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Original Article

Presepsin level as risk factor for mortality in premature infants with neonatal sepsis

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Abstract

Background Prematurity is a risk factor of neonatal sepsis and its associated morbidities and mortality. Most deaths in neonatal sepsis occur within the first seven days. Presepsin has been reported as one of the earliest biomarkers for predicting mortality.

Objective To determine the association between presepsin levels and mortality risk, as well as the optimal presepsin cut-off point for predicting mortality, in premature infants with neonatal sepsis.

Method This was a prospective cohort study on 62 preterm infants born at 28 to <37 weeks' gestation. We recorded clinical and laboratory characteristics, performed blood culture, and measured presepsin levels at initial diagnosis of sepsis. Subjects were followed for seven days and their outcomes (death or survival) recorded. We evaluated the association between clinical and laboratory characteristics, including presepsin levels, with sepsis outcome. We also constructed a receiver-operator characteristics curve to determine the optimal cut-off point of presepsin as a predictor of sepsis mortality.

Results Only blood culture results and presepsin level were significantly associated with sepsis outcome on the seventh day. The optimal presepsin cut-off value for predicting mortality was 1057 ng/mL, with an area under curve of 80.4%, sensitivity of 60.71%, and specificity of 88.24%. A presepsin level of >1057 ng/mL was associated with increased mortality [RR 3.02; 95%CI 68.3 to 89.4; P<0.001].

Conclusion In preterm infants with neonatal sepsis, an elevated presepsin level at diagnosis is a significant risk factor for mortality within seven days. Presepsin can be used as an early biomarker of sepsis outcomes. **[Paediatr Indones. 2021;61:165-70 ; DOI: 10.14238/pi61.3.2021.165-70**].

Keywords: *presepsin; neonatal sepsis; mortality; premature infant*

Infants, especially prematures, are prone to infection, due to immaturity of their immune systems. Neonatal sepsis, a systemic infection in newborn infants, remains the leading cause of neonatal deaths in developing countries.[1,2] Sepsis occurs in 16% to 30% of preterm infants.[3] In Ethiopia, 37% of preterm infants born in 2019 were treated for sepsis, with a mortality of 26.1%.[4] A study on neonatal sepsis in Bali found that 68.8% of newborns with sepsis were born premature.[5]

Neonatal sepsis is a systemic condition involving hemodynamic changes and clinical manifestations caused by bacterial, viral, or fungal infection that occurs within the first 28 days of life.[2] Blood culture to identify the causative organism is the gold standard for the definitive diagnosis of sepsis. However, isolation of the pathogen in sepsis is not always successful.[6]

Although there are recommendations for empirical antibiotics in infants with neonatal sepsis, mortality in neonatal sepsis is still high. A 2018 study

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in South Korea reported that 37.8% of infants with neonatal sepsis died within 14 days of infection; 70.6% of which occurred within seven days of infection.[7]

Presepsin, also known as soluble CD14 subtype (sCD14-ST), is a glycoprotein receptor that can induce immune pathways after interacting with the lipopolysaccharide-lipopolysaccharide binding protein complex (LPS-LBP), toll-like receptor-4 (TLR-4) and MD-2. Soluble CD14 (sDC14) is released from the surface of various immune cells, such as macrophages, monocytes, and neutrophils, after being stimulated by pathogenic bacteria. It then binds to the lipopolysaccharide (LPS) of Gram-negative bacteria or to peptidoglycan and lipoteichoic acid on Gram-positive bacteria. This binding will activate endotoxin signaling and cause the release of cytokines such as TNF-α, interferon-γ, IL-1ß, IL-8, and IL-6, which will lead to neutrophil recruitment through chemotaxis, activation of macrophages, and gene stimulation, resulting in death of the pathogenic bacteria. After being released from the cell surface, sCD14 is cleaved by the bacterial lysosome enzyme into an N-terminal peptide of 64 amino acids which is then called presepsin (sCD14-ST).[8]

Previous studies have shown that presepsin is a significant marker for neonatal sepsis and its outcomes: presepsin levels were higher in infants with sepsis than those without, in infants who developed septic shock than those who did not, and in infants who ultimately did not survive than those who did. Quantitative measurements at baseline can be a good predictor of the severity of sepsis and the risk of mortality.[9]

In the present study, we measured presepsin levels in premature infants with neonatal sepsis and evaluated the association between presepsin levels and mortality risk.

Methods

This was a prospective cohort study in premature infants with neonatal sepsis admitted to the Department of Pediatrics, Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia. We included preterm infants born at a gestational age of 28 to <37 weeks who suffered from sepsis, whose presepsin levels at the time of diagnosis of sepsis were available. Infants were excluded if they had major congenital abnormalities (permanent changes in body structure during the prenatal phase visible from birth affecting health, safety, or physical or cognitive function). We recorded date of birth, sex, birth weight, hematology values [hemoglobin, hematocrits, leukocytes, platelets, immature/total neutrophil (I/T) ratio], C-reactive protein level, blood culture results, and presepsin level upon diagnosis of neonatal sepsis. We followed subjects for seven days starting from the time of diagnosis of neonatal sepsis and recorded their outcomes (survival or death) on the seventh day. Subjects were recruited by consecutive sampling until the minimum number of subjects required was met. This study has received ethics approval from the Medical Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung.

We tested data normality for numerical data using the Kolmogorov-Smirnov test and compared means using the independent samples T-test for normally distributed variables and the Mann-Whitney test for variables not normally distributed. We constructed a receiver-operator characteristics (ROC) curve to determine the optimal presepsin cut-off point for prediction of mortality. The association between categorical variables (sex, birth weight, gestational age, and blood culture results) and sepsis outcomes (survival or death on the seventh day after diagnosis) were evaluated using the chi-square test. We also calculated the relative risk (RR) of mortality in preterm infants with high, compared to low, presepsin levels. Data analysis was performed using the *SPSS for Windows v. 21.0* (*IBM*, New York). We used a 95% confidence interval where applicable, and a P value of 0.05 was considered statistically significant.

Results

Baseline characteristics of study subjects are shown in **Table 1**. Out of 62 subjects, 37 (59.7%) were male. The subjects' gestational age at birth ranged between 28 to 36 weeks; most subjects (71%) were born between 28 and <34 weeks' gestation. Blood culture was sterile in 71% of subjects. On the seventh day after diagnosis of neonatal sepsis, 28 infants (45.2%) had died.

Table 2 shows the association between clinical characteristics and sepsis outcomes. Sex, birth weight, and gestational age was not significantly associated with

outcomes. Thirteen out of 18 infants with non-sterile, "positive" blood cultures died, *vs.* 15/44 (34%) infants with sterile blood cultures (P=0.006).

Baseline laboratory parameters in those who died *vs.* survived at the seventh day after diagnosis are compared in **Table 3**. Only median presepsin levels differed significantly between those who died and those who survived.

The ROC curve for presepsin in predicting mortality outcome had an area under curve (AUC) of 0.804 (95%CI 0.683 to 0.894) (**Figure 1**). The optimal presepsin cut-off value was 1057 ng/mL with a sensitivity of 60.71% and specificity of 88.24%. Presepsin values above this cut-off point had an RR for death of 3.02 (95%CI 1.75 to 5.21). A 2x2 table of presepsin level and sepsis outcomes using this cut-off point can be seen in **Table 4**.

Table 1. Baseline subject characteristics (N=62)

Characteristics	n (%)
Sex	
Male	37 (59.7)
Female	25 (40.3)
Birth weight (grams)	
≤1,000	8 (12.9)
1,001 to 1,499	20 (32.3)
1,500 to <2,000	15 (24.2)
2,000 to 2,499	13 (21.0)
≥2,500	6 (9.7)
Gestational age (weeks)	
28 to <32	22 (35.5)
32 to 34	22 (35.5)
>34 to <37	18 (29.0)
Blood culture	
Sterile	44 (71.0)
Non-sterile	18 (29.0)
Outcome on 7th day	
Died	28 (45.2)
Survived	34 (54.8)

Discussion

We recruited 62 preterm infants with neonatal sepsis, recorded baseline clinical and laboratory characteristics, measured presepsin levels at the time of diagnosis, and followed them for seven days to observe mortality or survival outcome. Infants who died had a higher median presepsin level than those who survived (1383.5 *vs.* 406.5 ng/mL; P<0.001). Significant predictors of death were a non-sterile blood culture (P=0.006) and presepsin levels >1057 ng/mL [RR 3.02; 95%CI 1.75 to 5.21; P<0.001].

In the present study, the mortality of preterm infants with neonatal sepsis within seven days of diagnosis was 45%, greater that reported in a Korean study (37.8%).[7] Our subjects were born at a gestational age of 28 to 36 weeks, with most subjects (71%) born between 28 to <34 weeks' gestation. The largest birth weight group was 1001 to 1499 grams (32.3%). Preterm birth, especially between 28 to 32 weeks' gestation, and low birth weight have been reported to be associated

Table 2. Association between clinical characteristics and sepsis outcome

Variables	Outcomes		P value
	Died (n=28)	Survived (n=34)	
Sex			
Male	20	17	0.087
Female	8	17	
Birth weight (grams)			
≤1,000	4	4	0.904
1,001 to 1,499	8	12	
1,500 to <2,000	7	8	
2,000 to 2,499	7	6	
≥2,500	2	4	
Gestational age (weeks)			
28 to <32	10	12	0.997
32 to 34	10	12	
>34 to <37	8	10	
Blood culture			
Sterile	15	29	0.006
Non-sterile	13	5	

Table 3. Comparison of baseline laboratory parameters in non-survivors vs. survivors

Variables	Outcomes on the 7th day		P value
	Died (n=28)	Survived (n=34)	
Mean hemoglobin (SD), g/dL	14.21 (2.63)	14.89 (3.14)	0.360
Mean hematocrit (SD), vol%	41.5 (7.9)	43.2 (9.7)	0.243
Median leukocytes (range), /mm3	12,410 (1710-44,050)	14,065 (1550-38,010)	0.216
Median platelets (range), mm3	100,000 (2000-538,000)	203,000 (13,000-555,000)	0.074
Median I/T ratio** (range)	0.030 (0.0-0.45)	0.025 (0.0-0.38)	0.994
Median CRP (range), mg/dL	1.885 (0.01-17.77)	0.225 (0.03-144.80)	0.072
Median presepsin (range), ng/mL**	1383.5 (168-3,197)	406.5 (100-2033)	<0.001

Table 4. Presepsin level and risk of death

Presepsin level, ng/mL	Outcomes on the 7th day		RR (95%CI)	P value
	Died (n=28)	Survived (n=34)		
>1057	17	4	3.02 (1.75 to 5.21)	<0.001
≤1057	11	30		

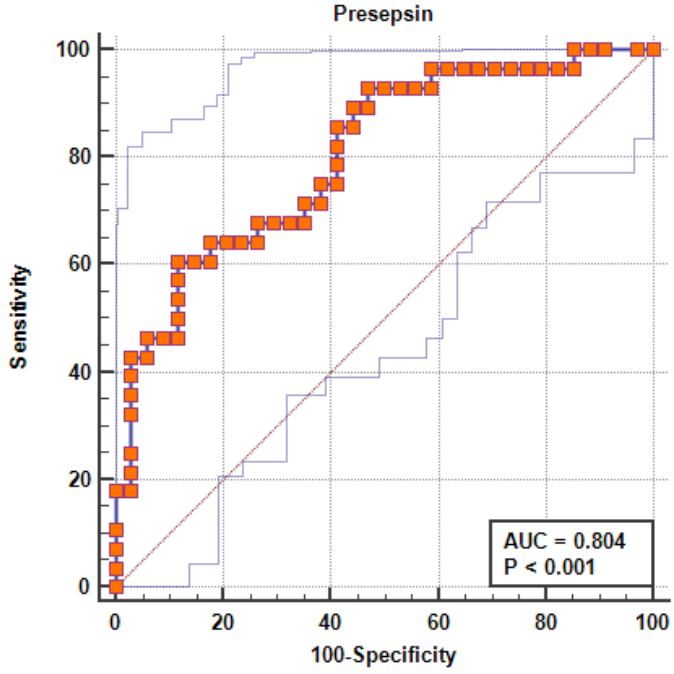

Figure 1. ROC curve of presepsin level as predictor of death

with a heightened risk of neonatal sepsis.[2,3,5] In a study in Ethiopia, the incidence of infection increased with lower birth weight.[4] Premature babies with low birth weight have a three- to ten-fold risk of infection compared to term babies with normal birth weight.[10] Low birth weight and prematurity are associated with immaturity of the cellular and humoral immune system, which are characterized by reduced lymphocyte proliferation and immunoglobulin production.[11]

Of the seven laboratory parameters measured, only presepsin level differed significantly between non-survivors and survivors. Median presepsin level

was significantly higher in infants who died within seven days of diagnosis than in those who survived. A previous study in premature infants in Jakarta reported similar findings; presepsin levels on the third and sixth days were higher in non-survivors than in survivors.[9] In sepsis, soluble CD14 (sCD14) is released from the surface of various immune cells, such as macrophages, monocytes, and neutrophils, after being stimulated by pathogenic bacteria. It then binds to lipopolysaccharide on Gram-negative bacteria, as well as to peptidoglycan and lipoteichoic acid on Gram-positive bacteria. After being released from the cell surface, sCD14 is cleaved by the bacterial lysosomal enzyme into an N-terminal peptide of 64 amino acids, which is then called presepsin or sCD14-ST.[12] Increased presepsin level in the circulating blood reflects the severity of bacteremia, and is therefore a reliable diagnostic and prognostic marker of neonatal sepsis.[13]

In the present study, we found an optimal presepsin cut-off value of 1057 ng/mL. At this value, an AUC of 0.804 was obtained, with a sensitivity of 60.71% and a specificity of 88.24% to predict mortality within seven days. We also found that the risk of death was three times higher in infants with increased presepsin levels than in those without.

A previous study reported that in preterm infants with neonatal sepsis, presepsin can predict mortality earlier than C-reactive protein (CRP) and procalcitonin (PCT). Elevated presepsin levels were seen in non-survivors, compared to survivors, as early as the third day, whereas CRP and PCT elevation was observed only on the sixth day.[9]

Several studies on presepsin in preterm infants with sepsis demonstrated that presepin levels were significantly higher in both early-onset sepsis (EOS) and late-onset sepsis (LOS).[14,15] A study in Egypt in newborns with risk factors for EOS showed that presepsin was significantly higher in infants with EOS than in controls. Infants with EOS who later developed septic shock had significantly higher levels of presepsin on the first day, and those who had a fatal outcome had significantly higher levels of presepsin than those who survived.[16]

Our study results reinforce findings of previous studies regarding the use of presepsin parameters in neonates, especially preterms, with sepsis. Presepsin levels can therefore be considered in making decisions for early aggressive antibiotic administration and closer monitoring.[9] Presepsin is simple, easy, precise, and less costly to measure compared to CRP or procalcitonin. This laboratory test can also be performed on critically ill neonates and very low birth weight infants in whom blood draws need to be limited due to their relatively small blood volume.[17]

This study has some limitations. Oxygen therapy was not included as a variable in the study analysis due to limited funds and facilities at the study site. Moreover, the positivity rate of blood culture was low (29%), owing to various factors including the volume of blood required for inoculation, which was difficult to obtain in very low birth weight and extremely low birth weight infants. In addition, neonates who underwent surgical intervention were not excluded from the study for purposes of optimizing the study's external validity.

We conclude that in preterm infants with neonatal sepsis, a high level of presepsin (>1057 ng/mL) is associated with an increased risk of death within seven days after diagnosis (RR 3.02; 95%CI 1.75 to 5.21; P<0.001). Determination of presepsin levels at diagnosis can be considered by clinicians working in second- and third-tier healthcare facilities to guide the aggressivess of antimicrobial therapy.

Conflict of interest

None declared.

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