ORIGINAL INVESTIGATION

Access this article online
Quick Response Code:

Website:
www.jcritintensivecare.org
DOI:
10.14744/dcybd.2024.3689

Procalcitonin to Albumin Ratio as a Predictor of Intensive Care Unit Mortality in Sepsis

Siti Afifah Abd Manas, Kamaruddin Ibrahim, Laila Ab Mukmin, Wan Fadzlina Wan Muhd Shukeri

Abstract

Aim: High procalcitonin (PCT) and low albumin (ALB) concentrations have been associated with mortality in sepsis. This study aimed to investigate the prognostic value of the PCT/ALB ratio for intensive care unit (ICU) mortality in patients with sepsis.

Study Design: A retrospective cohort study was conducted in a mixed ICU at a university-affiliated hospital in Malaysia over a 3-year period. Consecutive adult patients admitted to the ICU, who underwent simultaneous measurements of PCT and ALB and fulfilled the Sepsis-3 Criteria, were recruited. Serum PCT was measured in the ICU using a point-of-care analyzer (Finecare™ PCT Rapid Test, Guangzhou, China). The predictive performance of the PCT/ALB ratio was assessed by analysis of a receiver-operating characteristic (ROC) curve.

Results: A total of 185 patients diagnosed with sepsis were recruited. The primary outcome (i.e., all-cause ICU mortality) was 35.1%. Baseline PCT was significantly higher, and baseline ALB was significantly lower in non-survivors compared to survivors (25.4 [standard deviation, SD=31.2] vs. 9.8 [SD=20.0] ng/mL and 26.1 [SD=5.4] vs. 30.6 [SD=6.5] g/dL, respectively; P<0.001). The computed PCT/ALB ratio was significantly higher in non-survivors compared to survivors (1.04 [SD=1.29] vs. 0.36 [SD=0.72]; P<0.001). The area under the ROC curve (AUC) for the PCT/ALB ratio in discriminating ICU mortality was 0.731 (95% confidence interval [CI]: 0.658-0.804), which was higher than the AUC of PCT alone (AUC: 0.721, 95% CI: 0.647-0.796). The optimal cut-off value for the PCT/ALB ratio was > 0.15, with a sensitivity of 70.8% and a specificity of 63.3%.

Conclusions: The PCT/ALB ratio slightly improved the prediction of ICU mortality compared to the use of PCT alone. Thus, it may aid in the prognostication of sepsis, although further validation in a prospective multicenter study is required.

Keywords: Albumin; Mortality; Procalcitonin-to-albumin ratio; Procalcitonin; Sepsis.

Department of Anaesthesiology and Critical Care, Universiti Sains Malaysia, Kubang Kerian, Malaysia

Address for correspondence:
Wan Fadzlina Wan Muhd Shukeri, MD. Department of Anaesthesiology and Critical Care, Universiti Sains Malaysia, Kubang Kerian, Malaysia.
E-mail: wfadzlina@usm.my

Received: 09-01-2024
Accepted: 06-03-2024
Published: 01-04-2024

Introduction

For intensivists worldwide, sepsis is one of the most frequently encountered conditions. Its defining characteristic is organ dysfunction resulting from a dysregulated response to infection.[1] This dysfunction can be potentially fatal, and despite recent advances in intensive care, the overall mortality rate among patients who develop sepsis remains high.[2] It is crucial to risk-stratify patients with sepsis upon admission to the intensive care unit (ICU) or shortly thereafter to determine

How to cite this article: *Abd Manas SA, Ibrahim K, Ab Mukmin L, Wan Muhd Shukeri WF. Procalcitonin to albumin ratio as a predictor of intensive care unit mortality in sepsis. J Crit Intensive Care. 15(1):23—29.*

the direction of treatment, which can potentially impact outcomes.

In critical care settings, extensive evaluations have been conducted on the usefulness of procalcitonin (PCT), a positive acute phase protein. Various studies suggest that measuring PCT levels can serve as a tool for diagnosing sepsis[3] and predicting its prognosis[4], given the correlation between PCT levels and infection severity. However, the prognostic use of PCT is more controversial. Conversely, serum albumin (ALB), a negative acute phase protein, reflects nutritional status and has been shown to be an important determinant of outcomes in critically ill patients,[5] thus suggesting its potential as a prognostic biomarker in sepsis.[5]

Emerging evidence suggests that measuring a combination of positive and negative acute phase protein levels may enhance the predictive capacity of the former. Fairclough et al.[6] first proposed in 2009 the concept of using the ratio of a positive acute phase protein (i.e., C-reactive protein [CRP]) to serum ALB as a predictor of patient outcomes. Their hypothesis, later substantiated, indicated that the CRP/ALB ratio strongly correlates with mortality in acute medical ward patients. Since then, a positive correlation has been reported between the PCT/ALB ratio and mortality in hospitalized elderly patients at risk of bacterial infection [7] and in patients with intra-abdominal sepsis and acute kidney injury.[8] Studies have also reported a positive correlation between the PCT/ALB ratio and the severity of inflammation in conditions such as urosepsis [9], neonatal sepsis [10], and community-acquired pneumonia in elderly patients.[11]

The primary aim of this study was to evaluate the prognostic effectiveness of the PCT/ALB ratio in predicting ICU mortality rates among a general cohort of sepsis patients admitted to our hospital's ICU. Additionally, we sought to compare the prognostic value of the PCT/ALB ratio with that of PCT alone and the Sequential Organ Failure Assessment (SOFA) score, a widely used prognostic scoring system in sepsis, in predicting mortality.

Materials and Methods

Study Design

This retrospective cohort study was conducted in the mixed ICU of a university-affiliated hospital in Malaysia over a 3-year period from September 1, 2017, to August 31, 2020. Ethical approval was obtained from Universiti Sains Malaysia Human Research and Ethics Committee (HREC) (Approval Number: USM/JEPeM/20120699, Date: 6.04.2021). Given the study's retrospective nature, the institutional HREC waived the need for participant consent.

Study Population

The study included consecutive adult patients admitted to the ICU, from whom blood was collected within 24 hours of admission for simultaneous measurements of PCT and ALB. All included individuals met the sepsis-3 criteria for documented sepsis.[1] Patients with chronic conditions known to cause hypoalbuminemia, such as liver cirrhosis, nephrotic syndrome, heart failure, and malnutrition, were excluded. If a patient had multiple ICU admissions, only data from the first admission were considered for the study.

Study Procedure

Relevant baseline data were retrieved from the medical records of eligible patients, including demographic information (age and gender), clinical data, biomarker levels, and outcomes (i.e., all-cause ICU mortality). Clinical data included the admission category, baseline comorbidities determined using the Charlson Comorbidity Index, baseline illness severity measured by the Acute Physiology and Chronic Health Evaluation, microbiological culture results, and ICU treatment received within the first 24 hours. Biomarker data comprised serum PCT levels and serum ALB measurements upon ICU admission.

Serum PCT levels were measured in our ICU using a point-of-care analyzer and rapid quantitative tests (Finecare™; Wondfo, Guangzhou, China). Serum ALB levels were assessed in the main laboratory as part of routine ICU investigation work, with a reference range of 35 to 45 g/L. The PCT/ALB ratio was calculated by dividing the serum PCT level by the serum ALB level.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 26 (IBM software) and MedCalc® Version 20.023. Baseline characteristics of the patients were reported using counts (percentage) for categorical variables and mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables. The Shapiro-Wilk test was used to assess the normality of the distribution for each continuous variable. Patients were divided into two groups: ICU survivors and non-survivors. To determine the differences between the baseline characteristics of the

groups, an independent t-test or Mann-Whitney U test was used for continuous variables, depending on distribution normality. Chi-squared tests were utilized to compare categorical variables. Each test was two-sided, with statistical significance denoted by P-values of < 0.05.

The predictive performance of each biomarker was assessed by comparing the PCT, ALB, and PCT/ALB ratio values between the ICU survivor and non-survivor groups using an independent t-test or, for distributions deviating from normality, the Mann-Whitney U test. Upon finding significant differences, a receiver-operating characteristic (ROC) curve was constructed for each biomarker to determine the area under the curve (AUC), optimal cut-off point, specificity, sensitivity, and negative and positive likelihood ratios (LRs). Additionally, multivariable logistic regression analysis was performed to ascertain if the PCT/ALB ratio could independently predict ICU mortality, adjusting for potential confounders. The AUCs of the PCT/ALB ratio were compared with those of the SOFA scores using the DeLong test.

Sample Size Calculation

For this study, we aimed to demonstrate that the AUC of 0.7 for the PCT/ALB ratio was significantly different from the null hypothesis value of 0.5. To achieve this, 66 ICU survivors and 22 ICU non-survivors needed to be included, requiring a total of at least 88 patients with sepsis. A three-to-one ratio of survivors to non-survivors was utilized in the sample size calculation, targeting a significance level of 0.05 and a power of 0.8.

Results

Patient Selection

Eligibility screening was applied to 258 patients over the three years of the study. Of these, 73 (28.3%) were excluded from the analysis (Figure 1). Consequently, the final study population comprised 185 patients, with 65 (35.1%) dying in the ICU and being categorized as non-survivors in this analysis.

Baseline Characteristics

Table 1 displays the baseline demographic and clinical characteristics of the patients. No significant differences were identified between survivors and non-survivors in terms of age, gender, and admission category. However, non-survivors had a higher Charlson Comorbidity Index (3 [IQR]: 1.5-5] vs. 2 [IQR: 0-4], P<0.014), higher Acute Physiology and Chronic Health Evaluation II (APACHE

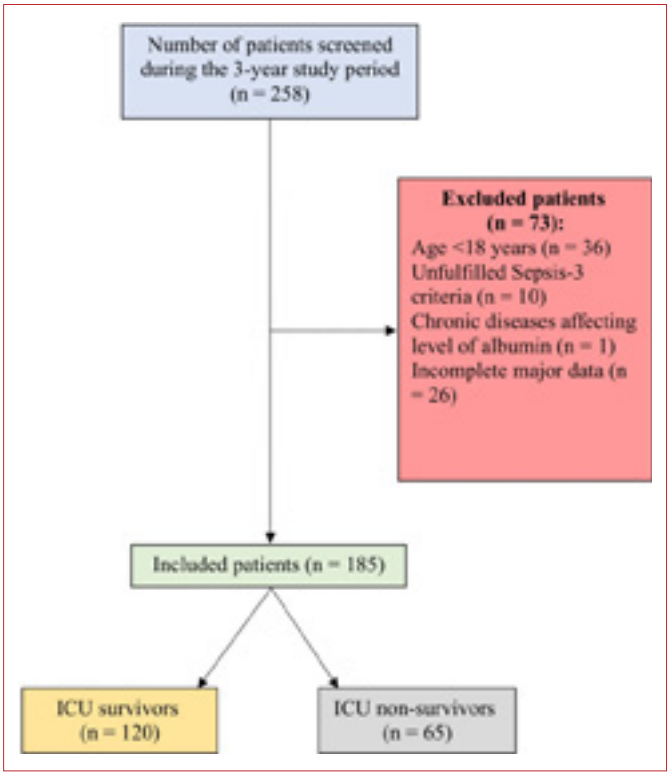

Figure 1. Schematic flow chart of the selection process of eligible patients.

Table 1. Patients' baseline characteristics (n=185)

Variables	Survivors (n=120)	Non-survivors (n=65)	p
Age (years)	48±17	53±19	0.103
Sex (male)	68 (56.7)	34 (52.3)	0.569
Category			
Medical	81 (67.5)	42 (64.6)	0.692
Surgical	39 (32.5)	23 (35.4)	
Charlson Comorbidity Index	2 (0, 4)	3 (1.5, 5)	0.014*
APACHE II score	10.1±7.3	16.4±8.2	<0.001*
SOFA score	5.7±3.9	8.6±5.0	<0.001*
Site of infection			
Pulmonary	84 (70.0)	43 (66.2)	0.150
Extra-pulmonary	36 (30.0)	22 (33.8)	
Microbiological culture			
Blood	16 (13.3)	19 (29.2)	0.008*
Other	37 (30.8)	31 (47.7)	0.023*
Mechanical ventilation	81 (67.5)	60 (92.3)	<0.001*
Inotrope or vasopressor	55 (45.8)	54 (83.1)	<0.001*
Renal replacement therapy	21 (17.5)	19 (29.2)	0.064

CCI: Charlson Comorbidity Index; APACHE II: Acute Physiological and Chronic Health Evaluation II Score; SOFA: Sequential Organ Failure Assessment Score.

II) scores (16.4 [SD: 8.2] vs. 10.1 [SD: 7.3], P<0.001), and higher SOFA scores (8.6 [SD: 5.0] vs. 5.7 [SD: 3.9], P<0.001).

Non-survivors also had a higher incidence of positive blood cultures (29.2% vs. 13.3%, P=0.008) and other cultures (47.7% vs. 30.8%, P=0.023) than survivors. Furthermore, a larger proportion of non-survivors received mechanical ventilation (92.3% vs. 67.5%, P<0.001) and inotrope or vasopressor agents (83.1% vs. 45.8%, P<0.001) within the first 24 hours of ICU admission.

Biomarker Profiles

As depicted in Table 2, comparison between ICU non-survivors and ICU survivors showed a significantly lower baseline serum ALB level in non-survivors (30 [SD: 6] vs. 26 [SD: 5] g/L, P<0.001) and a significantly higher serum PCT level (9.89 [IQR: 2.64-40.65] vs. 2.07 [IQR: 0.55-9.08] ng/mL, P<0.001). Accordingly, the PCT/ALB ratios were significantly higher in non-survivors than in survivors (0.40 [IQR: 0.11-1.63] vs. 0.06 [IQR: 0.02-0.31], P<0.001).

Prognostic Value of the PCT/ALB Ratio for ICU Mortality in Sepsis

As illustrated in Figure 2, the ROC curve analysis indicated that the AUC for the PCT/ALB ratio in discriminating between survivors and non-survivors was clinically significant, at 0.731. The optimal cut-off point was 0.12, yielding a sensitivity of 73.85% (95% CI: 61.5-84.0%) and a specificity of 60.83% (95% CI: 51.5-69.6%). The positive LR was 1.89 (95% CI: 1.45-2.46), and the negative LR was 0.43 (95% CI: 0.28-0.66).

In another ROC curve analysis, the PCT/ALB ratio outperformed both PCT and ALB used alone, which had an AUC of 0.721 (95% CI: 0.651-0.785) and 0.700 (95% CI: 0.629-0.765), respectively (Figure 3). Using the DeLong test, the difference in the AUC of the PCT/ALB ratio versus PCT alone was statistically significant (P=0.044), while the difference between the PCT/ALB ratio and ALB alone was not statistically significant (P=0.466).

Table 2. Biomarker profiles in the survivors versus non-survivors

Biomarker	Survivors (n=120)	Non-survivors (n=65)	p
Albumin (g/L)	30±6	26±5	<0.001*
Procalcitonin (ng/mL)	2.07 (0.55, 9.08)	9.89 (2.64, 40.65)	<0.001*
Procalcitonin: Albumin ratio	0.06 (0.02, 0.31)	0.40 (0.11, 1.63)	<0.001*

As illustrated in Figure 4, a notable finding was that the AUC of the PCT/ALB ratio was higher compared to the SOFA score, with an AUC of 0.680 (95% CI: 0.602-0.751). However, according to the DeLong test (P=0.189), the difference between these two parameters was not statistically significant.

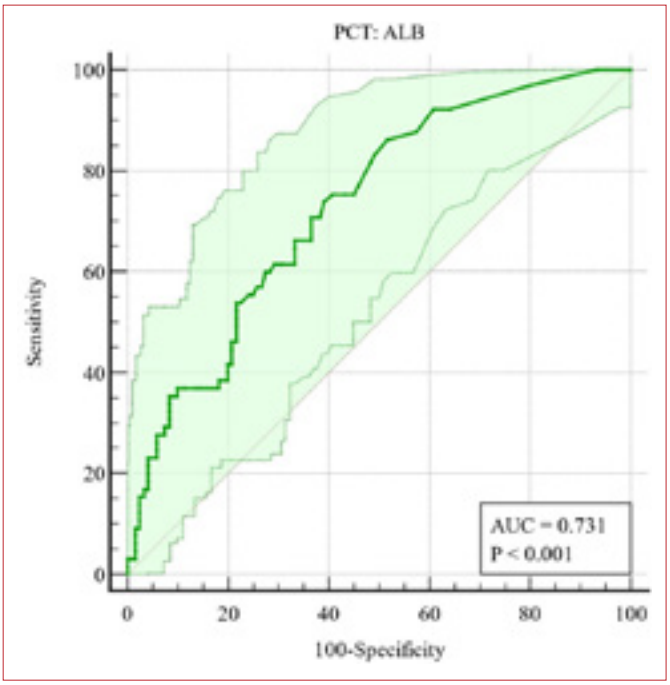

Figure 2. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) for ICU-mortality in sepsis.

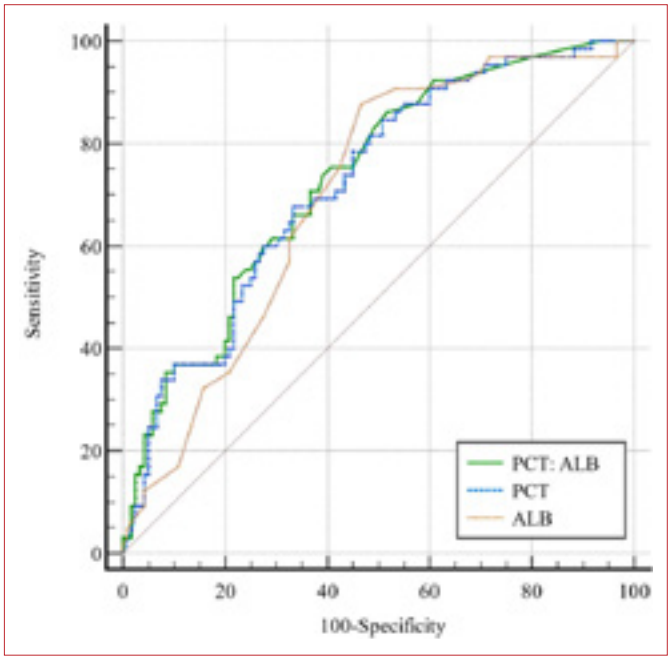

Figure 3. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) versus procalcitonin (PCT) alone versus albumin (ALB) alone for ICU-mortality in sepsis.

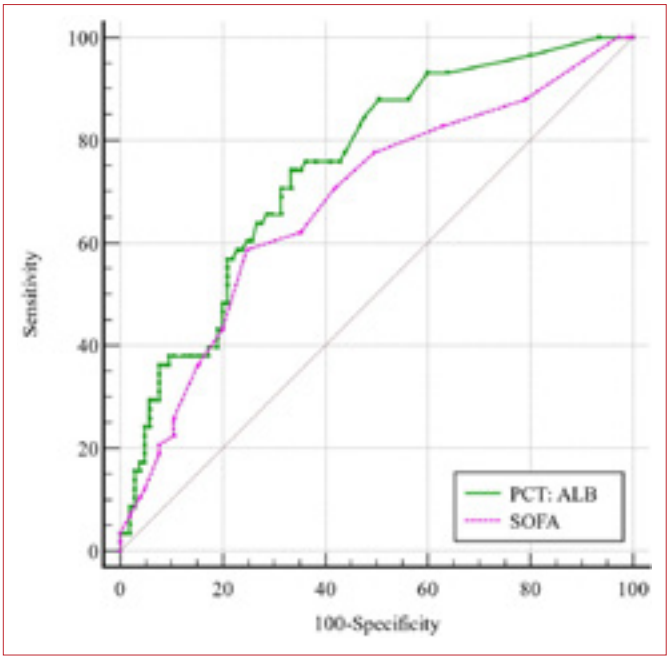

Figure 4. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) versus Sequential Organ Failure Assessment (SOFA) score for ICU-mortality in sepsis.

Independent Value of the PCT/ALB Ratio for ICU Mortality in Sepsis

Table 3 presents the results from the multivariate logistic regression analysis, indicating that after adjusting for illness severity using APACHE II scores and the extent of organ failure using SOFA scores, the PCT/ALB ratio still independently predicted ICU mortality in this cohort of sepsis patients. The adjusted odds ratio was 1.624 (95% CI: 1.080-2.441, P<0.020). Notably, the SOFA score was not an independent predictor of ICU mortality in our sepsis cohort.

Discussion

The analysis in this retrospective cohort study, which included 185 patients with sepsis, revealed significant associations between serum PCT and ALB levels at ICU admission and ICU mortality. Our findings indicate that these two biomarkers have clinical relevance in distinguishing between survival and death among patients with sepsis admitted to the ICU. An important discovery from our study is that combining PCT and ALB to form the PCT/ALB ratio resulted in a modest enhancement in mortality prediction accuracy, compared to using PCT alone. Furthermore, the PCT/ALB ratio showed predictive capabilities comparable to the admission SOFA score for outcomes in our sepsis cohort. The PCT/ALB ratio independently predicted ICU-based mortality in this cohort of patients with sepsis after adjusting for potential confounders of illness severity and organ dysfunction, as indicated by APACHE II and SOFA scores, respectively.

Table 3. Independent value of procalcitonin to albumin ratio (PCT: ALB) for ICU-mortality in sepsis

	B	Adjusted OR	95% CI	p
PCT: ALB	0.485	1.624	1.080 – 2.441	0.020
APACHE II	0.061	1.063	1.002 – 1.129	0.044
SOFA	0.070	1.072	0.966 – 1.191	0.191
Constant	-2.285	0.102	-	<0.001

The ability to predict outcomes in patients with sepsis might assist in guiding treatment decisions. Prognostication using biomarkers that reflect specific pathophysiological processes could be particularly beneficial. For instance, serum ALB, frequently used in ICUs as a biomarker, may be valuable as it reflects two common conditions among such patients: inflammation and malnutrition. However, routinely measured laboratory parameters, such as serum ALB, display limited accuracy in predicting mortality.[12] On the other hand, the role of PCT in diagnosing sepsis is well established.[3] Nonetheless, its prognostic value in patients with sepsis remains a subject of debate. While the initial PCT value may aid in assessing the severity of illness in a patient with sepsis, its reliability as a prognostic indicator is not consistent.[13, 14] This study demonstrates that compared to using PCT alone, the PCT/ALB ratio may be a more reliable predictor of mortality in patients with sepsis. This is likely due to the PCT/ALB ratio's ability to encapsulate the broader pathophysiological processes involved in sepsis.

The innovation of these findings lies in the combination of PCT and serum ALB for predicting mortality in a general sepsis patient cohort in the ICU. Previous research has employed similar methodologies, wherein PCT was combined with serum ALB, yielding promising outcomes [7–11], although the patient cohorts differed. For instance, in a cohort of elderly patients with community-acquired pneumonia, the PCT/ALB ratio was significantly higher in non-survivors than in survivors, exhibiting an AUC of 0.700.[11] Furthermore, a study on elderly patients at risk of bacterial infection found that those with elevated PCT levels and reduced ALB levels had higher mortality rates.[7] In a recent study, the PCT/ALB ratio has been identified as an independent risk

factor for prognosticating outcomes in sepsis patients with acute kidney injury caused by intra-abdominal infections.[8] The most recent evidence concerning the PCT/ALB ratio comes from a study of 187 patients with post-cardiac arrest syndrome following non-traumatic out-of-hospital cardiac arrest [15], where the PCT/ALB ratio 48 hours after admission was more effective in predicting the neurological outcome at one month than PCT levels alone 48 hours after admission.[15] Consistent with the literature, our study found that the ability to identify a high ICU mortality risk in sepsis patients improved slightly when a combination of PCT and ALB was used as a prognostic ratio at the time of patient admission. In addition to the findings on the prognostic value of the PCT/ALB ratio, we believe that this study is important because it was conducted in a low-income setting. To date, the majority of data on ICU admission of patients with sepsis are from studies conducted in high-income countries.

Although we demonstrated an improvement in the discriminative ability of the PCT/ALB ratio compared to PCT alone, the clinical significance of combining PCT and ALB would carry a clinically meaningful difference remains a question. Critics of the DeLong test argue that comparing AUCs from nested models is an approach with serious validity problems.[15] Therefore, it raises the question of why one should use the PCT/ALB ratio over PCT alone, especially when the latter is more intuitive in practice. However, from a pathophysiological standpoint, joint interpreting PCT and ALB better represents the condition of critically ill sepsis patients. Current literature also supports the idea that a multi-marker approach, combining two or more biomarkers, enhances our capacity to risk-stratify sepsis patients.[16]

Despite the promising findings of this study, several key limitations need to be mentioned. This study was based on data from a single center, and it is unclear whether the findings can be generalized to other settings and patient populations. We attempted to control for confounding factors by creating a logistic regression model for the PCT/ALB ratio, but this might not account for all unmeasured confounders or collinear effects. Additionally, routinely measuring PCT in clinical practice may not be feasible, as the test is not always readily available. However, using a point-of-care device to measure PCT, as in this study, proves to be highly practical for daily use in clinical settings.

Conclusion

The combined use of PCT with serum ALB, represented as the PCT/ALB ratio, independently predicted ICU mortality, demonstrating slightly better performance than when PCT was used alone in our sepsis cohort. More extensive, prospective research, involving multicenter studies, is needed to validate these findings and assess whether measurements of the PCT/ALB ratio can be successfully integrated into clinical practice. Such integration could improve mortality predictions and bedside clinical decision-making for patients with sepsis.

Ethics Committee Approval: Ethical approval was obtained from Universiti Sains Malaysia Human Research and Ethics Committee (HREC) (Approval Number: USM/JEPeM/20120699, Date: 6.04.2021).

Informed Consent: Written informed consent was obtained from all recruited patients or their legally acceptable representatives.

Peer-review: Externally peer-reviewed.

Author Contribution: Concept: W.F.; Design: W.F., S.A., K.I., L.M.; Supervision: W.F., S.A., K.I., L.M.; Resources: Materials: W.F.; Data Collection and/or Processing: S.A., W.F.; Analysis and/or Interpretation: W.F., S.A., K.I., L.M.; Literature Search: W.F., S.A.; Writing Manuscript: W.F., S.A.; Critical Review: W.F., S.A., K.I., L.M.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801—10.[CrossRef]
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200—11.
3. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(5):426—35. [CrossRef]
4. Jain S, Sinha S, Sharma SK, et al. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. BMC Res Notes. 2014;7:458. [CrossRef]
5. Takegawa R, Kabata D, Shimizu K, et al. Serum albumin as a risk factor for death in patients with prolonged sepsis: An observational study. J Crit Care. 2019;51:139—44. [CrossRef]
6. Fairclough E, Cairns E, Hamilton J, et al. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond). 2009;9(1):30—3. [CrossRef]
7. Higashikawa T, Okuro M, Ishigami K, et al. Procalcitonin and al-

bumin as prognostic biomarkers in elderly patients with a risk of bacterial infection. J Int Med Res. 2018;46(7):2606—14. [CrossRef]

8. Chen L, Wu X, Qin H, et al. The PCT to Albumin Ratio Predicts Mortality in Patients With Acute Kidney Injury Caused by Abdominal Infection-Evoked Sepsis. Front Nutr. 2021;8:584461. [CrossRef]
9. Luo X, Yang X, Li J, et al. The procalcitonin/albumin ratio as an early diagnostic predictor in discriminating urosepsis from patients with febrile urinary tract infection. Medicine (Baltimore). 2018;97(28):e11078. [CrossRef]
10. Li T, Li X, Liu X, et al. Association of Procalcitonin to Albumin Ratio with the Presence and Severity of Sepsis in Neonates. J Inflamm Res. 2022;15:2313—21. [CrossRef]
11. Alanli R, Kucukay MB, Yalcin KS. Procalcitonin/albumin ratio: could it be a novel marker indicating severity of inflammation in pneumonia? A retrospective study in elderly patients with community-acquired pneumonia. Journal of Geriatric Science. 2020;3(1):11—7.
12. Hu J, Lv C, Hu X. Effect of hypoproteinemia on the mortality of sepsis patients in the ICU: a retrospective cohort study. Sci Rep 2021;11:24379. [CrossRef]
13. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PLoS One. 2018;13(11):e0206527. [CrossRef]
14. Liu D, Su L, Han G, et al. Prognostic Value of Procalcitonin in Adult Patients with Sepsis: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(6):e0129450. [CrossRef]
15. Demler OV, Pencina MJ, D'Agostino RB Sr. Misuse of DeLong test to compare AUCs for nested models. Stat Med. 2012;31(23):2577—87.
16. Casserly B, Read R, Levy MM. Multimarker panels in sepsis. Crit Care Clin. 2011;27(2):391—405. [CrossRef]