

The relationship between pancreatic stone protein, procalcitonin, and C-reactive protein levels and the sequential organ failure assessment (SOFA) score in septic patients

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Abstract

Objective: This study aimed to determine the relationships among procalcitonin (PCT), C-reactive protein (CRP), pancreatic stone protein (PSP), and the Sequential Organ Failure Assessment (SOFA) score in septic patients during the first 72 hours of intensive care unit (ICU) care.

Design: Prospective observational cohort with a two-time-point.

Setting: Intensive Care Unit of Dr. Wahidin Sudirohusodo General Hospital, Makassar, from November 2024 to February 2025.

Patients and participants: 40 patients with sepsis meeting Sepsis-3 criteria were enrolled in the study.

Measurements and results: PSP, PCT, and CRP levels were measured within the first 72 hours after sepsis diagnosis, analyzed using an enzyme-

linked immunosorbent assay (ELISA) kit, and correlated with the SOFA score using the Spearman test. The results showed that all three biomarkers were positively correlated with the SOFA score. PCT showed a strong and significant correlation with SOFA ($r=0.663$, $p<0.001$), CRP also showed a strong and significant correlation ($r=0.650$, $p<0.001$), while PSP showed a moderate but significant correlation ($r=0.430$, $p=0.004$). PCT and CRP were significantly associated with a higher risk of mortality ($p<0.05$), but not significantly in PSP ($p>0.05$).

Conclusion: PCT and CRP have potential as markers of prognosis and severity of sepsis in the early phase of intensive care, and PSP has potential as a marker of severity and higher risk of mortality in sepsis.

Keywords: C-reactive protein, pancreatic stone protein, procalcitonin, sepsis, SOFA score.

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Background

Sepsis is defined as organ dysfunction caused by a dysregulated host response to infection. (1) In 2017, sepsis accounted for 49 million cases and 11 million deaths globally. Despite advancements in hospital management, sepsis continues to be a leading cause of mortality, responsible for approximately 20% of all deaths worldwide. (2) In Indonesia, the incidence remains elevated, with rates reaching 30.29% and mortality ranging from 11.56% to 49%. (3) Sepsis has a clinical manifestation that is nonspecific and often mimics other conditions. No definitive diagnostic test exists. Early detection of sepsis can improve patient outcomes. Common clinical variables and instruments include the Sys-

temic Inflammatory Response Syndrome (SIRS) criteria, vital signs, the Quick Sequential Organ Failure Assessment (qSOFA), and the National Early Warning Score (NEWS). (4,5) Organ dysfunction is defined by a Sequential Organ Failure Assessment (SOFA) score increase of more than 2 points, which correlates with a 10% rise in in-hospital mortality. A SOFA score below 9 is associated with a 35% increased risk of death. (1) In recent years, several biomarkers, including lactate and procalcitonin (PCT), have been validated for sepsis identification. Biomarkers should be accurate and reproducible. Pancreatic stone protein (PSP) may be a promising option, demonstrating superior diagnostic and prognostic accuracy compared to C-reactive protein (CRP) and PCT. (1) Studies show that PSP levels correlate with disease severity, ranging from less than 20 ng/ml in uninfected adults to several hundred ng/ml in severe sepsis and several thousand ng/ml in septic shock. PSP levels rise above the normal range before clinical signs and symptoms appear, supporting its use for early detection in the preclinical phase. These features underscore PSP's potential as a prognostic and diagnostic tool in sepsis management. (6)

A previous meta-analysis found that PCT had a combined sensitivity of 77% and specificity of 79% for diagnosing sepsis in critically ill patients. (7) Coelho et al. reported that a 0.5-fold increase in CRP levels from baseline on day 2 was associated with a poor prognosis (sensitivity 91%, specificity 59%). Conversely, a decrease in CRP levels of 0.31 or more on day 2 after antibiotic administration (day 0) indicated a good prognosis (sensitivity 75%, specificity 85%). (8) Comparative associations between PCT, CRP, and PSP and SOFA scores, as well as sepsis mortality, have not been previously studied. This study is important because the persistently high mortality rate associated with sepsis underscores the need for accurate diagnostic markers. Early and precise diagnostic markers are crucial to guide the therapeutic management of septic patients in the intensive care unit (ICU). Therefore, this study aimed to determine the relationships among PCT, CRP, and PSP levels and the SOFA score in septic patients during the first 72 hours of ICU care.

Materials and methods

Design and participants

This study was a prospective observational cohort with a two-time-point design that aimed to assess the relationship between PSP, PCT, and CRP levels and the SOFA score in patients with sepsis. The

study was conducted at the ICU of Dr. Wahidin Sudirohusodo General Hospital in Makassar from November 2024 to February 2025. The study population consisted of all septic patients with SOFA scores greater than 2 at ICU admission based on clinical judgement. Samples were selected using consecutive sampling until the specified number was reached, based on the sample size calculation for the correlation test between two numeric variables, with a minimum of 40 samples to maintain a test power of 80%. The inclusion criteria included patients aged 18–65 years who met the Sepsis-3 definition of sepsis and provided informed consent to participate in the study. Exclusion criteria included patients with a history of chemotherapy, hematologic malignancies, myocardial infarction <24 hours, chronic kidney disease, chronic pancreatitis, or pancreatic cancer. Subjects who died or returned home at their own request after being included in the sample were categorized as dropouts.

Data collection

The characteristics of the research subjects, including age, gender, and body mass index (BMI) status. BMI status was recorded based on the World Health Organization (WHO) Asia-specific criteria. The study procedures included explaining the study purpose, obtaining informed consent, and collecting 3 ml of venous blood on the first (T1) and third (T2) days of treatment to assess PSP, PCT, and CRP levels. Blood samples were drawn according to standard procedures using aseptic technique with vacutainers. PSP, PCT, and CRP levels were analyzed by an enzyme-linked immunosorbent assay (ELISA) kit (ELABSCIENCE). Gender and age data were obtained from medical records. PSP <12 ng/ml, CRP <5 mg/l, and PCT <0.05 ng/ml were considered normal. (9–11) The degree of organ dysfunction was assessed using the SOFA score, which included central nervous system, respiratory, cardiovascular, liver, kidney, and coagulation functions. A SOFA score ≥ 0.6 indicated a high risk of mortality.

Data analysis and research ethics

Statistical analysis was performed using SPSS version 22.0. The Kolmogorov-Smirnov normality test was used to assess the data distribution. Correlations between variables were analyzed using the Pearson test when the data were normally distributed and the Spearman test when they were not. A p-value ≤ 0.05 was considered statistically significant. The research was conducted with approval from the Biomedical Research Ethics

Results

This study involved 44 septic patients treated in the ICU of Dr. Wahidin Sudirohusodo General Hospital, Makassar. The majority were male (59.1%), with a mean age of 49.07 ± 16.80 years. Most were overweight (59.1%) and had respiratory comorbidities (88.6%). The results showed an increase in PCT, CRP, and PSP levels from the first 24 to 72 hours of treatment. The median initial levels were 21.05 (0.01–103.2), 89.35 (3.0–388.0), and 84.32 (7.0–471.7), respectively. These increased to 21.9 (0.23–121.2), 109.5 (32.8–2038.0), and 91.07 (22.1–307.5). This increase indicated a positive relationship between the three biomarkers and high SOFA scores (≥ 2) in septic patients (**Table 1**).

The Spearman correlation test results demonstrated significant relationships between PCT, CRP, and PSP and SOFA scores in the first 24 hours. Specifically, PCT exhibited a moderate positive correlation ($r=0.550$, $p<0.001$), whereas CRP demonstrated a strong positive correlation ($r=0.615$, $p<0.001$). Additionally, PSP showed a moderate, statistically significant positive correlation ($r=0.445$, $p=0.020$). Together, these findings indicated that the three biomarkers were closely associated with the severity of sepsis in ICU patients (**Table 2**).

Spearman correlation test results for the first 72 hours showed that all three biomarkers — PCT, CRP, and PSP — were significantly associated with the SOFA score. PCT showed a strong positive correlation ($r=0.663$, $p<0.001$), while CRP also had a strong positive correlation ($r=0.650$, $p<0.001$). In contrast, PSP showed a moderate positive correlation but remained statistically significant ($r=0.430$, $p=0.004$). These results confirmed that increases in these three biomarkers were closely associated with the severity of sepsis in ICU patients after 72 hours of treatment (**Table 3**).

Mann-Whitney test comparative analysis identified significant differences in PCT and CRP levels between high-risk (SOFA >6) and low-risk (SOFA <6) mortality groups at both 24 and 72 hours. Specifically, within the first 24 hours, PCT and CRP levels were higher in the high-risk group, with medians of 33.85 (0.01–103.2) and 112.65 (29.0–388.0), respectively. In contrast, the low-risk group exhibited lower levels ($p=0.004$ and $p=0.001$). In contrast, PSP did not show a statistically significant difference between groups at this time ($p=0.114$). At 72 hours, PCT and CRP levels remained significant-

ly elevated in the high-risk group. PSP continued to show no significant differences between the groups (**Tables 4** and **5**). Taken together, these results suggested that PCT and CRP were more sensitive indicators of mortality prognosis than PSP in septic patients.

Discussion

Procalcitonin and organ dysfunction

These findings suggested that PCT levels at 24 and 72 hours following sepsis were correlated with the SOFA score. This supported the potential of PCT as a biomarker for sepsis. These results were in line with the study by Zhang et al., which found that PCT had an area under the curve (AUC) of 0.732 for sepsis diagnosis, not significantly different from the AUC of 0.872 for the SOFA score in the same study. There was a strong correlation between PCT and SOFA scores. (12)

The results of this study indicated that changes in PCT levels within the first 24 hours were associated with an increased risk of patient mortality. Similar results were reported by Jain et al., who found that PCT levels of 7 ng/ml or more predicted death with a hazard ratio of 2.6 (1.1–6.3) in sepsis. (13) Similar results were reported in another study, which showed that a decrease in PCT of more than 80% within 72 hours of initial assessment indicated a higher risk of mortality and the need for more intensive management. (14)

C-reactive protein as a prognostic marker

In this study, CRP levels measured within the first 24 hours showed a stronger correlation with the SOFA score than PCT and PSP. However, at 72 hours, the correlation between CRP and SOFA was slightly lower than that observed for PCT. This result can be explained by the fact that CRP levels can increase in response to a wide range of infections, including those caused by viruses, bacteria, protozoa, and fungi. Non-infectious conditions such as burns, poisoning, autoimmune disorders, and neoplasms can also increase CRP concentrations. Nevertheless, CRP remains useful in ruling out bacterial infections when levels are below 10 mg/l, especially if confirmed by repeat testing at 8- to 12-hour intervals. Therefore, CRP can serve as a biomarker for diagnosing sepsis. (15,16) CRP is secreted within 4 to 6 hours after a stimulus, peaks at 36 to 50 hours, and has a half-life of approximately 1 hour. (16,17)

These findings indicate that elevated CRP levels are associated with an increased risk of mortality. Higher CRP levels in the first 72 hours also correlated with a greater risk of increased mortality.

This study aligned with previous studies that have reported a relationship between CRP levels and sepsis mortality. According to Devran et al.'s study, CRP levels can predict mortality in patients with respiratory failure due to sepsis who are treated according to sepsis protocols. Its predictive value is comparable to that of the initial Acute Physiology and Chronic Health Evaluation (APACHE) II assessment and SOFA scores on the first and third days of ICU admission. (18) Similar results were reported by Gebhardt et al., who found that changes in CRP levels from the first to the third day were more accurate in predicting mortality than initial CRP values. (19) A study by Ho et al. also found that, within the first 24 hours after ICU discharge, the average CRP level was 174 mg/l in patients who did not survive and 85.6 mg/l in those who did. (20) However, this study only linked CRP levels with SOFA score categories that are considered to increase the risk of mortality in sepsis.

Pancreatic stone protein: emerging biomarker

This study identified a positive correlation between PSP and SOFA scores at 24 and 72 hours. Although this correlation was lower than that observed with PCT and CRP, the moderate association suggested that PSP might be a useful biomarker for diagnosing sepsis. The role of PSP in sepsis diagnosis was consistent with previous findings that PSP provided superior diagnostic performance for sepsis compared with PCT and CRP in ICU patients. (21) This may be explained by PSP's early sepsis defense by binding and activating polymorphonuclear neutrophils (PMNs), which may contribute to microcirculatory failure. PSP is a C-type lectin receptor that activates damage-associated molecular patterns (DAMPs), which are involved in the activation of PMNs. This process signals the activation of a protein kinase cascade and contributes to the development of organ failure. (22) However, the lower diagnostic potential of PSP for sepsis is consistent with a multicenter study that reported significant increases in PCT, CRP, and PSP within the first 3 days after sepsis diagnosis. CRP levels increased earliest on the second day, followed by PCT on the third day. PSP levels began to increase on the fifth day. (23) This was due to another role of PSP: promoting bacterial aggregation, thereby preventing the penetration of the intestinal barrier. (23–25)

In addition to PCT and CRP, this study found that elevated PSP levels were associated with a higher risk of mortality, as determined by the SOFA score criteria. However, this association was not statistically significant. A previous study by Que et

al. found that PSP, a novel acute-phase protein measured within the first 24 hours of ICU admission, could predict mortality in patients with severe sepsis and septic shock. (26) In line with this study, it was reported that serial PSP measurements during the first 24 hours of ICU admission could serve as a biomarker to identify patients at high risk of mortality. PSP performed better than CRP and PCT, which are commonly used to diagnose infectious diseases. However, its overall accuracy for this indication was low; therefore, it should not be used to predict outcome. (27)

The results of this study suggested that PCT, CRP, and PSP could serve as biomarkers of severity, as indicated by the SOFA score. PCT and CRP can be biomarkers of increased risk of death based on the SOFA criteria. Combining these biomarkers may improve diagnostic accuracy. This is due to the limitations of each marker. CRP has been shown to exhibit high sensitivity but limited specificity. (28) CRP is frequently used in postoperative monitoring, but its diagnostic accuracy varies depending on the clinical context and patient population. In individuals with trauma, recent surgery, or autoimmune disease, elevated CRP levels do not always indicate sepsis. These elevations are often caused by sterile inflammation. Conversely, CRP testing can produce false-negative results in cases of local infection, where the inflammatory response is insufficient to elevate CRP levels. (29) While CRP alone provides moderate diagnostic accuracy in differentiating sepsis from non-septic conditions, its effectiveness is enhanced when combined with PCT. No single sepsis biomarker is considered ideal. However, studies using multiple biomarkers may help identify patients who require intensive monitoring, thereby supporting timely diagnosis and appropriate therapy. (30) However, this study did not assess the diagnostic accuracy of a biomarker combination for diagnosing sepsis. Further research will be useful to clarify the results.

Strengths and limitations

This study had moderate to high novelty value because it combined three biomarkers (PCT, CRP, and PSP) and their correlation with the SOFA score, which was associated with severity and a high risk of mortality. This topic is still rarely studied. Furthermore, this study provided a potential basis for developing a multi-biomarker prediction panel for severity and mortality in the ICU. This study was limited by its small sample size and single-center design. Serial biomarker measurements were not performed over 72 hours. This study measured only the high mortality risk based on the SOFA score

criteria. It did not assess additional clinical outcomes, including mortality, length of hospital stay, and duration of ventilator use.

Clinical implications and future research

These results imply that PCT, CRP, and PSP may be useful to employ together in the early diagnosis of sepsis. In particular, PCT and CRP measurements in sepsis can be recommended for monitoring sepsis prognosis. Building on these findings, further investigation into multi-biomarker panels may improve sepsis assessment, facilitate targeted treatment strategies, and enhance patient outcomes. Therefore, future research should prioritize large-scale, multicenter clinical trials to validate the effectiveness and reliability of these biomarkers.

Additionally, studies examining combinations of multiple biomarkers may further improve diagnostic accuracy and prognostic precision.

Conclusion

PCT, CRP, and PSP may serve as multi-biomarkers for assessing the severity of sepsis. Additionally, PCT and CRP may predict a higher risk of mortality in patients in the ICU. Future research should involve larger sample sizes and multi-center study designs. Such studies are strongly recommended to validate these findings and establish optimal cutoff values for these biomarkers. Ultimately, this approach would facilitate their use as a clinical basis for assessing the condition and prognosis of patients with sepsis.

Table 1. Sample characteristics

Variable	Results
Gender, n (%)	
- Male	26 (59.1)
- Female	18 (40.9)
Age, mean±SD	49.07±16.80
BMI status, n (%)	
- Underweight	2 (4.5)
- Normal	16 (36.4)
- Overweight	26 (59.1)
Confounding factors, n (%)	
- Respiratory	39 (88.6)
- Cardiovascular	29 (65.9)
- Renal	19 (43.2)
- Neurology	24 (54.5)
PCT (T1), median (range)	21.05 (0.01–103.2)
CRP (T1), median (range)	89.35 (3.0–388.0)
PSP (T1), median (range)	84.32 (7.0–471.7)
SOFA first 24 hours (T1), n (%)	
- Total score >2	44 (100)
- Total score <2	0 (0)
PCT (T2), median (range)	21.9 (0.23–121.2)
CRP (T2), median (range)	109.5 (32.8–2038.0)
PSP (T2), median (range)	91.07 (22.1–307.5)
SOFA first 72 hours (T2), n (%)	
- Total score >2	42 (95.5)
- Total score <2	2 (4.5)

Legend: SD=standard deviation; BMI=body mass index; PCT=procalcitonin; T1=first day; CRP=C-reactive protein; PSP=pancreatic stone protein; SOFA=Sequential Organ Failure Assessment; T2=third day.

Table 2. Relationship between procalcitonin, C-reactive protein, pancreatic stone protein, and the SOFA score

	SOFA score (T1)	
	r	p-value
PCT (T1)	0.550	<0.001
CRP (T1)	0.615	<0.001
PSP (T1)	0.445	0.002

Legend: SOFA=Sequential Organ Failure Assessment; T1=first day; PCT=procalcitonin; CRP=C-reactive protein; PSP=pancreatic stone protein.

Table 3. Relationship between procalcitonin, C-reactive protein, pancreatic stone protein, and the SOFA score in the first 72 hours

	SOFA score (T2)	
	r	p-value
PCT (T2)	0.663	<0.001
CRP (T2)	0.650	<0.001
PSP (T2)	0.430	0.004

Legend: SOFA=Sequential Organ Failure Assessment; T2=third day; PCT=procalcitonin; CRP=C-reactive protein; PSP=pancreatic stone protein.

Table 4. Comparative test of procalcitonin, C-reactive protein, and pancreatic stone protein on patient mortality risk based on the SOFA score in the first 24 hours

T1	High risk mortality (SOFA \geq 6)	Low risk mortality (SOFA<6)	p-value
PCT	33.85 (0.01–103.2)	0.03 (0.02–77.4)	0.004
CRP	112.65 (29.0–388.0)	4.0 (2.0–318.0)	0.001
PSP	86.76 (13.0–193.1)	9.5 (7.0–471.7)	0.114

Legend: SOFA=Sequential Organ Failure Assessment; T1=first day; PCT=procalcitonin; CRP=C-reactive protein; PSP=pancreatic stone protein.
Values are in median (range).

Table 5. Comparative test of procalcitonin, C-reactive protein, and pancreatic stone protein on patient mortality risk based on the SOFA score in the first 72 hours

T2	High risk mortality (SOFA \geq 6)	Low risk mortality (SOFA<6)	p-value
PCT	23.80 (0.23–121.2)	7.62 (0.50–34.5)	0.001
CRP	117.45 (39.0–2038.0)	71.0 (32.8–86.0)	0.000
PSP	100.95 (22.1–307.5)	82.1 (24.5–121.89)	0.132

Legend: SOFA=Sequential Organ Failure Assessment; T2=third day; PCT=procalcitonin; CRP=C-reactive protein; PSP=pancreatic stone protein.
Values are in median (range).

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