and identify diagnostic cutoffs. A significance level of $p < 0.05$ was established.

Results

During this study, 358 patients admitted with suspected sepsis were assessed for eligibility. Out of these, 275 patients were excluded for a variety of reasons. Subsequently, 83 participants were enrolled in the research (Fig. 1).

Patients that were enrolled in the investigation were 46.28 ± 2.11 (mean ± SE) years old. Among the study population, 60.25% of male patients had sepsis-like symptoms, compared with 39.75% of female patients. The culture revealed 66 (79.51 %) patients positive. In this study, 22 out of the 83 enrolled patients died within 28 days of ICU admission, constituting a mortality rate of 26.5%. Subsequently, 61 patients were discharged, accounting for 73.49% of the study participants. The etiology and origin of sepsis in culture-positive patients are presented in Table 1.

In culture-negative individuals, PCT levels were 4.37 ± 1.98 ng/mL on day 1 and 6.17 ± 2.62 ng/mL on day 7. The PCT levels in culture-positive individuals ranged from 15.43 ± 3.82 ng/mL on day 1 to 31.35 ± 8.74 ng/mL on day 7. The PCT levels in patients who died after 7 days in the intensive care unit (ICU) or 28 days of

Table 1: The etiology and source of sepsis in patients positive for culture ($n = 66$)

Source of sepsis	*Organism grown in culture*	*Number (n)*
Patients discharged and positive for culture ($n = 47$)		
Blood	*Acinetobacter baumannii*	15
	Klebsiella pneumoniae	2
	Enterobacter cloacae	1
Sputum/tracheal aspirate	*Klebsiella pneumoniae*	10
	Acinetobacter baumannii	2
	Escherichia coli	2
Bronchial aspirate	*Acinetobacter baumannii*	4
	Klebsiella pneumoniae	3
Wound	*Escherichia coli*	4
	Acinetobacter baumannii	1
	Klebsiella pneumoniae	1
Abdomen	*Escherichia coli*	2
Patients died and positive for culture ($n = 19$)		
Blood	*Acinetobacter baumannii*	6
	Escherichia coli	2
	Klebsiella pneumoniae	2
Bronchial aspirate	*Acinetobacter baumannii*	4
	Klebsiella pneumoniae	2
Sputum/tracheal aspirate	*Escherichia coli*	1
	Klebsiella pneumoniae	1
Abdomen	*Escherichia coli*	1

follow-up were 13.96 ± 1.76 ng/mL on D1 and 64.51 ± 2.81 ng/mL on D7. Procalcitonin levels in individuals who were discharged from the ICU and were still alive after 28 days were 82.48 ± 8.97 ng/mL on D1 and 1.034 ± 0.51 ng/mL on D7.

The mean PK-2 level in culture-negative patients was 131.30 ± 7.67 ng/L on day 1 and 142.18 ± 12.18 ng/L on day 7. The mean PK-2 level in culture-positive individuals was 116.93 ± 5.30 ng/L on day 1 and 37.13 ± 4.14 ng/L on day 7. On day 1, the mean PK-2 level was 209 ± 17.64 ng/L, whereas, on day 7, it was 30.03 ± 14.88 ng/L in individuals who died within 28 days of follow-up or after 7 days in ICU. The mean PK-2 level in patients discharged from the ICU was 98.72 ± 9.94 ng/L on day 1 and 210.77 ± 9.99 ng/L on day 7.

According to the ROC curve's coordinates, 149.34 ng/L of PK-2 was the ideal value on day 1 for obtaining the best sensitivity and specificity in the diagnosis of sepsis. At the same time, that of PCT was 1.495 ng/mL. Procalcitonins sensitivity was 64.7% at this value, but PK-2's was 70.6%. However, PK-2 and PCT both had 50% specificity. Figure 2 shows that the area under the ROC (AUROC) curve for PCT was 0.505 ($p < 0.05$), and for PK-2, it was 0.621 ($p < 0.05$).

On day 7, the PK-2 value was 100.51 ng/L, and the PCT value was 4.33 ng/mL, indicating the best prognosis for 28-day mortality. Prokineticin-2 and PCT had AUROC values of 0.99 ($p < 0.05$) and 0.997 ($p < 0.05$), respectively, which allowed them to distinguish between people who were at risk of death and those who had a chance of survival. Prokineticin-2 predicted 28-day mortality

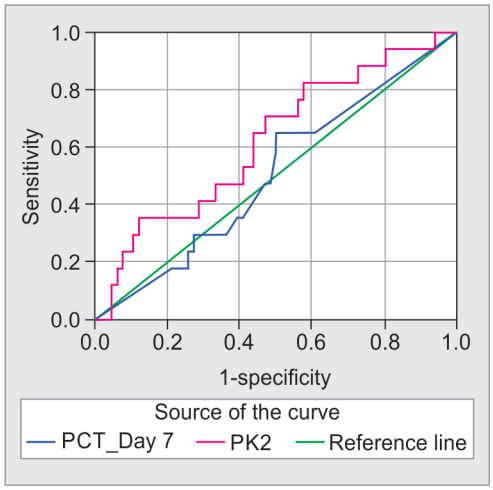

Fig. 2: The ROC curve for PK-2 and PCT levels on Day 1 in relation to culture positive for patients with sepsis

Table 2: PCT and PK-2 patterns from D1 to D7 in the culture-negative and positive groups

Culture	*Mean*	*Standard error*	*95% CI*		*p-value*
			Lower	*Upper*	
Negative					
Pair-1					
PCT D1–PCT D7	1.20	0.62	1.01	4.38	0.602
Pair-2					
PK-2 D1–PK-2 D7	10.88	4.51	6.48	14.88	0.389
Positive					
Pair-1					
PCT D1–PCT D7	15.92	4.98	64.86	192.86	0.027
Pair-2					
PK-2 D1–PK-2 D7	79.80	10.44	41.45	97.23	0.032

CI, confidence interval; PCT, procalcitonin; PK-2, prokineticin-2; *The values showed the changes during the first week of ICU admission

with a sensitivity of 98.4% and a specificity of 95.5% at this cutoff. Procalcitonin predicted 28-day mortality with a sensitivity of 95.5%, along with a specificity of 95.1% at this threshold.

Procalcitonin and PK-2 levels in the culture-negative group did not significantly change from D1 to D7, according to the results of the paired sample *t*-test. The culture-positive group shows a significant rise in PCT levels from D1 to D7 ($p = 0.027$). Furthermore, PK-2 levels from D1 to D7 change significantly ($p = 0.032$) (Table 2). Procalcitonin levels in the mortality group changed significantly between D1 and D7 ($p < 0.001$). Over the same period, PK-2 also showed significant changes ($p < 0.001$). Additionally, PCT levels in the discharge group showed significant changes from D1 to D7 ($p < 0.001$), and PK-2 values also showed a significant change ($p < 0.001$) (Table 3).

Sequential organ failure assessment (SOFA) score was evaluated to determine severity of organ dysfunction. Figure 3 illustrates association between the SOFA score and PK-2 levels. It demonstrates that for every one unit change in PK-2 value, the SOFA score changes by –0.04, indicating a negative correlation between the SOFA score and PK-2 ($p < 0.01$) (Fig. 3).

Table 3: PCT and PK-2 patterns from D1 to D7 in the death and discharge groups

Outcome	Mean	Standard error	95% CI		p-value
			Lower	Upper	
Death					
Pair-1					
PCT D1–PCT D7	50.55	2.65	56.07	45.02	<0.001
Pair-2					
PK-2 D1–PK-2 D7	179.03	9.04	145.06	213.04	<0.001
Discharge					
Pair-1					
PCT D1–PCT D7	79.05	6.34	63.49	99.71	<0.001
Pair-2					
PK-2 D1–PK-2 D7	112.04	7.96	127.98	96.10	<0.001

CI, confidence interval; PCT, procalcitonin; PK-2, prokineticin-2; *The values showed the changes during the first week of ICU admission

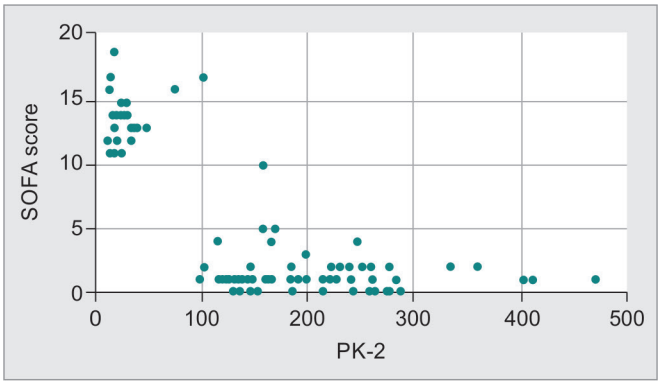

Fig. 3: Correlation between SOFA score and serum PK-2 level

Discussion

Sepsis continues to be a highly lethal condition, and the precise causes of death are still not well understood.[9] The reliance on culture reports, considered the gold standard for diagnosis, is hindered by delayed results, emphasizing the critical need for quicker diagnostic and prognostic tools. Despite the utilization of current biomarkers, there is a notable gap in sensitivity as well as specificity for accurate sepsis diagnosis and prognosis. In the current study, the diagnostic and short-term prognostic value of PCT and PK-2 for patients with sepsis during the first week of ICU stay were compared.

Prokineticin-2 is a newly identified inflammatory marker of sepsis, and research related to the role of PK-2 in patients with sepsis is limited. Initially identified in a yellow-bellied toad species (*Bombina variegata*), PK2 plays diverse roles in humans, including involvement in neurodevelopment, circadian rhythm regulation, muscle function, pain perception, and immune responses.[7] It augments the phagocytic bactericidal activity of macrophages.[10]

The research done by Yu et al. provided additional evidence supporting the potential utility of PK-2.[11] They assessed Prokineticin-2 levels in 47 adult patients diagnosed with sepsis and 30 individuals in good health, serving as control subjects. They observed that in all the patients with sepsis, PK-2 levels were markedly lowered compared with controls, aligning with the findings in our study. They emphasized that the distinctiveness of PK-2 as an innovative biomarker in sepsis diagnostics is in its downregulation during sepsis, akin to a negative acute phase reaction protein. In contrast, levels of other known biomarkers tend to be increased.[11] Moreover, they observed that the administration of recombinant PK-2 in an animal model exhibits a protective function by enhancing survival rates and mitigating multiorgan dysfunction in sepsis.[11,12]

We first tried to establish a diagnostic threshold value for PK-2 in sepsis patients due to the apparent uniqueness of PK-2 as a sepsis biomarker and the paucity of existing research. For the diagnosis of sepsis, PK-2's ideal sensitivity and specificity were attained at 149.34 ng/L. The PK-2's sensitivity for identifying sepsis at this cutoff point was 70.6%. An analogous investigation for PCT was conducted, and 1.495 ng/mL was determined to be the suitable cutoff threshold. PCT's sensitivity at that level was marginally lower than PK-2's, which was 64.7%. The PCT and PK-2 both had moderate specificities set at 50%. Our analysis revealed that 100.51 ng/L was an appropriate cutoff value of PK-2 for anticipating 28-day mortality at day 7. Prokineticin-2 had a sensitivity of 98.4%, along with a specificity of 95.5% at this threshold. The optimal PCT value for prognostication at day 7 was 4.33 ng/mL. At this threshold, PCT had a 95.5% sensitivity and a 95.1% specificity for predicting 28-day mortality. We were unable to find a cutoff for PK-2 for diagnosis and prognosis of patients with sepsis in the literature.

In our investigation, PK-2 was evaluated on days 1 and 7. There was a significant drop in the deceased's PK-2 value between days 1 and 7 ($p < 0.001$). However, PK-2 showed a significant increase in the survivors from day 1 to day 7 ($p < 0.001$). This suggests that PK-2 level trends can be used to evaluate treatment effectiveness.

The present study had many limitations. The study was conducted on a smaller sample size and at a single center. A multicenter investigation should be carried out to improve the findings' reliability as well as generalizability. This broader approach will allow for a more comprehensive evaluation of biomarker cutoffs for diagnosing sepsis, specifically tailored to the characteristics of the Indian population. It is important to highlight that PCT was assessed through point-of-care testing in the ICU, whereas PK-2 was measured using the ELISA test in the laboratory. Using distinct testing methods between the two biomarkers may introduce variability and potential errors in the results. Prokineticin-2 was assessed on days 1 and 7; instead, if taken at shorter regular intervals, it would have led to more accurate results.

Conclusion

In adult patients admitted to ICU, prokineticin-2 may be a reliable indicator of sepsis. This research also establishes new cutoff values for PK-2 relevant to diagnosing and prognosis patients with sepsis. Nonetheless, more research on a larger scale is required to authenticate and corroborate these findings.

Ethics Approval

IRB approval was taken from the Institutional Ethics Committee (IEC Reg No.- AIIMS/IEC/2022/3986 dated 22 March 2022)).

Authors' Contributions

Design conception: KB and NK. Data collection: KB, NK, AS, and SG. Statistical analysis: NK. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: KB. Writing and editing: KB, NK, AS, TM, BP, and SG. Critical revision of the manuscript for important intellectual content, final review, and approval: All authors.

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