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Original article

Prognostic accuracy of procalcitonin and other biomarkers in septic shock patient in PICU

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Abstract. *Background and aim:* Septic shock is one of the main causes of sepsis. Sepsis is a life-threatening acute systemic inflammatory response to infection. Many studies have tested the usefulness of biomarkers of sepsis prognosis in PICU patients. This study aims to prove that CRP, procalcitonin, CRP/albumin ratio, and culture results, are prognostic markers of mortality in pediatric sepsis shock patients. *Methods:* A retrospective with cross-sectional study design using the medical records of critically ill children with septic shock aged 1 month to 18 years, admitted to the PICU of Dr. Soetomo Hospital from February 2022 to July 2023. The inclusion criteria were patient with sepsis shock were reviewed for laboratory results and clinical conditions from the time of admission until 30 days after PICU treatment. Patients with incomplete data, patients with AKI stage failure or loss, chronic renal failure, autoimmune diseases, malignancy, trauma (burns, fractures, surgery), heart disease, and HIV patients could not participate in the study. *Results:* A total of ninety-six medical records of critically ill sepsis patients in PICU were observed, only 69 patients were followed up, and 27 patients were excluded. A total of 33 (47.8%) patients died, most patients died in the age group of 1-12 months (51.5%) and male (81.9%). There was a significant association between sex and mortality in septic shock children, with being female increases the chance to survive by 3.600-time, 95% CI [1.196010.838], *P*=0.023. There was a significant association between PCT levels and mortality of sepsis shock patients (P=0.041). There was no significant difference between CRP levels, CRP/albumin ratio (CAR), and culture results with patient mortality status. *Conclusions*: Procalcitonin is superior as a prognostic biomarker of mortality in critically ill patients with sepsis shock, compared to CRP, CRP/albumin ratio, and culture. (www.actabiomedica.it)

Key words: septic shock, sepsis, CRP, procalcitonin, CRP/albumin ratio, culture result

Introduction

Sepsis occurs due to the body's response to infection, with the consequence of high rate mortality in pediatric population, particularly in neonates (1). Sepsis is accompanied by circulatory failure such as hypotension despite adequate resuscitation (2). The death due to sepsis noted more than 50% in Indonesia, from 14,076 sepsis patients (3), which increase the national economic burden with the mean cost of US$ 1,072.63 (95%CI: 105.41-3,625.69) (4). At Cipto Mangunkusumo Hospital (RSCM), 19.3% of 502 pediatric patients admitted had sepsis with a mortality of 54% (5). Septic shock is the highest cause of mortality and morbidity in sepsis patient, with the mortality rate during the first 24-h of ICU was 4.9% (6), while other stated 24.2-32% (7,8). A cohort study found that the mortality rate of pediatric septic shock increased by 17% than pediatric sepsis, which count as 7%, within 24-h during PICU admission (9). So that early diagnosis is

needed (10). Early identification and diagnosis for sepsis is needed to determine the medical strategies early to reduce the mortality (11). Due to the highest rate of mortality, several investigations to predict the outcomes in sepsis patient has been enrolled. Blood culture is the golden standard for diagnosing sepsis (12) to identify the blood pathogens (13), and influence the treatment to tract the antimicrobial susceptibility and pattern (14). However, this procedure takes about 2 to 4 days to identify the microorganisms causing sepsis and determine the antibiotic susceptibility of the patient (15). Other biomarkers are also used to diagnose sepsis, such as procalcitonin (PCT), C-reactive protein (CRP) and albumin to predict the later outcomes (14,16). Several studies have shown an increase in the biomarkers CRP and PCT in patients with sepsis/septic shock at 12 hours and 4 hours after the systemic infection (17,18). Albumin is the largest component of protein in the circulation (19). Albumin has a very important roles in the disease pathology, as it serves as the regulator of acid-base balance, fluid distribution, and transporter for substances such as hormones and drugs. Albumin synthesis is decreased in critically ill patients, including sepsis due to the increment of microvascular permeability (20). A decrease in albumin may be associated with chronic disease, nutrition, and inflammatory status. The combination of CRP and albumin as a marker of systemic inflammation and nutritional function can determine the prognosis of sepsis patients (21). So, it is important to increase the albumin concentration in septic patient as it has protective effect against mortality (22). The aim of our study was to enroll the best prognostic markers to predict septic shock outcome between CRP, procalcitonin, CRP/Albumin ratio, and culture results in pediatric patients.

Methods

Study design

This study was a retrospective study with medical record assessment of critically ill patients with septic shock aged 1 month - 18 years in the Pediatric Intensive Care Unit (PICU) of Dr. Soetomo General Academic Hospital from February 2022 - July 2023. Patients who met the criteria for sepsis shock were evaluated for clinical condition and laboratory results (CRP, procalcitonin, CRP/albumin ratio, and culture results) from the time of admission to 30 days after PICU treatment, followed by monitoring the mortality prognosis. We collected the parameters simultaneously. The authors collected CRP, PCT, albumin, microbiology culture, and CRP/Albumin ratio during the admition of the septic shock patient in PICU. Shock septic patient diagnose by score p-SOFA. Sepsis shock criteria were determined based on the third international consensus definitions for sepsis and septic shock 2016 (23). Patients with incomplete data, acute kidney injury (AKI) stage failure or loss, chronic renal failure, autoimmune disease, malignancy, trauma (burn, fracture, surgery), cardiovascular disease, and HIV were excluded from the study. The sample size in this study was obtained with a total sampling technique. There were 96 patients were admitted with a diagnosis of sepsis, and there were 27 medical records didn't meet the inclusion criteria, so we excluded; therefore, 69 samples were used in this study. As a result, 69 samples were used in this study. The information from the patients' medical records, including demographic data, laboratory results, and culture results, were analyzed to evaluate the association between the studied biomarkers and mortality.

Ethical clearance

The ethical eligibility of the study, 2548/105/4/XI/2023 was issued by the Health Research Ethics Committee (KEPK), Dr. Soetomo General Academic Hospital.

Statistical analysis

Data analysis was performed using the SPSS ver. 22. In order to determine the relationship between two independent variables, we conducted the Pearson correlation test. If the data were not normally distributed, the Spearman correlation test was performed. To test the effect of independent variables on the dependent variable, the Chi-square test was performed. If the parametric test did not meet the requirements, the Fischer test was performed. The results were significant if the p-value was <0.05.

Results

Characteristics of research subjects

The total number of patients in the analysis was 69, with 36 patients survived and 33 patients died, or 47.83% of mortality rate, with median age of 13 [1.00-178.00] months-old. No significant different in age distribution, body weight, body height, PCT, CRP, ALB, and CAR (P>0.05). Infant (1-12 months old) was the predominant age group in this study (49.28%), followed by children under 5 years (28.99%), children aged 5-10 years (13.04%), and the rest was adolescents. No significant different in mortality rate in relation with age distribution (P=0.651). Patients aged 1-12 months had the highest number of deaths (51.5%), followed by those aged 1-<5 years (27.3%), 10-18 years (12.1%), and 5-<10 years (9.1%) (Table 1).

Total number of males were predominant in this study, 68.1%. The majority of patients who died were male (81.9%), while a fewer number of female patients died (18.1%). Sex was correlated with mortality

Table 1. Basic subject's characteristics.

Characteristics	All subjects	Survived (n = 36)	Died (n = 33)	*P* value
Age (in months), median [min-max]	13.00 [1.00-178.00]	16.50 [1.00-140.00]	9.00 [1.00-178.00]	0.597[d]
Age category, n(%)				
• 1-12 months (infants)	34	17 (47.2%)	17 (51.5%)	0.651[a]
• 1-<5 years (younger child)	20	11 (30.5%)	9 (27.3%)	
• 5-<10 years (older child)	9	6 (16.7%)	3 (9.1%)	
• 10-18 years (adolescent)	6	2 (5.6%)	4 (12.1%)	
Body weight (in kg), median [min-max]	7.5 [2.10-65.00]	8.15 [2.30-49.00]	7.5 [2.10-65.00]	0.723[d]
Body height (in cm), mean + SD	79.24 + 30.19	78.57 + 26.58	79.96 + 34.10	0.850[c]
Gender, n(%)				
• Male	47 (68.1%)	20 (55.5%)	27 (81.9%)	0.019[a*]
• Female	22	16 (44.5%)	6 (18.1%)	
Nutritional status, n(%)				
• Severely wasted and Wasted	26	12 (33.4%)	14 (42.5%)	0.576[b]
• Normal	38	20 (55.6%)	18 (54.5%)	
• Overweight and Obese	5	4 (11.1%)	1 (3.0%)	
Division of treatment, n(%)				
• Hepatology	1	0 (0.0%)	1 (3.1%)	0.778[b]
• Respirology	40	22 (61.1%)	18 (54.4%)	
• Neurology	23	11 (30.6%)	12 (36.3%)	
• Gastroenterology	4	3 (8.3%)	1 (3.1%)	
• Nephrology	1	0 (0.0%)	1 (3.1%)	
PCT (in ng/mL)[1], median [min-max]	4.66 [0.00-100.00]	2.97 [0.07-99.86]	6.69 [0.00-100.00]	0.141[d]
CRP (mg/L)[1], median [min-max]	2.25 [0.10-27.32]	1.28 [0.10-27.32]	2.7 [0.10-26.10]	0.121[d]
Albumin (in mg/dL), mean + SD	3.20 + 0.62	3.25 + 0.59	3.16 + 0.66	0.544[c]
CRP/Albumin Ratio (CAR)[1], median [min-max]	0.70 [0.02-9.56]	0.37 [0.02-9.52]	0.82 [0.02-9.56]	0.113[d]
Microbiological culture, n(%)				
• Positive	49	24 (66.7%)	25 (75.7%)	0.406[a]
• Negative	20	12 (33.3%)	8 (24.3%)	

[a]Pearson chi-square test; [b]Fischer's exact test; [c]Independent sample T-test; [d]Mann-Whitney U test

Table 2. Prognostic biomarkers of mortality in sepsis.

Cut off biomarker	Survived n (%)	Died n (%)	p-value	OR	95% CI
CRP (mg/l)					
< 2.075	21 (58.3%)	12 (36.4%)	0.113	2.45	0.928 – 6.467
≥2.075	15 (41.7%)	21 (63.6%)			
PCT (ng/mL)					
<5.44	23 (63.9%)	12 (36.4%)	0.041	3.096	1.159 – 8.271
≥5.44	13 (36.1%)	21 (63.6%)			
CRP/Albumin ratio (CAR)					
< 0.5765	21(58.3%)	11(33.3%)	0.066	2.8	1.050 - 7.470
≥ 0.5765	15(41.7%)	22(66.7%)			
Microbiology culture					
Positive	24 (66.67%)	25 (75.75%)	0.406	1.563	0.544 – 4.490
Negative	12 (33.33%)	8 (24.25%)			

in pediatric septic shock patients (r=0.282, p=0.019), means that being female increases the chance to survive by 3.600-time, 95% CI [1.196010.838], *P*=0.023. while being male had he survival chance by 0.278-times (95% CI [0.092-0.836], *P*=0.023). No significant different in nutritional status distribution (*P*>0.05), in the group of living patients, 55.6% had normal nutritional status and 33.4% were undernourished.The most prevalent case of septic shock came from respirology division (57.97%), followed by neurological case (33.33%), the rest were divided into hepatological, gastroenterology, and nephrology. The majority of deceased patients were admitted to the divisions of respirology (39.3%) and neurology (36.3%), while the majority of living patients were admitted to the divisions of respirology (41.7%) and neurology (30.6%).no significant different in division distribution between death and survive group (*P*=0.778). No significant different in blood microbiological culture between survive and death group (*P*=0.406), even the percentage of positive result was higher in death patient (75.7% vs. 66.7%). Microbiology culture results are obtained from various types of specimens, including blood, urine, sputum, Central Venous Catheter (CVC), pleural fluid, Endotracheal Tube (ETT), Liquor Cerebrospinalis (LCS), and superficial pus. In this study, it was found that in the group of surviving patients, there were 24 (66.67%) patients with positive culture results, while 12 (33.33%) patients had negative culture results. In the group of died patients, 25 (75.75%) patients had positive culture results, while 8 (24.25%) patients had negative culture results (Table 2).

Table 3. Area Under the Curve (AUC) of ROC curves with variables PCT, CRP, CRP/Albumin Ratio, and microbiology culture.

Variable	Area	*P*-value	95% CI
PCT	0.694	0.006	0.571-0.817
CRP	0.609	0.121	0.475-0.743
CRP/Albumin Ratio (CAR)	0.611	0.113	0.477-0.745

CRP level of 2.075 mg/L can be used as a cut-off to determine the mortality rate in pediatric sepsis patients with sensitivity and specificity of 63.6% and 58.3% (Table 3, Figure 1). In this study, more than half (63.6%) of pediatric sepsis patients who died had CRP levels ≥2,075 mg/L. There was no significant difference between CRP levels and mortality in pediatric sepsis patients with a p-value of 0.113 (Table 3).

The ROC curves shown the performance of four diagnostic variables: CRP, PCT, and CRP/Albumin ratio. Our findings showed that PCT performed the best to predict septic shock outcomes, with an AUC of 0.694, followed by CRP/Albumin Ratio, and CRP, with AUCs of 0.611 and 0.609 respectively. Microbiology

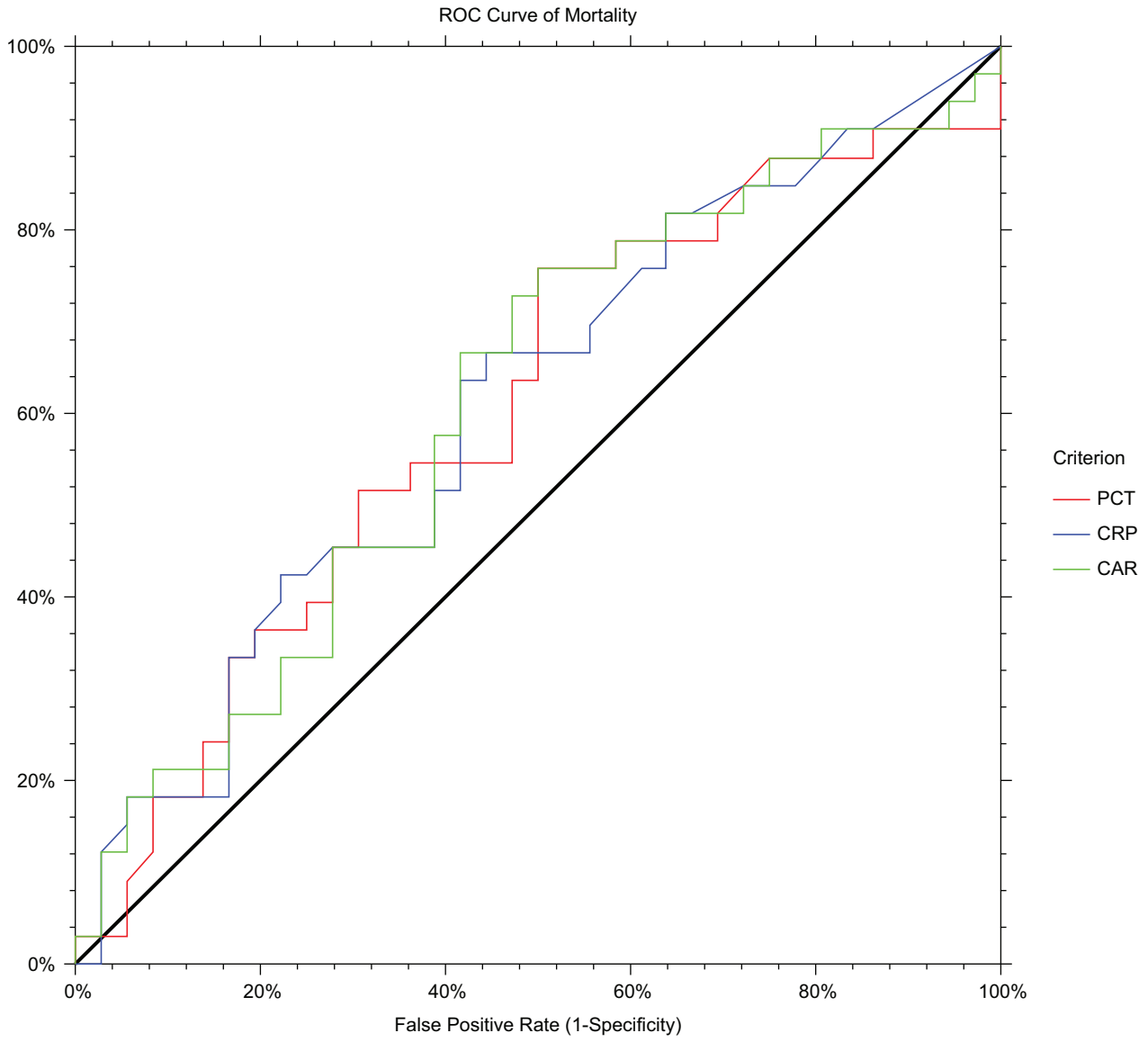

Figure 1. The Receiver Operational Characteristic (ROC) Curves of CRP, PCT and CRP/Albumin Ratio in determining mortality.

culture performed the lowest predictable outcome with an AUC of 0.545, showing similar discriminatory ability to random guessing. Overall, PCT showed better predictive ability than the other variables (Figure 1).

The Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curves for the four variables of PCT, CRP, CRP/Albumin Ratio, and Culture Results are reflected in Table 3. The highest AUC value was obtained by PCT, indicating a fairly high statistical significance. CRP, CAR, and microbiological culture showed no significant different even when AUC more than 0.500, Oth the fourth tools, the Culture Result had the lowest AUC.

Discussion

The prevalent of sepsis in pediatric population is increase due to very low birth weight and chronic condition. The mortality mostly due to severe sepsis and

septic shock (24), with mortality rate of 88.2% in Indonesia (25). The highest incident was infant population, followed by adolescents in US (26). Other noted that infants had the highest case fatality by 82.6% (27), followed by 1-5 years old children (28), which in line with this study: septic shock were prevalent infants. Other study noted that newborns and adolescents had the lowest survival rates in infections and sepsis condition (29). However, no significant different in age distribution toward the mortality in pediatric sepsis patients. The mortality of septic shock patients was influnced not only by age diagnosis, but also redommended medical standard of treatment, lack of mechanical ventilation, presence of hypotension at admission (30), the use of fourth-line antibiotics, corticosteroids, vasopressors, the decrease of serum calcium (31), comorbidity and recurrent ventilator-associated pneumonia (32). Sex difference is important to identify in clinical medicine, as it distinct the sexual hormones, chromosome, and gene expression from autosome (33). Sex difference influences sepsis and septic shock, it more prevalent in male than female; this difference gave a distinct response to pathogens, especially on pathogen–cell receptor interactions, which is suggested mediated by sex hormones. The sex difference made females are less susceptible to sepsis and seem to recover more effectively than males (34), which in line with a findings that there was a significant relationship between age and gender with mortality in pediatric sepsis patients (35). In contrast with this findings, several study found that age and sex different did not correlated with the mortality (36–38). The potential explanations for these diverse findings include the complex interactions of various factors affecting sepsis. Our study revealed that undernutrition was still prevalent. Poor nutritional status is one of the risk factors for infection. Undernutrition compromised immune defense and accentuated fluid loss to the third space (39). This causes children with poor nutritional status to be more susceptible to infections due to the lack of essential nutrients such as protein, vitamins, and minerals that are needed for optimal immune function. In addition, malnutrition damages the integrity of the gastrointestinal mucosa, reduce gastric acid production, and increase susceptibility to pathogens. This allows pathogens to more easily penetrate the digestive system and cause infection (40,41). Severe undernutrition in PICU was associated with increased the risk of mortality by 3.00-times 95% CI: 1.2-7.7; P = 0.02 (42). Undernutrition in critically ill patient complicating the treatment as overfeeding and underfeeding are harmful in septic shock (39). Our study revealed no significant different regarding nutritional status between survivors or dead children, which in line with other: there was no significant difference between nutritional status and mortality prevalent (36,43). Others also stated the similar findings, that nutritional status does not significantly affect mortality in pediatric sepsis patients (37,38). However, other study has found a significant relationship between nutritional status and mortality in pediatric sepsis patients (38), which contradict this result. The possible explanation for these varying findings is that although nutritional status is an important factor, other variables such as comorbidities, severity of illness, and access to healthcare may have a greater influence on mortality in pediatric sepsis patients. The heterogeneity of pediatric sepsis patients, including differences in etiology, clinical presentation, and response to treatment, may have also contributed to these various findings. So, it can be suggested that the relationship between poor nutritional status and the risk of infection in patients is bidirectional and may be challenging to distinguish. Therefore, management of infection must be accompanied by optimal management of nutritional status, in order to reduce the risk of mortality, especially in pediatric patients with sepsis (44–47). Approximately 50% of 10.6 million deaths of children under 5 years of age per year globally are related to five infectious diseases (pneumonia, diarrhea, malaria, measles, AIDS) (44,48). The causative agent of sepsis vary based on age, underlying condition and geographical, including bacteria, virus, fungi, and parasite (48). Our study found that mostly the underlying causes of sepsis came from respirology division. Infants with sepsis mostly due to chronic lung disease or congenital heart disease, children due to neuromuscular disease, while adolescents due to cancer (49). Others found that pneumonia, as one of respiratory disease, is the most common causes of adult sepsis in Europe (50,51). Even bacteria have been believed as the causes of sepsis, 42% patients with negative blood culture showed virus infections as

the cause of sepsis (52), which in line with this findings. We found that PCT level of >5.44 ng/mL can be used as a cut-off to determine the mortality rate in pediatric sepsis patients with a sensitivity and specificity of 63.6% and 63.9%. More than half (63.6%) of pediatric sepsis patients who died had procalcitonin levels ≥5.44 ng/mL. This suggests that procalcitonin level may be an important factor for predicting mortality in pediatric sepsis patients in this study (*P*=0.041). The statement was supported with other finding: there was a significant relationship between PCT levels on day one and mortality, although PCT could not be used as an independent predictor of mortality (53). However, another study found that PCT concentration did not significantly affect mortality (54). Schuetz et al. stated that PCT levels on the first day were poor predictors of mortality at 28 days of PICU admission, when compared to serial PCT measurements. The study also stated that changes in PCT levels during the first 4 days can predict the prognosis of patients with sepsis shock. An increase in PCT levels from the first day was significantly associated with a 3-times increased risk of mortality, with the cut-off value of 2.0 μg/L measured during the 4th day of admission, with the incidence of death during 28-day of ICU admission of 65% than those with PCT below that value (35%) (55). For pediatric population, a meta-analysis study stated that PCT < 6.38 ng/dl had 81.8% sensitivity and 80.8% specificity in determining the mortality in critically ill patient with non-specific causes (56). However, the variety of PCT in pediatric patients remains a challenge to used it as the diagnostic tool to predict the mortality (57). It was stated that medical ventilation support, ionotropic drug, and blood component of transfusion impacting the PCT level in critically ill patient (56). A meta-analysis design cut-off value of PCT for neonates and pediatric population was 2.0-2.5 ng/ml (85% sensitivity and 54% specificity) (58). However, a study stated that PCT and CRP had no sufficient data for prognosing the outcome of sepsis pediatric patient, but can be used for antibiotic use in selected infection groups, which efficient for antibiotic prescription (59). A study conducted by Kumar et al. also showed that serum PCT levels on day 3 were the best predictor of mortality in pediatric sepsis patients, with a cut-off of > 3.2 ng/mL having 92.80% accuracy for determining mortality (60). Lubis et al. conducted a study in Indonesia, found that PCT concentration significantly influenced mortality in concentration >5.4 ng/mL (54). This heterogeneity findings suggested that the significance of procalcitonin levels as a predictor of mortality is influenced by several clinical factors, such as varying sepsis severity, type of underlying infection, differences in sepsis care and management approaches, and varying comorbidity risk factors within the study population. Variability in these clinical factors may affect the relationship between procalcitonin levels and mortality in different studies. It is important to consider these clinical factors when evaluating findings from studies on the role of PCT in predicting mortality. PCT levels are still not an independent measure of mortality, but their use in combination with other clinical, laboratory and radiological parameters can significantly improve diagnostic and prognostic accuracy (18,61–66). Our study determine that cut off value for CRP level was >2.075 mg/L to predict the mortality rate in pediatric sepsis patients with sensitivity and specificity of 63.6% and 58.3%, although no significant difference between CRP levels and mortality in pediatric sepsis. This suggests that CRP levels may not be a major factor in predicting mortality in pediatric sepsis patients. This is consistent with another study which stated that CRP concentration did not significantly affect mortality in pediatric sepsis patients (67). Lubis et al. found the relationship with mortality in cut-off >2.05 mg/dL. The study highlighted that CRP concentrations could not be independently used as a predictor of mortality (54), that almost similar with our result. A study in Brazil conducted by Arslan et al. found a good discriminatory of CRP, along with Pediatric Index of Mortality (PIM), ferritin and lactate in predicting the mortality. The cut-off value for CRP was > 6.7 mg/mL (68), that was higher than our result. Although this study did not find a significant association between CRP levels and mortality in pediatric patients with sepsis shock, it is important to consider the complex pathophysiology of sepsis. Sepsis is a heterogeneous syndrome with diverse etiologies, clinical presentations, and patient characteristics. Therefore, the lack of significance in the association between CRP levels and mortality in pediatric patients with sepsis shock in some published

studies may reflect the influence of various confounding factors that were not fully accounted for in the study design. These varying study results demonstrate the limitations of CRP as an independent prognostic marker in pediatric patients with sepsis shock. CRP is a biomarker of inflammation and infection whose diagnostic and prognostic value can be influenced by multiple factors, including the timing of measurement, comorbidities, and the presence of concurrent infections or inflammatory conditions (69). CRP levels may vary among individuals based on their age, gender and physical condition, further complicating its interpretation as a prognostic indicator. Despite variable findings, it is important to recognize the broader clinical utility of CRP in sepsis management particularly in pediatric patients. CRP cannot be used as a definitive predictor of mortality by itself, but it remains a valuable reference for clinicians to assess disease severity, monitor treatment response and guide therapeutic decisions. When CRP concentrations are compared with other clinical parameters, such as vital signs, other laboratory values, and radiological findings, CRP can contribute to a comprehensive assessment of a patient's clinical status and contribute to risk stratification of sepsis patients, especially in children. More than half (63.6%) of pediatric sepsis patients who died had CAR levels ≥ 0.5765 in this study. There was no significant association between CAR and mortality in pediatric sepsis patients with a p-value of 0.066. This suggests that CRP/Albumin ratio may not be a major factor in predicting mortality in pediatric sepsis patients (Table 3). CRP and albumin are commonly used biomarkers in clinical settings due to their association with inflammation, infection and overall health status. The result of CAR is positively correlated to the patient's inflammatory status, the higher the ratio indicates a higher inflammatory status (70). CRP and albumin levels can be a marker of disease severity, prognosis, and treatment response, thus a potential predictor of mortality. CRP is produced by the liver in response to inflammation, infection or tissue injury. Higher CRP levels indicate a more severe inflammatory state, which may correlate with disease severity and worse prognosis (69). In sepsis, hypoalbuminemia is common and may reflect disease severity, systemic inflammation, and organ dysfunction. Low albumin levels usually indicate a more severe illness and poorer prognosis (71). Combining CRP and Albumin levels in the CAR may increase the predictive value for mortality to be more accurate, especially as a predictor of mortality in pediatric patients with sepsis shock. This study showed no significant difference between blood CRP/Albumin levels and mortality in pediatric patients with sepsis shock. Different things were found in similar studies, CRP/Albumin concentrations can be a risk factor for patient mortality (68). The study stated that the CAR within 24 hours of admission to the PICU was a good independent predictor of mortality in pediatric septic shock (72). In this study, the ROC curve results showed that the cut off of the CAR >25.83 could significantly predict mortality with an accuracy of 85.4%. The differences in findings in some previously published studies may be due to the heterogeneity of the patient population. A study conducted by Li et al. stated the the good acuracy of CAR to determine sepsis (AUC = 0.74, 95% CI, 0.71–0.77, $P < 0.001$) (73). Other design the cut-off > 25.83 and claimed to have a good discriminatory power to predict mortality with the sensitivity of 85.5% (AUC = 0.795, $P<0.0001$). Every unit of CAR value, increase the mortality risk by 1.075-times. The significancy value of CAR depended on the usage of inotropes and ventilator support (74). Ren et al. study design the cut-off value for CAR in determining the mortality in patients with pediatric septic arthritis at the time of admission was > 0.447, with AUC was 0.828. the risk for being non-survival was 6.85-times (74), while in septic arthritis children, the cut-off value of CAR was ≥1.165, which increased the mortality by 12.641-times than those with <1.165. the sensitivity was 71.4%, and specificity was 85.0%, with good discrimination (AUC = 0.793 [95% (0.694-0.893)]) (75). Variations in patient characteristics, such as age, comorbidities, nutritional status, disease severity, and response to treatment, may have contributed to the findings of these studies. In addition, CRP and albumin levels are dynamic biomarkers that may fluctuate during the course of the disease (22,69,76). The variation of CRP/Albumin concentrations during illness may be the cause of the various results in determining its relationship with mortality in pediatric patients with sepsis shock. A more homogeneous CRP/Albumin concentration

measurement time coupled with periodic concentration measurements over several days may be able to show the relationship between CRP/Albumin levels and mortality in pediatric patients with sepsis shock more accurately. In this study, there was no significant association between CRP/Albumin levels and mortality in pediatric patients with sepsis shock, but CRP/Albumin levels when combined with other clinical parameters, such as vital signs, other laboratory values, and radiological findings, will provide a more comprehensive assessment. There was no significant relationship between culture results and mortality in pediatric sepsis patients. This suggests that culture results may not be an important factor in predicting mortality in pediatric sepsis patients in this study, which in line with other: positive culture results did not significantly affect mortality rates in pediatric patients with sepsis (36). Other found a small positive result of culture (9%-14.3%), with more than half had severe organ dysfunction, which means that a a 1.5-times increased risk of organ dysfunction compared to patients with negative culture results, and associated with mortality (77). A study in Indonesia found that 20.2% septic children had positive culture results, which had a significant relationship between positive culture results and mortality rates (78). The relationship between positive culture results and mortality in pediatric patients with sepsis is complex and influenced by various factors. The timing of culture sampling relative to the onset of sepsis, the timing of culture sample administration relative to therapy, the patient's immune status, and the patient's comorbidities can affect accuracy and prognostic value. A positive culture is an important diagnostic finding, but its interpretation as a prognostic sign cannot be applied independently. Positive culture results, combined with clinical, laboratory and radiology findings will be able to more comprehensively estimate mortality rates in sepsis patients, especially pediatric patients with sepsis shock.

Strength and limitations

The study of infection biomarkers in pediatric critically ill patient with septic shock had yielded various outcomes and still limited in Indonesia. This study described that PCT, not only has demonstrated superior diagnostic accuracy, but also superior predictor of mortality Prognostic for sepsis. This information can be used for improving earlier diagnosis and better prognostic of septic shock patient. This study was performed in critically ill patient with septic shock, with limited factors of source of infection, and several infection biomarkers. More information related source of infection factors and more various infection biomarkers needed to explore to investigate the most superior infection biomarkers in diagnostic and prognostic purposes, especially the superior infection biomarker with the lowest cost would be highly needed.

Conclusion

PCT can be used as a biomarker to predict the mortality prognosis of pediatric patients with septic shock. However, CRP, CAR, and microbiological culture results cannot be considered as examinations to determine the outcome of pediatric patients with sepsis shock.

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