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THE ROLE OF PRESEPSIN, C-REACTIVE PROTEIN AND PROCALCITONIN AS A MARKER OF THERAPY RESPONSE AND PROGNOSIS FOR LATE ONSET NEONATAL SEPSIS IN PRETERM NEONATES

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ABSTRACT

Introduction : C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used diagnostic and monitoring markers of neonatal sepsis. There is currently a new sepsis marker, Soluble CD14 subtype (sCD14-ST) presepsin. This study aims to determine the benefits of serial serum presepsin examination, CRP and PCT as well as the correlation between presepsin levels with CRP and PCT levels as a marker of therapy response and prognosis of late-onset neonatal sepsis (LONS) in preterm neonates.

Method : This is a prospective cohort study. The subjects consisted of 40 healthy preterm neonates and 40 preterm neonates with LONS whose presepsin, CRP and PCT levels are going to be examined and monitored on the 3rd and 6th day of LONS after treatment. Preterm neonatal patients with LONS were divided into two groups, 20 neonates who are responsive to therapy and the other 20 who are non-responsive to therapy. The mortality of the preterm neonates with LONS is determined at day 30 monitoring.

Results : The median levels of presepsin, CRP and PCT in preterm neonates with LONS were 1559 pg / mL (427 - 4835 pg / mL), 16.35 mg / L (0.1 - 245.6) and 4.11 ng / mL (0.17 - 54.18) respectively which were significantly

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higher than in healthy preterm neonates 406 pg / mL (195 - 562 pg / mL), 1.22 mg / L (0.1 - 3.69) and 0.03 (0.01 - 0.04) with p <0.05. The median levels of presepsin, CRP and PCT in LONS preterm neonates on the 3rd and 6th day, was significantly lower in the responsive to therapy group compared to the non-responsive to therapy group (p <0.05). The median levels of presepsin days 3 and 6 in the non-survivor group were significantly higher than in the survivor group (p <0.05) whereas the median CRP and PCT levels in the non-survivor group were significantly higher than the survivor group (p < 0.05) only on the 6th day after therapy. Presepsin levels did not correlate with CRP and PCT levels on day 3 and day 6 after therapy in both responsive to therapy and non-responsive groups (p> 0.05). The cut-off point of presepsin, CRP and PCT on the 6th day after therapy was determined for the prognosis of preterm neonates with LONS, with the highest area under the curve (AUC) was presepsin, PCT and CRP consecutively.

Conclusion : Presepsin is the earliest and best-performing marker of sepsis for the prognosis of preterm neonatal mortality when compared to CRP and PCT.

INTRODUCTION

Neonatal death is of utmost concern recently because the proportion of infant mortality during this period is very high. Most neonatal deaths are caused by infection.[1] Infection in neonates can progress quickly into neonatal sepsis, a bloodstream infection characterized by the discovery of bacteria in the blood in the neonatal period (0 - 28 days) .[3,4] Neonatal Sepsis is classified into Early-onset Neonatal Sepsis (EONS) occurring ≤72 hours after birth and Late-onset Neonatal Sepsis (LONS) occurring >72 hours after birth.[2]

The problem often encountered in establishing the diagnosis of neonatal sepsis is because the clinical manifestations of neonatal sepsis are not specific especially in LONS and blood cultures are often negative, making it difficult to distinguish between neonatal sepsis and other noninfectious diseases.[1,2] To date, C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used diagnostic and monitoring markers for neonatal sepsis in the NICU.[3] Serial CRP measurements are often used to monitor therapeutic responses and as a parameter of safety to determine the duration of antibiotics in neonatal sepsis. However, CRP levels may also be elevated under various non-infectious inflammatory conditions such as ischemic or traumatic tissue damage, meconium aspiration syndrome, hemolysis and chorioamnionitis.[4] Procalcitonin (PCT) is widely used for the diagnosis and monitoring of neonatal sepsis because of its high sensitivity[5] but PCT is not specific because it can be physiologically elevated for the first 24 hours of infant life.[6] PCT levels can also increase in conditions associated with inflammatory responses such as trauma and surgery.[5]

Currently, there is a new sepsis marker: Soluble CD14 subtype (sCD14-ST) presepsin. During early phases of inflammation and sepsis, Presepsin level rises significantly in the blood circulation. It has been reported that measurement of presepsin level is useful for diagnosis, treatment monitoring, stratification of severity, and prognostic purposes for neonatal sepsis.[1] Serial examination of presepsin levels can also be used as a marker for monitoring after the patient has received antibiotic therapy.

In this study, the purpose is to find the benefits of presepsin, CRP and PCT examination as marker for monitoring the response of antibiotic therapy and the prognosis of late-onset neonatal sepsis (LONS) in preterm neonates and the correlation between presepsin levels with CRP and PCT levels in the responsive to therapy and non-responsive groups.

METHODS

This study is a prospective cohort study. The data is analyzed and presented descriptively and analytically. The study was conducted in Infectious Disease Division of Clinical Pathology Department, Dr. Cipto Mangunkusumo Hospital, in collaboration with Neonatology Division of Pediatrics Department, Dr. Cipto Mangunkusumo Hospital, during September - December 2016.

Research Subjects

The subjects of the study were preterm neonates with LONS and healthy preterm neonates who were admitted to Neonatology Ward of Dr. Cipto Mangunkusumo Hospital and fulfilled the inclusion criteria of preterm neonates with LONS >3 days with gestational age ≥28 weeks and birth weight >1000 gr.

Materials and Research Tools

The study material came from venous blood of preterm neonates with LONS treated in RSCM Children's Health Department Neonatology Division. Blood samples were taken in healthy preterm neonates and preterm neonates patients diagnosed with LONS on

the first day. Blood samples were taken for preterm neonates with LONS on the 3rd and 6th day after receiving antibiotic therapy. Examination of sCD14-ST Presepsin was carried out using PATHFAST ™ analyzer tool, [7.8] CRP examination using Cobas 501,[9] and PCT inspection using BRAHMS Kryptor tool.[10]

RESULTS

Subjects characteristic

The number of research subjects were 80 neonates consisting of 40 healthy preterm neonates and 40 preterm neonates diagnosed with LONS. Characteristics of study subjects are presented in Table 1.

Table 1. Characteristics of Research Subjects

Characteristic	LONS			Healthy Neonates (n=40)
	Responsive (n=20)	Non Responsive (n=20)	Total (n=40)	
Gender, n(%)				
Male	9 (45)	15 (75)	24 (60)	18 (45)
Female	11 (55)	5 (25)	16 (40)	22 (55)
Age (days)	9 ± 4	12 ± 7	14 ± 6	18 ± 3
Birth Weight (grams)	1618 ± 512	1419 ± 465	1519 ± 493	1669 ± 421
Gestation (week)	32 ± 3	31 ± 3	31 ± 3	32 ± 4
Labor methods, n(%)				
Spontaneous	7 (35)	9 (45)	16 (40)	14 (35)
Sectio Cesarean	13 (65)	11 (55)	24 (60)	26 (65)
Presepsin Levels (pg/mL)	1504 (427 – 2879)	1567 (619 – 5238)	1559 (427 – 4835)	406 (195 – 562)
CRP Levels (mg/L)	15.05 (0.1 – 132.9)	17.25 (0.2 – 245.6)	16.35 (0.1 – 245.6)	1.22 (0.1 – 3.69)
PCT Levels (ng/mL)	4.46 (0.24 – 34.38)	5.39 (0.22 – 88.22)	4.11 (0.17 – 54.18)	0.03 (0.02 – 0.06)
Respiratory devices, n(%)				
Yes	12 (60)	15 (75)	27 (67.5)	
No	8 (40)	5 (25)	13 (32.5)	
Culture, n(%)				
Positive	4 (20)	6 (30)	10 (25)	
Steril	16 (80)	14 (70)	30 (75)	
Septic Criteria, n (%)				
Sepsis	6 (30)	0 (0)	6 (15)	
Severe Sepsis	10 (50)	10 (50)	20 (50)	
Septic Shock	4 (20)	10 (50)	14 (35)	
30 day mortality, n(%)				
Yes	0 (0)	14 (70)	14 (35)	
No	20 (100)	6 (30)	26 (65)	

Comparison of Presepsin, CRP and PCT levels in Normal Preterm Neonates and Preterm Neonates Diagnosed with Late-onset Neonatal Sepsis.

The normality distribution of presepsin, CRP and PCT levels in normal preterm neonates and preterm neonates diagnosed with neonatal LOS was completed using Shapiro-Wilk test. [11] The distribution of data of levels of presepsin, CRP and PCT in normal preterm neonates and preterm neonates with LONS is not normal with $p<0.05$, and therefore the data is presented with the median and range results as shown in tabel 2.

Table 2. Levels of Presepsin, CRP dan PCT in normal preterm neonates and preterm neonates diagnosed with late-onset neonatal sepsis.

	Presepsin levels (pg/mL) Median (Range)	CRP levels (mg/L) Median (Range)	PCT levels (ng/mL) Median (Range)
Healthy preterm neonates	406 (195 – 562)	1.22 (0.1 – 3.69)	0.03 (0.01 – 0.04)
Preterm neonates with LONS	1559 (427 – 4835)	16.35 (0.1 – 245.6)	4.11 (0.17 – 54.18)

The difference in levels of presepsin, CRP and PCT between normal preterm neonates and preterm neonates with LONS was evaluated using Mann Whitney test.[11] Levels of presepsin, CRP and PCT in preterm neonates with LONS is significantly higher than in normal preterm neonates ($p<0.05$). Boxplot representation of levels of presepsin, CRP and PCT are presented in images 1, 2, and 3 respectively.

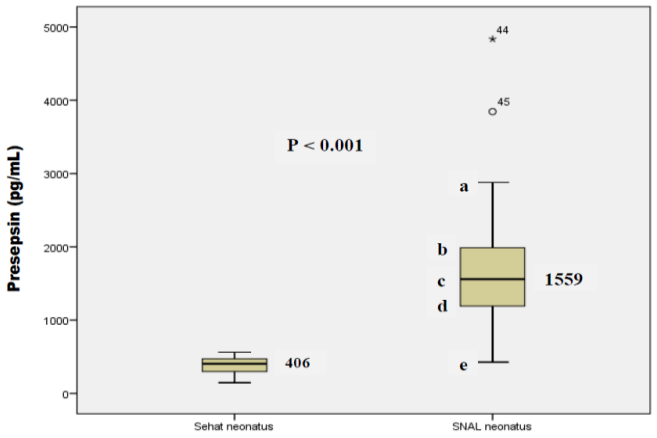

Figure 1. *Box-plot* Presepsin levels in normal preterm neonates and preterm neonates with LONS.

a. Upper limit; b. 75 percentile; c. median; d. 25 percentile; e. lower limit; o. *outlier;* *.extreme data

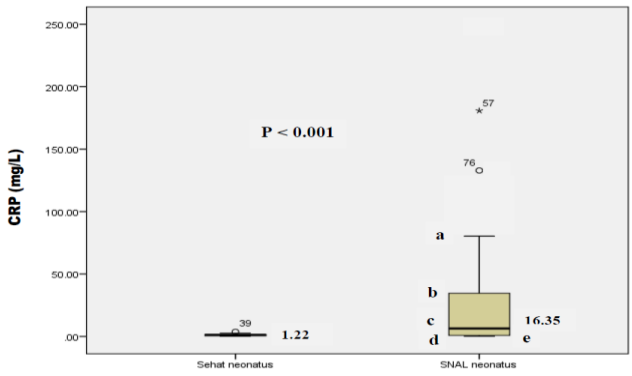

Figure 2. *Box-plot* CRP levels in normal preterm neonates and preterm neonates with LONS.

a. Upper limit; b. 75 percentile; c. median; d. 25 percentile; e. lower limit; o. *outlier;* *.extreme data

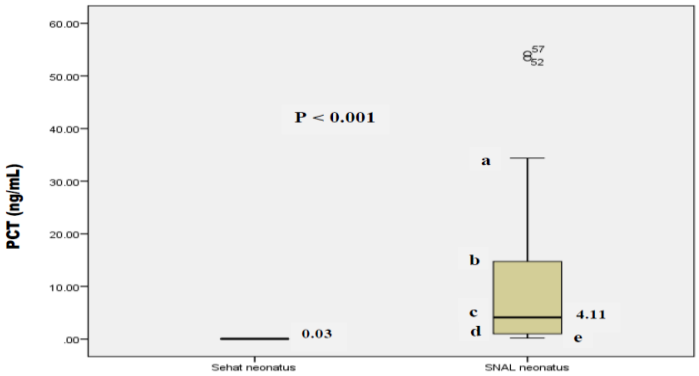

Figure 3. *Box-plot* PCT levels in normal preterm neonates and preterm neonates with LONS.

a. Upper limit; b. 75 percentile; c. median; d. 25 percentile; e. lower limit; o. *outlier.*

Comparison of Presepsin, CRP and PCT Levels in Premature Neonates diagnosed with LONS in Therapy Responsive and Non Responsive groups.

Data distribution of levels of presepsin, CRP and PCT is not a normal distribution with a $p<0.05$. The median and range of levels of presepsin, CRP and PCT in Premature neonates diagnosed with LONS in both the groups, responsive and non-responsive to therapy is shown in Table 3.

Table 3. Presepsin, CRT and PCT levels of premature neonates diagnosed with LONS in therapy responsive and non-responsive patients.

	n (%)	Presepsin Levels (pg/mL) Median (Range)	CRP Levels (mg/L) Median (Range)	PCT Levels (ng/mL) Median (Range)
LONS of Preterm neonates	40 (100)	1559 (427 – 4835)	16.35 (0.1 – 245.6)	4.11 (0.17 – 54.18)
Respons to therapy 3rd day				

	n (%)	Presepsin Levels (pg/mL) Median (Range)	CRP Levels (mg/L) Median (Range)	PCT Levels (ng/mL) Median (Range)
Responsive	20 (50)	1203 (369 – 3151)	1.42 (0.1 – 111.68)	0.48 (0.12 – 16.42)
Non Responsive	20 (50)	1816 (881 – 4835) p = 0.015	17.85 (0.49 – 251.5) p = 0.023	5.03 (0.16 – 93.2) p = 0.006
6th day				
Responsive	20 (50)	819 (301 – 2071)	1.22 (0.1 – 19.89)	0.3 (0.09 – 4.93)
Non Responsive	20 (50)	2289 (1723 – 6052) p < 0.001	18.19 (0.3 – 253.8) p = 0.002	5.4 (0.17 – 54.18) p = 0.002

Presepsin, CRP and PCT levels for the 3rd and 6th days in the treatment responsive group were significantly lower than in the non-responsive group (p <0.05). Boxplots of presepsin, CRP and PCT levels of each group are presented in Images 4, 5 and 6.

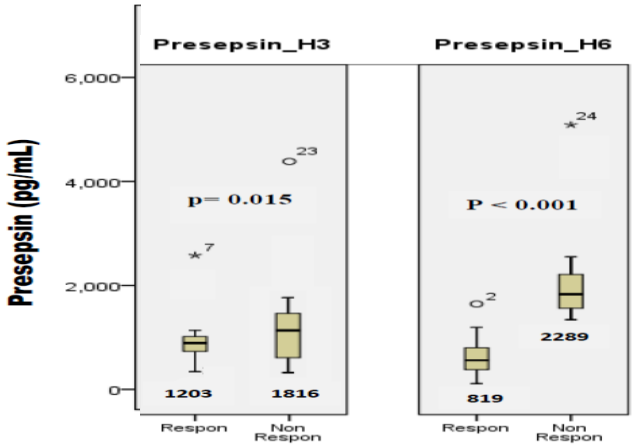

Figure 4. *Boxplot* Presepsin Levels of preterm neonates with LONS between Responsive and Non Responsive Group.

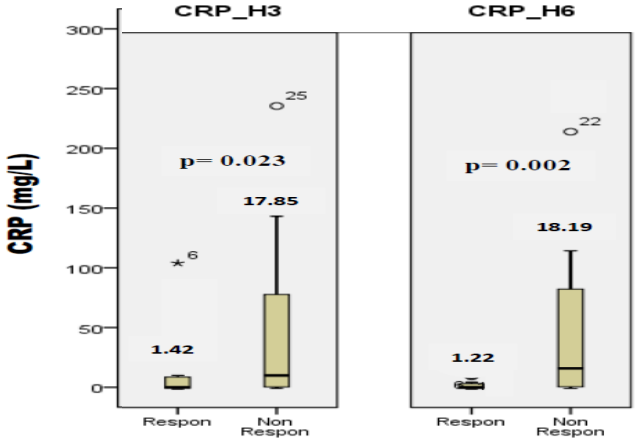

Figure 5. *Boxplot* CRP Levels of preterm neonates with LONS between Responsive and Non Responsive Group.

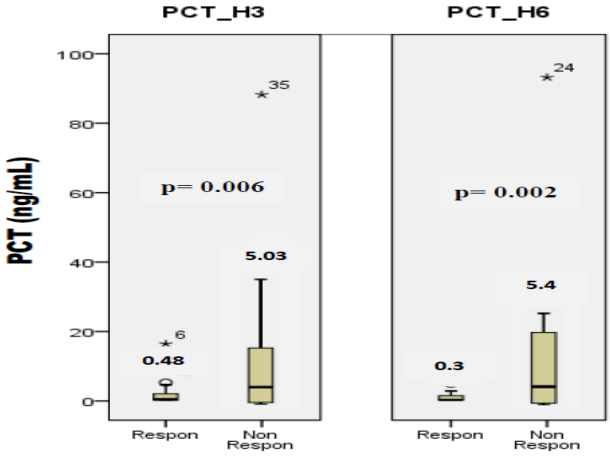

Figure 6. *Boxplot* PCT Levels of preterm neonates with LONS between Response and Non Response Group.

Comparison of Presepsin, CRP and PCT Levels in preterm neonates with LONS Survivor and Non Survivor Groups

In this study, 14 patients died from 40 preterm neonates with LONS. 70% dead patients are from the non-response therapy group. Median and range level of presepsin, CRP and PCT of preterm neonates with LONS in survivor and non-survivor groups seen in Table 4.

Table 4. Presepsin, CRP and PCT Levels of preterm neonates with LONS Survivor and Non survivor.

	n (%)	Presepsin Levels (pg/mL) Median (Range)	CRP Levels (mg/L) Median (Range)	PCT Levels (ng/mL) Median (Range)
LONS of Preterm Neonates	40 (100)	1559 (427 – 4835)	16.35 (0.1 – 245.6)	4.11 (0.17 – 54.18)
30 days Mortality				

	n (%)	Presepsin Levels (pg/mL) Median (Range)	CRP Levels (mg/L) Median (Range)	PCT Levels (ng/mL) Median (Range)
Day 3				
Survivor	26 (65)	1209 (369 – 3151)	1.95 (0.1 – 153.5)	0.59 (0.12 – 88.22)
Non Survivor	14 (35)	2096 (619 – 5238)	11.85 (0.49 – 251.5)	2.21 (0.22 – 19.13)
		p = 0.004	p = 0.067	p = 0.071
Day 6				
Survivor	26 (65)	1025 (301 – 3118)	1.43 (0.1 – 90.06)	0.44 (0.09 – 18.59)
Non Survivor	14 (35)	2374 (1794 – 6052)	40.74 (0.3 – 253.8)	5.12 (0.2 – 93.2)
		p < 0.001	p = 0.004	p = 0.003

Presepsin levels of day 3 and 6 in non-survivor group were significantly higher than survivor group (p <0.05). CRP and PCT levels on 3rd day of survivor group is not significantly different with non-survivor group (p> 0.05) while on the 6th day, level of CRP and PCT in non-survivor group were significantly higher than survivor group (p <0.05). Boxplots of presepsin, CRP and PCT levels of each group are presented in Figs. 7, 8, and 9.

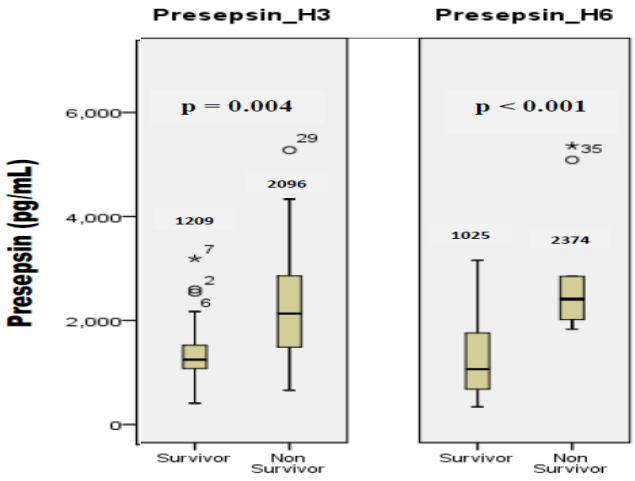

Figure 7. *Boxplot* Presepsin Levels of preterm neonates with neonatal LOS between Survivor and Non Survivor Group.

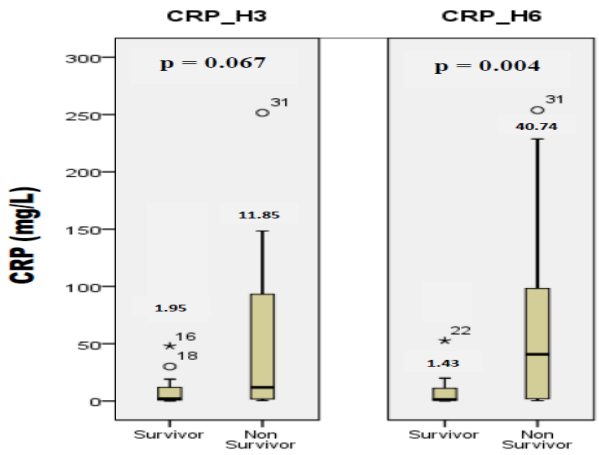

Figure 8. *Boxplot* CRP Levels of preterm neonates with neonatal LOS between Survivor and Non Survivor Group.

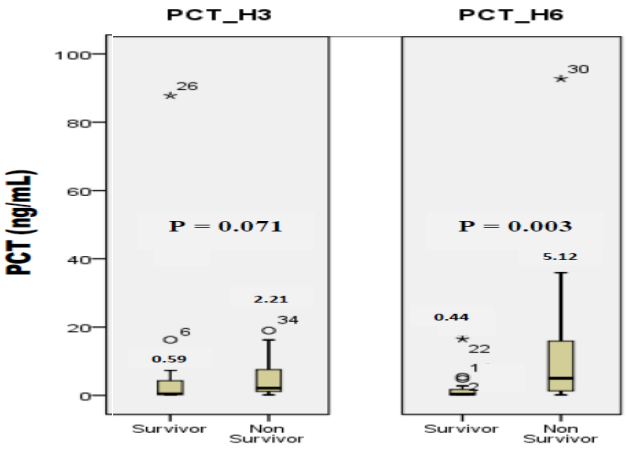

Figure 9. *Boxplot* PCT Levels of preterm neonates with LONS between Survivor and Non Survivor Group.

Presepsin Correlation with CRP and PCT Levels in preterm neonates with LONS with Therapy Responsive and Non Responsive groups

3rd and 6th day presepsin levels correlated with CRP and PCT levels in preterm neonates with LONS with therapy responsive and non-responsive groups using Spearman Correlation Test.[11] Presepsin levels correlated with CRP and PCT levels in preterm neonates with LONS with Therapy Responsive and Non-Responsive groups as seen in Table 5.

Table 5. Correlation between Presepsin Levels of preterm neonates with LONS with CRP and PCT levels

	Day 3 presepsin correlation		Day 6 presepsin correlation	
	CRP	PCT	CRP	PCT
Therapy Responsive				
Correlation	0.217	0.136	0.224	0.250
P value	0.358	0.988	0.342	0.288
Non Therapy Responsive				

Correlation	0.230	0.235	0.296	0.141
P value	0.329	0.319	0.205	0.552

Day 1 There is moderately positive correlation between presepsin level and CRP (r = 0.598) and presepsin level and PCT level (r = 0.478) with p values of 0.000 and 0.008 (p <0.05)

Role of Presepsin Level, CRP and PCT at 6th Day After Therapy in prognosis of preterm neonates with LONS

The making of ROC curve to obtain presepsin cut-off level, CRP and PCT between survivor group and non-survivor in determination of prognosis of preterm neonates with LONS was done at presepsin level, CRP and PCT on 6th day after therapy (p <0.05). AUC presepsin was found at 0.896 (95% CI 0.799 - 0.992), AUC CRP at 0.771 (95% IK 0.611 - 0.930) and AUC PCT at 0.784 (95% IK 0.636 - 0.933). ROC curve of presepsin levels, CRP and PCT 6th day after therapy were presented in Figure 10.

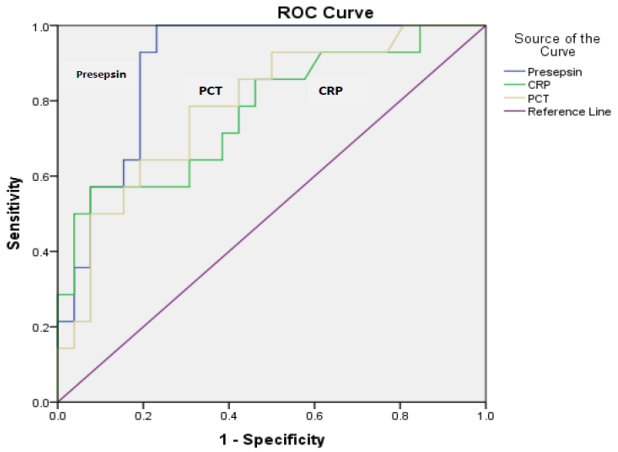

Figure 10. ROC Curve of Presepsin Levels, CRP and PCT 6th Day After Therapy.

On the ROC curve was determined cut-off value of presepsin levels, CRP and PCT 6th day that have prognostic value in determining 30 day mortality of preterm neonates with LONS. The cut-off value, sensitivity and specificity of presepsin level, CRP and PCT of 6th day applied in this study are presented in Table 6.

Table 6. Sensitivity, Specificity and Cut-off Presepsin Level, CRP and PCT at 6th Day.

	Cut-off	**Sensitivity (%)**	**Specificity (%)**
Presepsin (pg/mL)	1637	92,9	80.8
CRP (mg/L)	36.48	85.7	53.8
PCT (ng/mL)	13.81	78.6	69.2

DISCUSSION

This study obtained median levels of presepsin, CRP, and PCT on 1st day in preterm neonates with LONS group is higher than healthy preterm neonate group. Significant differences in presepsin level, CRP and PCT between preterm neonates with neonatal LOS group and healthy preterm neonate group were consistent with precepsin secretion, CRP and PCT that raised in inflammatory conditions due to sepsis.

Serial examination of presepsin, CRP, and PCT levels to monitor therapy response in preterm neonates with LONS in this study shown that median presepsin, CRP, and PCT levels on 1st day in therapy response group are not significantly different compared to levels in non-response group, but 3rd and 6th day presepsin, CRP, and PCT levels showed significant differences between the therapy response groups compared with non-response group. In non-response group, median of presepsin, CRP, and PCT levels on 3rd and 6th day are significantly higher. It shows that presepsin has same ability as CRP and PCT as marker of therapy response monitoring.

Serial examination of presepsin, CRP, and PCT levels to determine mortality prognosis of preterm neonates with LONS in this study obtained median presepsin levels that is not significantly different on 1st day between the group and non-survivor group, but median presepsin level of preterm neonates with LONS on 3rd and 6th day after therapy showed significant differences between survivor and non-survivor groups. Median of CRP and PCT levels showed that there is no significant difference on 1st and 3rd between survivor and non-survivor groups, only median CRP and PCT levels of preterm neonates with LONS on 6th day after therapy showed significant difference between survivor and non-survivor. This study explained that median presepsin levels showed significant differences between survivor and non-survivor group started on 3rd day after therapy, while median levels of CRP and PCT showed significant differences later on 6th day. This study suggests that role of presepsin as marker of mortality prognosis could predict mortality earlier than CRP and PCT.

This study found that presepsin level of preterm neonates with LONS on 3rd and 6th day in therapy response and non-response groups is not correlated with CRP and PCT levels. Study by Tantula et al[12] also obtained presepsin levels on 3rd and 6th day after therapy is not correlated with CRP and PCT levels. Study by

Malgorzata dkk[13] about diagnostic test of neonatal sepsis obtained a correlation of presepsin level on 1st day positively moderate correlated to CRP and PCT levels. Study of Tantula et al[12] obtained a correlation of presepsin levels on 1st day has moderate positive correlation with CRP levels and had strong positive correlation with PCT levels. In this study we found moderately positive correlation between presepsin levels on 1st day with CRP and PCT levels. These results corresponded with study of Malgorzata dkk[13] and Tantula et al. This suggests that presepsin levels correlate with CRP and PCT levels as diagnostic marker of neonatal sepsis but if it is used as marker for monitoring therapy response, presepsin levels do not correlate with CRP or PCT levels.

Cut-off value, AUC, sensitivity, and specificity of presepsin, CRP and PCT levels of preterm neonates with LONS were taken on 6th day after therapy to determine the mortality of preterm neonates with neonatal LOS neonate patients on 30th day. Based on the cut-off prognostic value, it can be determined that the higher level of presepsin, CRP and PCT shows higher prognosis of death. This study obtained presepsin AUC is wider than AUC CRP and PCT. It suggests that presepsin is the best mortality prognostic marker because it has the most extensive AUC with the highest sensitivity and specificity compare with CRP and PCT.

CONCLUSION

Presepsin has the same ability as CRP and PCT to monitor therapy response. Presepsin is also the best and the earliest predictor of mortality prognosis of preterm neonates with LONS compared to CRP and PCT. Presepsin is the best predictor for 30 days mortality of preterm neonates with LONS because it has the most extensive AUC compare to CRP and PCT.

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