EARLY PREDICTIVE VALUE OF PROCALCITONIN TO ALBUMIN RATIO FOR INTENSIVE CARE UNIT MORTALITY IN SEVERE SEPSIS PATIENTS

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~ Siti Afifah Abd Manas ~

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President
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Dr Louisa Chan Yuk Li
Organising Chairperson
ASMIC 2021

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LIST OF SYMBOLS AND ABBREVIATIONS

ALB	Albumin
APACHE II	Acute Physiological and Chronic Health Evaluation II Score
CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C- reactive protein
CVA	Cerebrovascular accident
DM	Diabetes mellitus
ESRD	End stage renal disease
HTN	Hypertension
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive care unit
IQR	Interquartile range
LR	Likelihood Ratio
OR	Odds ratio
PCT	Procalcitonin
PCT: ALB	Procalcitonin to Albumin ratio

ROC	Receiver-operating characteristic curve
SAPS	The Simplified Acute Physiology Score
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment Score
SPSS	Statistical Package for the Social Sciences
P	P-value
TLC	Total leucocyte count

ABSTRAK

Objektif: Paras prokalsitonin (PCT) yang tinggi dan albumin (ALB) yang rendah berkait rapat dengan kadar kematian di kalangan pesakit sepsis. Kajian ini bertujuan bagi melihat keupayaan nilai nisbah PCT kepada ALB (PCT: ALB) bagi meramal kadar mortaliti bagi pesakit sepsis di ICU.

Kaedah: Kajian pemerhatian retrospektif berasaskan pendaftaran selama 3 tahun di Unit Rawatan Rapi (ICU) di Hospital Universiti Sains Malaysia. Kemasukan pesakit dewasa ke ICU yang memenuhi kriteria Sepsis-3 dan yang menjalani pengukuran serentak PCT dan ALB telah dimasukkan sebagai peserta kajian. PCT serum diukur dengan penganalisis ujian yang terdapat di ICU (Finecare™ PCT Rapid Test). Prestasi ramalan PCT: ALB dinilai dengan analisis keluk ciri operasi penerima (ROC).

Keputusan: Seramai 185 pesakit sepsis telah diambil. Kadar kematian ICU ialah 35.1%. Garis dasar PCT menunjukkan jauh lebih tinggi manakala ALB garis dasar menunjukkan jauh lebih rendah pada pesakit yang meninggal dunia berbanding dengan yang terselamat masing-masing antara [9.8 (IQR 2.64 - 40.65) dengan 2.07 (IQR 0.55 – 9.08) ng/mL dan antara 26 (SD = 5) dengan 30 (SD = 6) g/L, P <0.001]. PCT: ALB menunjukkan jauh lebih tinggi pada bukan terselamat berbanding dengan yang terselamat antara [0.40 (IQR 0.11 – 1.63) dengan 0.06 (IQR 0.02 – 0.31), P <0.001]. Kawasan PCT di bawah keluk ROC: Diskriminasi bagi ALB adalah lebih tinggi 0.731 (95% CI 0.615-0.840) daripada PCT (AUC 0.721, 95% CI 0.651-0.785) bagi kematian di ICU. Nilai pemisah ideal untuk PCT: ALB ialah 0.12 dengan kepekaan 73.85% dan kekhususan 60.83%.

Kesimpulan: PCT: ALB ialah alat berpotensi yang boleh dipercayai untuk membantu dalam prognostikasi sepsis walaubagaimanapun memerlukan pengesahan lanjut dalam kajian prospektif di beberapa ICU.

ABSTRACT

Objective: High procalcitonin (PCT) and low albumin (ALB) concentrations have been associated with mortality in sepsis. The present study aimed to investigate the prognostic value of PCT to ALB ratio (PCT: ALB) for ICU mortality in septic patients.

Methods: This was a registry based retrospective observational study conducted in the Intensive Care Unit (ICU) of Hospital Universiti Sains Malaysia over a 3-year period. Consecutive adult patients admitted to the ICU who underwent simultaneous measurement of PCT and ALB who fulfilled the Sepsis-3 criteria were recruited. Serum PCT was measured with a point-of-care analyzer available in the ICU (Finecare™ PCT Rapid Test). Predictive performance of PCT: ALB was assessed by analysis of the receiver-operating characteristic (ROC) curve.

Results: A total of 185 sepsis patients were recruited. The primary outcome of all-cause ICU mortality was 35.1%. Baseline PCT was significantly higher while baseline ALB was significantly lower in the non-survivors compared to the survivors [9.8 (IQR 2.64 - 40.65) vs 2.07 (IQR 0.55 – 9.08) ng/mL and 26 (SD = 5) vs 30 (SD = 6) g/L, respectively, P <0.001]. The computed PCT: ALB was significantly higher in the non-survivors compared to the survivors [0.40 (IQR 0.11 – 1.63) vs 0.06 (IQR 0.02 – 0.31), P <0.001]. The area under the ROC curve of PCT: ALB for discrimination of ICU-mortality was 0.731 (95% CI 0.615-0.840) which was higher than PCT alone (AUC 0.721, 95% CI 0.651-0.785). The ideal cut-off value for PCT: ALB was 0.12 with sensitivity of 73.85% and specificity of 60.83%.

Conclusion: PCT: ALB is a potentially reliable tool to aid in the mortality prediction of sepsis although this requires further validation in a prospective multi-center study.

CHAPTER 1: INTRODUCTION

Sepsis is one of major health issues in intensive care unit (ICU) which is known to be associated with high morbidity and mortality. It has also been associated with ICU burden globally, being one of the most common reasons to non-coronary ICU worldwide. (Mayr, Yende & Angus, 2014). ICU-mortality related to sepsis remains high, being documented as 25.8% to 35.3% (Sakr *et al.*, 2018) despite recent advances of treatment and intensive care. However, the occurrence of sepsis and the rate of associated ICU mortality varies across regions, whereby Asia is one of the regions with higher burden of mortality of the disease (Sakr *et al.*, 2018; Rudd *et al.*, 2020).

It is important to predict the prognosis of patients with sepsis the moment it is recognized, in guiding the direction of treatment, including to initiate or decide on the duration of antibiotic, as this can eventually help to improve the survival of each patient with sepsis. To date, many studies have evaluated biomarkers or clinical scoring systems for better prediction of mortality among patients with sepsis. However, most of the tools can be complicated, not timely, and expensive. A simple, quick, and feasible biomarker is therefore needed to predict the outcome of patients with sepsis upon their ICU admission.

Currently, procalcitonin (PCT) is widely investigated as a prognostic biomarker in sepsis (Schuetz *et al.*, 2017; Briassoulis *et al.*, 2019; Kim *et al.*, 2019). For example, the MOSES study stated that high single baseline PCT values and failure to reduce by 80% or more of PCT value from its baseline were independent predictors of 28-day mortality among patients with sepsis (Schuetz *et al.*, 2017). Apart from being a reliable sepsis biomarker, PCT measured with a point-of-care device, has the advantages of being

rapid, simple, and feasible to be done bedside with the availability of point-of-care PCT analyser.

Albumin (ALB), being the most abundant protein available, is also a potent marker of outcome in sepsis, (Levitt & Levitt, 2016; Higashikawa *et al.*, 2018; Arnau-Barrés *et al.*, 2019; Kendall, Abreu & Cheng, 2019) as its level tends to decrease during acute phase of infection due to reduction in synthesis and increase capillary permeability causing redistribution of albumin to interstitial tissue (Levitt & Levitt, 2016).

A few studies have shown that low baseline value and strong negative trend of serum albumin level have shown reduced the survival rate in patients with sepsis (Park *et al.*, 2018; Kendall, Abreu & Cheng, 2019; Takegawa *et al.*, 2019). For example, Kendall et al have observed that the probability of survival in sepsis patient reduced by 63.4% and 76.4% when the baseline of serum albumin less than 2.45g/dL and less than 1.45g/dL, respectively (Kendall, Abreu & Cheng, 2019).

It is possible that combination of PCT and albumin may provide a better prediction of outcome in sepsis. This is because inflammation and malnutrition processes may co-exist during sepsis period. Serum PCT reflects the severity of inflammation, a key characteristic in the pathophysiology of sepsis while ALB reflects the nutritional status. Both markers have been shown to be important determinants of outcome in the critically ill patients. There are several studies that have combined inflammatory biomarkers such as lactate, C-reactive protein (CRP) or total leucocyte count (TLC) with albumin as prognostication tools for mortality in sepsis. However, to our knowledge, the association between PCT to ALB ratio (PCT: ALB) with mortality in sepsis has not been reported.

Therefore, in this study, we aimed to evaluate the prognostic value of combination of PCT and albumin, in the form PCT: ALB, for predicting ICU-mortality in patients with

sepsis. We also compared the prognostic information of PCT: ALB with that of the widely used prognostic scoring system in sepsis, namely, the Sequential Organ Failure Assessment (SOFA) score in their ability to predict mortality outcome.

CHAPTER 2: STUDY OBJECTIVES

2.1 GENERAL OBJECTIVE

To investigate prognostic value of PCT: ALB as a predictor of ICU-mortality in sepsis.

2.2 SPECIFIC OBJECTIVES

- To compare the level of PCT, ALB and PCT: ALB between ICU survivors and non-survivors with sepsis.
- To assess the prognostic value of PCT, ALB and PCT: ALB for prediction of
- ICU-mortality in patients with sepsis.
- To determine the independent value PCT: ALB for prediction of ICU-mortality in patients with sepsis.
- To compare the prognostic value of PCT: ALB with that of the SOFA score for prediction of ICU-mortality in patients with sepsis.

2.3 NULL HYPOTHESES

- There is no significant difference in the mean value of PCT, ALB, and PCT: ALB between ICU survivors and non-survivors with sepsis.
- The prognostic value of PCT, ALB and PCT: ALB for prediction of ICU-mortality in patients with sepsis is not significant.
- The prognostic value of PCT: ALB is not superior to that of the SOFA score for prediction of ICU-mortality in patients with sepsis.
- The PCT: ALB is not an independent predictor of ICU-mortality in patients with sepsis.

2.4 ALTERNATIVE HYPOTHESES

- There is a significant difference in the mean value of PCT, ALB and PCT: ALB between ICU survivors and non-survivors with sepsis.
- The prognostic value of PCT, ALB and PCT: ALB for prediction of ICU-mortality in patients with sepsis is good.
- The prognostic value of PCT: ALB is superior to that of the SOFA score for prediction of ICU-mortality in patients with sepsis.
- The PCT: ALB is independently predictive of ICU-mortality in patients with sepsis.

CHAPTER 3: MANUSCRIPT

3.1 TITLE PAGE

Title:

Early Predictive Value of Procalcitonin To Albumin Ratio For Intensive Care Unit Mortality In Severe Sepsis Patients

Running head:

Procalcitonin to albumin ratio as a sepsis mortality predictor

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3.2 ABSTRACT

Objective: High procalcitonin (PCT) and low albumin (ALB) concentrations have been associated with mortality in sepsis. The present study aimed to investigate the prognostic value of PCT to ALB ratio (PCT: ALB) for ICU mortality in septic patients.

Methods: This was a registry based retrospective observational study conducted in the Intensive Care Unit (ICU) of Hospital Universiti Sains Malaysia over a 3-year period. Consecutive adult patients admitted to the ICU who underwent simultaneous measurement of PCT and ALB who fulfilled the Sepsis-3 criteria were recruited. Serum PCT was measured with a point-of-care analyzer available in the ICU (Finecare™ PCT Rapid Test). Predictive performance of PCT: ALB was assessed by analysis of the receiver-operating characteristic (ROC) curve.

Results: A total of 185 sepsis patients were recruited. The primary outcome of all-cause ICU mortality was 35.1%. Baseline PCT was significantly higher while baseline ALB was significantly lower in the non-survivors compared to the survivors [9.8 (IQR 2.64 - 40.65) vs 2.07 (IQR 0.55 – 9.08) ng/mL and 26 (SD = 5) vs 30 (SD = 6) g/dL, respectively, P <0.001]. The computed PCT: ALB was significantly higher in the non-survivors compared to the survivors [0.40 (IQR 0.11 – 1.63) vs 0.06 (IQR 0.02 – 0.31), P <0.001]. The area under the ROC curve of PCT: ALB for discrimination of ICU-mortality was 0.731 (95% CI 0.615-0.840) which was higher than PCT alone (AUC 0.721, 95% CI 0.651-0.785). The ideal cut-off value for PCT: ALB was 0.12 with sensitivity of 73.85% and specificity of 60.83%.

Conclusion: PCT: ALB is a potentially reliable tool to aid in the mortality prediction of sepsis although this requires further validation in a prospective multi-center study.

Keywords: *procalcitonin, albumin, sepsis, mortality*

3.3 INTRODUCTION

Sepsis, a condition characterised by life-threatening organ dysfunctions caused by a dysregulated host response to infection, is one of the most common diseases encountered by intensivists worldwide. The overall mortality rate for sepsis remains high despite recent advances in the field of intensive care (Sakr *et al.*, 2018; Rudd *et al.*, 2020). The ability to stratify sepsis patients upon ICU admission or shortly thereafter is therefore important, in order to determine the direction of therapies, which can potentially impact the outcome.

High procalcitonin (PCT) (Schuetz *et al.*, 2017; Kim *et al.*, 2019) and low albumin (ALB) concentrations have been associated with mortality in sepsis (Levitt & Levitt, 2016; Kendall, Abreu & Cheng, 2019; Takegawa *et al.*, 2019). This is because serum PCT reflects the severity of inflammation, a key characteristic in the pathophysiology of sepsis, while that of ALB reflects the nutritional status, which also has been shown as an important determinant of outcome in the critically ill patients. However, the role of ALB as marker for malnutrition has been criticized and it is better recognized as inflammatory marker (Levitt & Levitt, 2016; Keller, 2019).

Emerging evidence suggests that acute phase proteins, when used in combination with serum albumin, may enhance the predictive capacity of each other (Kim *et al.*, 2015; Higashikawa *et al.*, 2018; Luo *et al.*, 2018; Karampela *et al.*, 2020; Recep Alanli, 2020). This is probably because such a combination of biomarkers incorporates deviations of these parameters into a single direction during illness (Gibot *et al.*, 2012). However, to our knowledge, the association between PCT to ALB ratio (PCT: ALB) with mortality in the context of sepsis has not been widely investigated.

In the current study, we aimed to evaluate the prognostic value of combination of

PCT and albumin, in the form PCT: ALB, for predicting ICU-mortality in a cohort of sepsis patients admitted to our ICU. We also aimed to compare the prognostic information of PCT: ALB with that of the widely used prognostic scoring system in sepsis, namely, the Sequential Organ Failure Assessment (SOFA) score in their ability to predict mortality outcome.

3.4 METHODOLOGY

3.4.1 Study Design

This study was a registry based retrospective observational study conducted in a mixed ICU of a university-affiliated hospital in Malaysia over a 3-year period beginning from 1st September 2017 until 31st August 2020. The study commenced after obtaining ethical approval from the institutional Human Research and Ethics Committee (HREC) (study protocol code: USM/JEPeM/20120699). Because of the retrospective nature of the study design, our institutional HREC granted waiver of consents from the study participants.

3.4.2 Study Population

The inclusion criteria for this study were consecutive adult patients admitted to the ICU who underwent blood collection for simultaneous measurement of procalcitonin (PCT) and albumin (ALB) within 24 hours of their admission and who had documented sepsis as per the Sepsis-3 criteria (Singer *et al.*, 2016). Patients with chronic conditions that might cause hypoalbuminemia such as liver cirrhosis were excluded. If a patient had more than one ICU admissions, only the first episode was analysed.

3.4.3 Study Procedure

In eligible patients, relevant baseline data were retrieved from their medical record including their demographic, clinical, biomarkers and outcome data which was the all-cause ICU-mortality. Specifically, the demographic data were age and sex; the clinical

data were category of admission, baseline comorbidity as assessed by Charlson Comorbidity index, baseline severity of illness as assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score, baseline organ dysfunction as assessed by SOFA score, site of infection, microbiological culture results and the ICU treatment received in the first 24 hours; and the biomarkers data were serum PCT, and serum albumin measured on ICU admission.

Serum PCT in this study was measured with a point-of-care analyser using the *Finecare*™ PCT Rapid Quantitative Test (Wondfo, Ghuangzhou), which was available in our ICU. The reference range of serum PCT is 0.1 to 100 ng/mL. Serum albumin was measured in the central laboratory as part of the routine investigations in ICU. The reference range of serum albumin is 35 to 45 g/L. The PCT: ALB was calculated by dividing serum PCT level by serum albumin level.

3.4.4 Statistical Analysis

The statistical analysis in this study was performed using SPSS Version 26 (IBM software) and MedCalc® Version 20.023. Patients' baseline characteristics were reported as mean (standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous variables and counts (percentage) for categorial variables. Normality of distribution of the continuous variables was tested with the Shapiro-Wilk test. The patients were classified into two groups: ICU survivors or non-survivors. The difference in the baseline characteristics between the two groups were compared with independent t-test or Mann-Whitney U test for continuous variables, depending on the normality of distribution. For categorial variables, Chi-squared test was used. All tests were two-sided and P-values of <0.05 were considered as statistically significant.

To determine the predictive performance of the biomarker, the values of PCT, albumin and the PCT: ALB were first compared between the ICU survivors and non-survivors groups using independent t-test or Mann-Whitney U test, if it deviates from normality of distribution. If this was significant, we proceeded to construct the receiver operating characteristic (ROC) curve to determine the area under the curve (AUC), ideal cut-off point, sensitivity, specificity, positive likelihood ratio (LR) and negative LR of each biomarker. Finally, we performed a multivariate logistic regression analysis, adjusting for potential confounders, to determine whether the PCT: ALB was an independent predictor of ICU-mortality. Comparison of the ROC curve of PCT: ALB with that of the SOFA score was performed using the DeLong test.

3.4.5 Sample Size Calculation

In this study, we wanted to show that the AUC of 0.7 for PCT: ALB was significantly different from the null hypothesis value of 0.5. Using the ratio of the sample in negative to positive groups of 3:1, significance at 0.05 and power of 0.8, we needed to study 66 ICU survivors and 22 ICU non-survivors, giving a total of at least 88 critically patients with sepsis to be studied.

3.5 RESULTS

3.5.1 Patients' Selection

Throughout the 3-year's ICU registry data, a total of 258 patients were screened for eligibility. Seventy-three (28.3%) of these 258 patients were excluded from the analysis (Figure 1). As such, we were left with 185 patients to be analysed of which the outcome of all-cause ICU-mortality was reached in 65 (35.1%) of these patients. These patients were classified as non-survivors in this analysis.

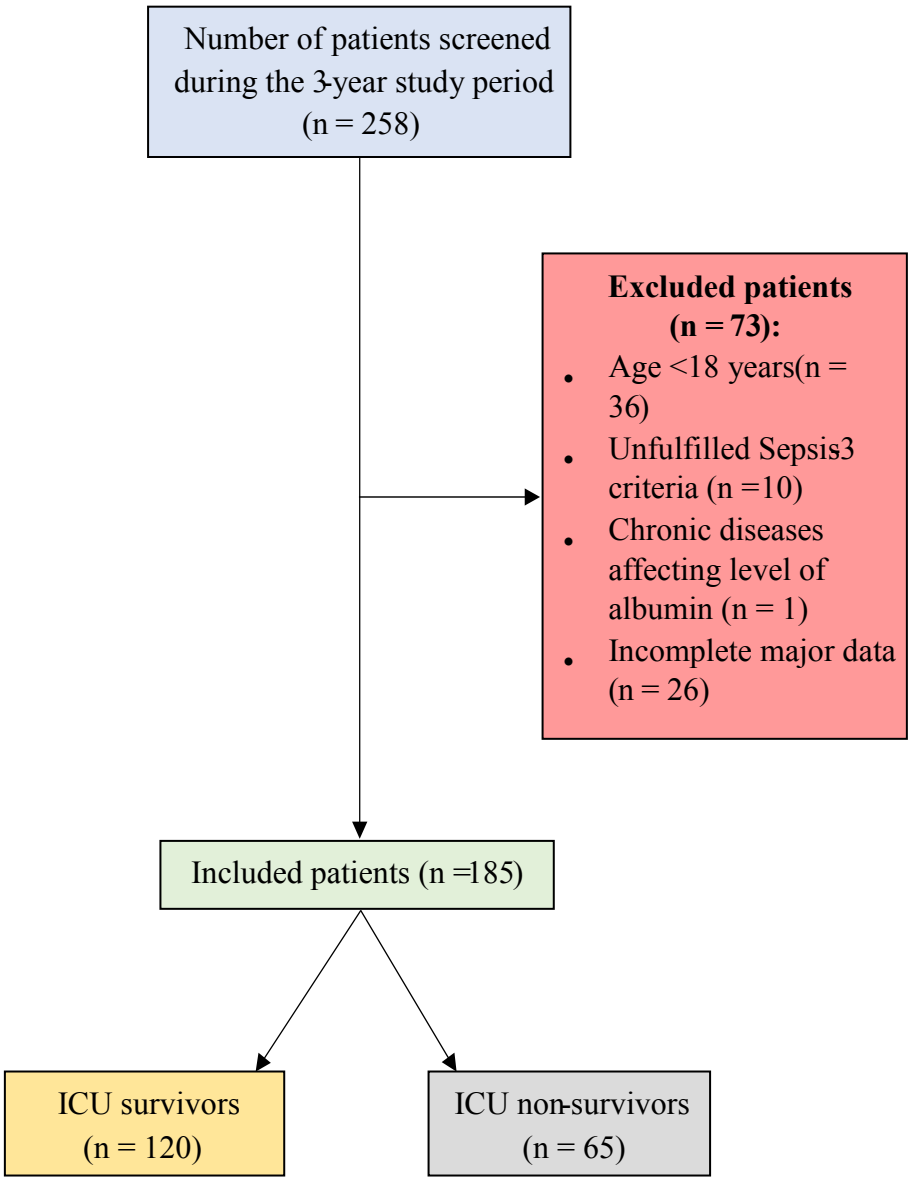


Figure 3.1. Schematic flow chart of the selection process of eligible patients.

3.5.1 Baseline Characteristics

The baseline demographic and clinical characteristics of the study population (survivors and non- survivors) being analysed are presented in Table 3.1. Values were expressed as means ± standard deviation or numbers in percentage. There was no significant difference between the survivors and the non-survivors in terms of age, sex, and category of admission. However, the non-survivors had higher Charlson Comorbidity Index (3 [IQR, 1.5, 5] versus 2 [IQR, 0, 4], $P < 0.014$], higher APACHE II score (16.4 [SD, 8.2] versus 10.1 [SD 7.3], $P < 0.001$) and higher SOFA score (8.6 [SD, 5.0] versus 5.7 [SD, 3.9] $P < 0.001$).

It was also noted that a higher proportion of the non-survivors had positive blood (29.2 versus 13.3%, $P = 0.008$) and other culture (47.7 versus 30.8%, $P = 0.023$) than the survivors. More non-survivors received mechanical ventilation (92.3 versus 67.5%, $P < 0.001$) and inotropic or vasopressor (83.1 versus 45.8%, $P < 0.001$) in the first 24 hours of their ICU admission.

Table 3.1. Patients' baseline demographic and clinical characteristics (n = 185)

Variables	**Survivors (n = 120)**	**Non-survivors (*n* = 65)**	***P -value***
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 (days)	81 (67.5)	60 (92.3)	<0.001*
Inotrope or vasopressor usage	55 (45.8)	54 (83.1)	<0.001*
Renal replacement therapy	21 (17.5)	19 (29.2)	0.064

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

3.5.2 Biomarker Profiles

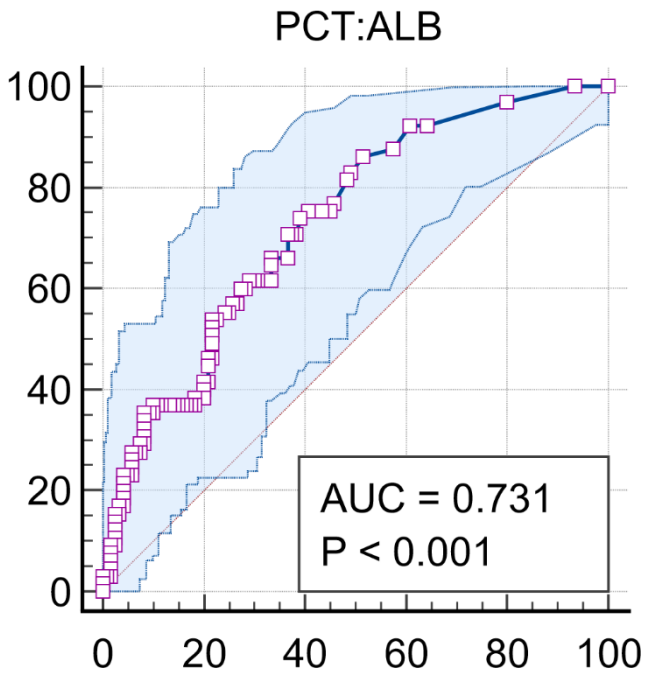
Baseline serum level of ALB was found to be significantly lower (26 [SD, 5] versus 30 [SD, 6] g/L, P <0.001) and serum level of PCT was found to be significantly higher (9.89 [IQR, 2.64-40.65] vs. 2.07 [IQR 0.55-9.08] ng/mL, P <0.001) in the ICU non-survivors compared to the ICU survivors (Table 3.2). Understandably, the calculated ratio of PCT to ALB was significantly higher in the ICU non-survivors compared to the ICU survivors (0.40 [IQR, 0.11-1.63] versus 0.06 (IQR, 0.02-0.31], P <0.001).

Table 3.2. Biomarker profiles in the survivors versus non-survivors

Biomarker	**Survivors (*n* = 120)**	**n-survivors = 65)**	***P-value***
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*

3.5.3 Prognostic Value of Procalcitonin to Albumin Ratio for ICU-Mortality in Sepsis

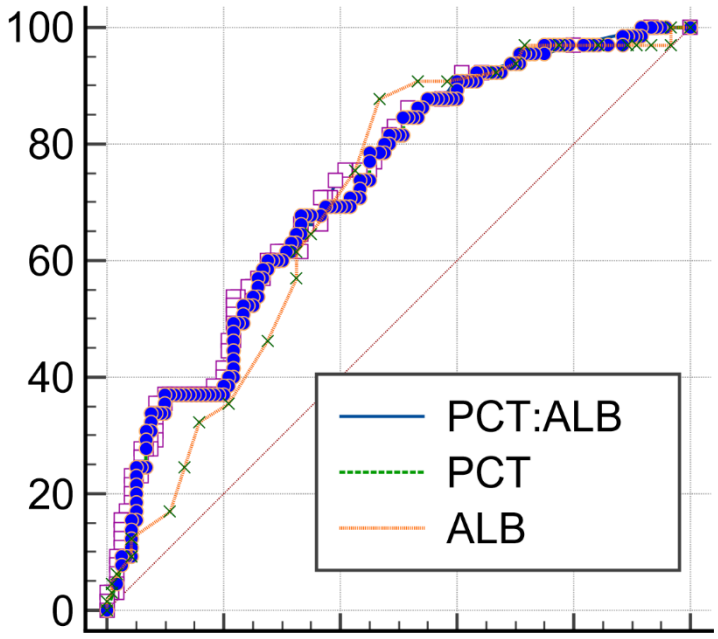
Analysis of the ROC curve using multivariate logistic regression analysis after adjusting for potential confounders, as shown in Figure 3.2 revealed that the AUC of the PCT: ALB for discriminating survivors from non-survivors is clinically valid with a value of 0.731. The ideal cut-off point was 0.12, at which the sensitivity and specificity are fair, 73.85% (95% CI, 61.5-84.0%) and 60.83% (95% CI, 51.5-69.6%), respectively. The positive Likelihood Ratio (LR) was 1.89 (95% CI, 1.45-2.46) and the negative LR was 0.43 (95% CI, 0.28- 0.66), which means sepsis patients who had higher a PCT:ALB ratio is nearly twice as likely to die compared to those with lower ratio.



AUC	Sensitivity (%)	Specificity (%)	95% CI	
			Sensitivity (%)	Specificity (%)
0.731	73.85	60.83	61.5 -84.0	51.5-69.6

Figure 3.2. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) for ICU mortality in sepsis

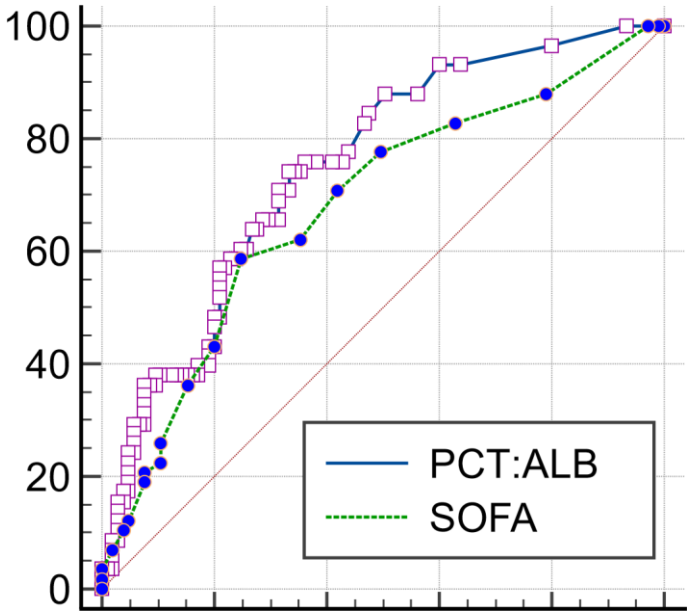
In another ROC curve analysis, the PCT: ALB outperformed the PCT and ALB used alone, which had an AUC of 0.721 (95% CI, 0.651-0.785) and 0.700 (95% CI, 0.6290.765), respectively (Figure 3.3). Using the DeLong test, the difference in the AUCs of PCT: ALB versus PCT was statistically significant ($P = 0.044$).



	AUC	95% CI	DeLong Test
PCT: ALB	0.731	0.615 – 0.840	PCT: ALB vs PCT = 0.044
PCT	0.721	0.651 - 0.785	
ALB	0.700	0.629 – 0.765	

Figure 3.3. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) versus procalcitonin (PCT) alone versus albumin (ALB) alone for ICU-mortality in sepsis

Of note, we found that the AUC of the PCT: ALB ratio was higher than that of the SOFA score, which had an AUC of 0.680 (95% CI, 0.602-0.751), as depicted in Figure 3.4. However, the difference was not statistically significant from the DeLong test (P = 0.189).



	AUC	95% CI	DeLong test
PCT: ALB	0.731	0.615 – 0.840	PCT: ALB vs SOFA = 0.189
SOFA	0.680	0.602 – 0.751	

Figure 3.4. Prognostic value of procalcitonin to albumin ratio (PCT: ALB) versus Sequential Organ Failure Assessment (SOFA) score for ICU-mortality in sepsis

3.5.4 Independent Value of Procalcitonin to Albumin Ratio for ICU-Mortality in Sepsis

In a multivariate logistic regression analysis as shown in Table 3.3, after adjusting for severity of illness by APACHE II score and degree of organ failures by SOFA score, the PCT: ALB remained as an independent predictor of ICU-mortality in our sepsis cohort, with adjusted odd ratio of 1.624 (95% CI, 1.080-2.441, $P < 0.020$). Of note, the SOFA score was not an independent predictor ICU-mortality in our sepsis cohort.

Table 3.3. Comparison of multivariate logistic regression analysis 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

3.6 DISCUSSION

This is a registry based retrospective observational study of 185 patients admitted to our ICU with sepsis over 3 years period. We found that serum PCT and ALB measured on ICU admission had significant associations with ICU mortality. Both biomarkers were clinically valid to discriminate patients with sepsis who went on to die or survive the ICU stay. Of note, when the PCT was used in combination with ALB, the PCT: ALB had a superior predictive performance than either biomarker used alone. In this analysis, the PCT: ALB was comparable to the admission SOFA score in predicting the outcome of our sepsis cohort. After adjusting for potential confounders of severity of illness by APACHE II score and organ dysfunction by SOFA score, the PCT: ALB remained as an independent predictor of ICU-mortality in our sepsis cohort.

Early prediction of the outcome of patients with sepsis could be helpful in guiding therapies but remains challenging. Biomarkers of certain pathophysiologic processes may have value to aid prognostication of patients with sepsis. For example, serum albumin, a routinely measured biomarker in the ICU, represents inflammation and malnutrition, which are all common in patients with sepsis (Kaysen *et al.*, 2004). However, routinely measured laboratory parameters display limited accuracy in predicting mortality, as with serum albumin. On the other hand, the role of PCT for the diagnosis of sepsis is now clearly established (Schuetz *et al.*, 2017; Kim *et al.*, 2019). However, its prognostic value remains controversial. In the current study, we have shown that combination of PCT and ALB, in the form of PCT: ALB, may be a more reliable aid for mortality prediction in sepsis than its individual constituent biomarkers, probably because it reflects wider pathophysiologic processes involve in sepsis.

Our results are novel with respect to the combined use of PCT and serum albumin for mortality prediction in patients with sepsis. A few previous studies have attempted a

similar strategy of combining acute phase proteins with serum albumin, with promising results. For example, previous studies have demonstrated that the combined ratio of C-reactive Protein to ALB improved the prediction of patients with sepsis who were at an increased risk of mortality (Ranzani *et al.*, 2013; Kim *et al.*, 2015). In line with previous evidence, we now report for the first time that combining PCT with albumin in a single prognostic ratio considerably improved our ability to identify patients with sepsis who are at high risk of ICU-mortality upon their admission. More importantly, we believe that we have added new knowledge to the critical care literature, since data regarding the patients with sepsis being admitted to the ICU mainly come from high-income countries.

Although our results are encouraging, this study has several pertinent limitations. The prognostic performance of PCT: ALB in this study predicted our single-centred data set, but whether it is applicable to external population is unknown. While we have attempted to control for confounding factors by modelling the PCT: ALB in a logistic regression model, we may have failed to account for other unmeasured confounders or collinear effects. There are some potential bias in this study, such as early administration of albumin or antibiotic prior to ICU admission and timing of PCT sampling with regard to the disease timeline was not standardised might affect the PCT and ALB level during admission to ICU.

In addition, the measurement of PCT may not be widely available, thus limiting its value in daily clinical practice. However, the PCT in this study was measured with a point-of-care device, which is considerably practical if it is to be applied in daily clinical practice.

3.7 CONCLUSION

The combined use of PCT with serum albumin in the form of PCT: ALB independently predicted ICU-mortality with a good performance in our sepsis cohort. Further larger multi-centre prospective studies are warranted to validate our current findings, and to assess whether the PCT: ALB may be successfully integrated with physicians' clinical practice to improve prediction of mortality and clinical decision-making at the bedside of the patients with sepsis.

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