Relationship between Procalcitonin and C-Reactive Protein on Pelod Score in Pediatric Surgery Sepsis Patients at Dr Soetomo General Hospital Surabaya

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Background

The incidence of sepsis in the world was estimated around 1.8 million cases / year , whereas 25-38% of them requiring treatment in intensive care unit , with mortality of 1,400 cases / day . In Indonesia, child's mortality rate due to sepsis is still very high, around 50% -70%, and if accompanied with septic shock and multiple organs dysfunction, the rate is increased (80%) . One of the scoring system that can describe the severity degree of multiple organs dysfunction in children is PELOD (Pediatric Logistic Organ Dysfunction) score. But this assessment is time consuming, because many parameters that have to be calculated. One of the ways to shorten the time is by using diagnostic markers such as procalcitonin (PCT) and C-Reactive Protein (CRP).

Method: The research is a study of analytic observational to determine the relationship between PELOD score with a value of procalcitonin and CRP in patients of children with sepsis and determine *the cutoff point* of procalcitonin and CRP can be associated with incidence of septic shock. Research carried out for three months started in January 2020 until April 2020. Patients who meet the criteria for inclusion and exclusion requested approval. Laboratory blood tests were done from day 1-3 of the sepsis.

Results: In the study it was obtained the result that the age of majority is in the category of 5-10 years that as many as 11 patients (36.7%). In the category of the type of sex the most are men - men that 19 patients (63.3%) and patients mostly great suffering sepsis that 23 patients (76.7%). Analysis between CRP with PELOD Score by using the *chi-square test* , the obtained results that there is a relationship that significant between CRP with PELOD Sc ore on a day to 1-3 with a value of p value of each 0,001 ($p < 0,05)$; 0.002 ($p < 0.05)$; 0.004 ($p < 0.05)$, which means that there is significant relationship between CRP with PELOD Score . Analysis between PCT with PELOD Score by using the *chi-square test* , the obtained results that there is a relationship that significant between PCT with PELOD Score on a day to 1-3 with a value of p value respectively 0.005 ($p < 0,05)$; 0.001 ($p> 0.05)$; 0.016 ($p> 0.05)$, which means that there is a relationship which is significantly meaningful between PCT with PELOD Score. In research it obtained the value of the boundary between the groups of patients with sepsis with shock, sepsis is Pelod score value of 29 is the boundary between groups of sepsis and shock, sepsis, CRP value of 88 is the boundary between groups of sepsis and shock, sepsis, PCT value 9 is the boundary between groups of sepsis and shock sepsis .

Conclusion: There is a significant relationship between the PCT with PELOD Score and significant relationship between the CRP with PELOD Score.

Keywords: *PELOD, sepsis, CRP, procalcitonin*

Background

Sepsis is a clinical syndrome as a manifestation of an immunological inflammatory process due to the body's response to stimulation of microorganisms that triggers multi-organ dysfunction (MODS). The incidence of

sepsis in the world is estimated at 1.8 million cases / year, of which 25-38% require treatment at ICU and a mortality of 1,400 cases / day. In our country the child mortality rate due to sepsis is still high, 50% -70% and if there is septic shock and multi-organ dysfunction, mortality increases to 80%[1]

The severity of multi-organ dysfunction contributes to the increased mortality in septic patients. Prevention of status from septic children to septic shock is the key to reducing mortality in septic children. One of the scoring systems that can describe the degree of severity of multi-organ dysfunction syndrome in children is the PELOD (Pediatric Logistic Organ Dys-function) score. PELOD score has been validated in multicentre studies to measure multi-organ dysfunction syndrome in children[2,3,4]. The PELOD score assesses function in 6 body systems, namely respiration, cardiovascular, neurological, hepatic, renal, and hematological. Leteurtre et al. Found that mean PELOD scores were significantly higher in patients who died at a score of 20 or more than in patients living at scores below 20.[5] So that increasing the PELOD score can increase the incidence of mortality in pediatric patients who experience sepsis.

In addition to preventing worsening of multi-organ dysfunction, early diagnosis of sepsis is essential to control the mortality rate for sepsis patients[6]. Currently, blood culture as the main standard in the diagnosis of sepsis caused by bacteria has many deficiencies, including requiring a long examination time and sometimes not yet available in all hospitals[1]. In addition, a positive culture result can also be because contamination factors and negative blood culture have not been able to exclude sepsis. Because of this, various studies have been carried out to determine the faster and more accurate markers of sepsis. One of them uses diagnostic markers such as procalcitonin (PCT) and C-Reactive Protein (CRP) according to the recommendations of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) Consensus Conference in 1991.

Procalcitonin is a calcitonin prohormone that is produced in response to endotoxin or mediators released due to bacterial infection and has a strong correlation with the severity of bacterial infection. In normal circumstances, PCT levels in the blood <1 ng / ml. If there is inflammation by bacteria, the PCT level is always> 2 ng / ml while in viral infections the PCT level is <0.5 ng / ml. Several studies have stated that procalcitonin levels in sepsis are between 0.5-3.5 ng / ml, in severe sepsis 6.2-9.1 ng / ml and in septic shock 10.8-38.5 ng / ml[7]. The meta-analysis research also showed a significant relationship with increasing procalcitonin associated with increased mortality[8]

Meanwhile, CRP is an acute phase reactant that is synthesized in hepatocyte which will increase if there is an inflammatory process or bacterial infection. Under normal conditions CRP can be <8 mg / L and increases with infection. Research conducted by Wu et al. explained that an increase in CRP levels affects the survival rate and mortality rate with the average CRP value in patients who died of 88.5 ± 22.9 mg / L being greater than patients living 67.1 ± 17.5 mg / L[6]

However, it is currently unclear whether the increase in procalcitonin and CRP is only influenced by the presence of bacterial infection or is also influenced by multi-organ dysfunction caused by a systemic inflammatory response. Some literature focuses only on the association between sepsis and multi-organ dysfunction and sepsis severity score, but not many studies have looked at the association between procalcitonin levels and multi-organ dysfunction in sepsis. In addition, there are no studies looking for an association of increased procalcitonin and CRP with PELOD scores where PELOD is. Therefore, in this study we wanted to find out whether there is a relationship between increased procalcitonin and CRP associated with an increase in the degree of multi-organ dysfunction as assessed by the PELOD score in pediatric patients with sepsis.

Method

Research in the form of observational analytic research with *prospective cohort* design. Every patient who comes and is treated in the operating room Dr. Soetomo was determined whether it met the inclusion and exclusion criteria. Recorded patient data includes patient identity, physical examination, and laboratory examinations, then calculating the PELOD score. Blood laboratory tests are carried out regardless of the number of days treated. If someone with sepsis is found, a blood sample is taken within 24 hours.

Results

In this study, the results showed that the most age group was in the 5 - 10 years category, namely 11 patients (36.7%). Most of the sexes were male, namely 19 patients (63.3%) and most of the patients suffered from sepsis, namely 23 patients (76.7%).

Table 1. Characteristic of Research Subjects

Characteristics		n	Percentage
Age	0-1 year old	3	10.0
	1-5 years old	6	20.0
	6-12 years old	16	53.3
	>12 years old	5	16.7
Gender	Male	19	63.3
	Female	11	36.7
Diagnosis	NEC	2	6.7
	Acute Appendicitis	19	63.3
	Acute Appendicitis with Perforation	9	30.0
Sepsis Category	Sepsis	23	76.7
	Septic shock	7	23.3

In this study, it was found that most patients had CRP levels between 10 - 100 mg / l, which was 18 patients (60%). From these data, 11 patients (73.3%) had a pelod score> 100 mg / l. From these data, a correlation test between CRP and PELOD Score was carried out using chi-square test, it was found that there was no significant relationship between CRP and PELOD Score with p value = 0.001 ($p < 0.05$), which means that there is a significant relationship between CRP and PELOD Score. Significantly significant between CRP and PELOD Score. In this study, it was found that the odds ratio was 21.9, meaning that someone who had a high CRP had a 21.9 x higher risk of having a PELOD score> 20 than those who had a low CRP. An overview of the relationship between CRP and PELOD Score can be seen in Table 2.

Table 2. Relationship of CRP and PELOD Score in Day 1

CRP	PELOD		Total	P value	OR	CI
	Skor PELOD < 20	Skor PELOD > 20				
10 - 100 mg/l	14	4	18	0.001	21.9	95%
	93.3%	26.7%	60.0%			
> 100 mg/l	1	11	12			
	6.7%	73.3%	40.0%			
Total	15	15	30			
	100.0%	100.0%	100.0%			

In this study, the cutoff point with a CRP and PELOD score> 20 days I was 99, which is the lowest limit value for patients who have PELOD score> 20.

On the first day of this study, it was found that most patients had PCT levels between> 10 ng / ml, which was 15 patients (50%). From these data, 13 patients (86.7%) had a PELOD score of> 10 ng / ml. From these data, the relationship between PCT and PELOD Score was tested using chi-square test, it was found that there was a significant relationship between PCT and PELOD Score with p value = 0.005 (p <0.05) which means that there is a significant relationship. significant between PCT and PELOD Score. In this study, it was found that the odds ratio was 8.9, meaning that someone who has a high PCT has a risk of 8.9 x higher having a PELOD score> 20 than those who have a low PCT.

Table 3. Relationship of PCT and PELOD Score in Day 1

PCT	PELOD		Total	P Value	OR	CI
	Skor PELOD < 20	Skor PELOD > 20				
0,5 – 10 ng/ml	13	2	15	0.001	8.9	95%
	86.7%	13.3%	50.0%			
>10 ng/ml	2	13	15			
	13.3%	86.7%	50.0%			
Total	15	15	30			
	100.0%	100.0%	100.0%			

In this study, it was found that the threshold value with PCT and PELOD scores> 20 days I was 12, which is the lowest threshold value for patients having PELOD score> 20.

On day 2 of this study, it was found that most patients had CRP levels between 10 - 100 mg / l, namely 18 patients (60%). From these data, 11 patients (73.3%) had a PELOD score> 100 mg / l. From these data, the relationship between CRP and PELOD Score was tested on day 2 using chi-square test, it was found that there was a significant relationship between CRP and PELOD Score with p value = 0.002 (p <0.05) which means that there is a significant relationship between CRP and PELOD Score. In this study, it was found that the odds ratio was 14.7, meaning that someone who had a high CRP had a 14.7 x higher risk of having a Pelod score> 20 than those who had a low CRP. An overview of the relationship between CRP and PELOD Score can be seen in Table 4

Table 4. Relationship of CRP and PELOD Score in Day 2

CRP	PELOD		Total	*P value*	OR	CI
	Skor PELOD < 20	Skor PELOD > 20				
10 - 100 mg/l	14	4	18	0.002	14.7	95%
	93.3%	26.7%	60.0%			
> 100 mg/l	1	11	12			
	6.7%	73.3%	40.0%			
Total	15	15	30			
	100.0%	100.0%	100.0%			

In this study, it was found that the threshold value with a CRP and PELOD score> 20 days II was 97.5, which is the lowest limit value for patients having PELOD score> 20.

On day 2 of this study, it was found that most patients had PCT levels> 10 ng / ml, which was 15 patients (50%). From these data, 13 patients (86.7%) had a PELOD score of> 10 ng / ml. From these data, the relationship between PCT and PELOD Score was tested using chi-square test, it was found that there was a significant relationship between PCT and PELOD Score with p value = 0.001 (p <0.05) which means that there is a significant relationship. significant between PCT and PELOD Score. In this study, it was found that the odds ratio was 12.8, meaning that someone who had a high PCT had a 12.8 x higher risk of having a PELOD score> 20 than those who had low PCT. An overview of the relationship between PCT and PELOD Score can be seen in Table 5.

Table 5. Relationship of PCT and PELOD Score in Day 2

PCT	**PELOD**		**Total**	**P Value**	**OR**	**CI**
	Skor PELOD < 20	**Skor PELOD > 20**				
0,5 – 10 ng/ml	13	2	15	0.001	12.8	95%
	86.7%	13.3%	50.0%			
>10 ng/ml	2	13	15			
	13.3%	86.7%	50.0%			
Total	15	15	30			
	100.0%	100.0%	100.0%			

In this study, it was found that the threshold value with PCT and PELOD scores> 20 days II was 9.75, which is the lowest limit value for patients who have PELOD score> 20.

In the study on day 3, it was found that most patients had CRP levels between> 100 mg / l, which was 12 patients (40%). From these data, 9 patients (75%) had a PELOD score of> 20. From these data, a correlation test between CRP and PELOD Score was carried out using chi-square test, it was found that there was no significant relationship between CRP and PELOD Score with p value = 0.001 (p <0.05), which means that there is a significant relationship between CRP and PELOD Score. Significantly significant between CRP and PELOD Score. In this study, it was found that the odds ratio was 8, meaning that someone who had a high CRP had a risk of 8x higher having a PELOD score> 20 than those who had a low CRP. The description of the relationship between CRP and PELOD Score can be seen in Table 6.

Table 6. Relationship of CRP and PELOD Score in Day 3

CRP	PELOD		Total	*P value*	OR	CI
	Skor PELOD < 20	Skor PELOD > 20				
10 - 100 mg/l	15	3	18	0.001	8.0	95%
	83.3%	25.0%	60.0%			
> 100 mg/l	3	9	12			
	16.7%	75.0%	40.0%			
Total	18	12	30			
	100.0%	100.0%	100.0%			

In this study, it was found that the threshold value with a CRP and PELOD score> 20 days II was 81.5 which is the lowest limit value for patients who have PELOD score> 20.

In this study, it was found that most patients had PCT levels between 0.5 - 10 ng / ml, namely 21 patients (70%). From these data, those who have a PELOD score> 20 are at PCT levels> 10, namely 7 patients (58.3%). From these data, the relationship between PCT and PELOD Score was tested using chi-square test, it was found that there was a significant relationship between PCT and PELOD Score with p value = 0.006 (p <0.05), which means that there was a significant relationship significant between PCT and PELOD Score. In this study, it was found that the odds ratio was 3.2, meaning that someone who had a high PCT had a 3.2x higher risk of having a PELOD score> 20 than those who had a low PCT, as an illustration of the relationship between PCT and PELOD Score can be seen in Table 7.

Table 7. Relationship of PCT and PELOD Score in Day 3

PCT	PELOD		Total	P Value	OR	CI
	Skor PELOD < 20	Skor PELOD > 20				
0,5 – 10 ng/ml	16	5	21	0.006	3.2	95%
	88.9%	41.7%	70.0%			
>10 ng/ml	2	7	9			
	11.1%	58.3%	30.0%			
Total	18	12	30			
	100.0%	100.0%	100.0%			

In this study, it was found that the threshold value with PCT and PELOD scores> 20 days II was 9, which is the lowest limit value for patients having PELOD score> 20.

Discussion

Sepsis remains a major cause of morbidity and mortality in children. The highest incidence in infants. Sepsis is associated with extensive use of health care resources. Sepsis is the leading cause of death from infection, especially if it is not recognized and treated promptly. Both PCT and CRP are accepted markers of sepsis. The use of CRP measures may have a decisive effect on the health and progress of clinical cases, as it helps avoid misinterpretation and inappropriate intervention, such as in sepsis. In this study, it was found that most of the patients had CRP levels between 10 - 100 mg / l and the group had CRP levels> 100 and the results of the relationship test showed that there was a significant relationship between CRP and PELOD Score on 1st, 2nd, and 3rd day with p1 value = 0.001, p2 value = 0.002, p3 value = 0.001 (p <0.05) which means that there is a significant relationship between CRP and PELOD Score. The results of this study are in line with the research of Dewi et al.[9] This study shows a significant correlation between CRP and PELOD scores.

The PCT rate is highly correlated with the severity score regularly used in the intensive care unit, therefore, it can be used to determine the severity of the sepsis process. In this study, it was found that most of the patients had PCT levels between 0.5 - 10 ng / ml, namely 50%. From these data, those who have a PELOD score> 20 are at PCT levels> 10, which is 50%. From these data, the results show that there is a significant relationship between PCT and PELOD Score with p1 value = 0.001, p2 value = 0.001, p3 value = 0.006 (p <0.05), which means that there is a significant relationship between PCT and PELOD Score. . The results of this study are in line with the research of Dewi et al.[9] shows that in the septic shock group, there is a significant correlation between PCT and PELOD scores.

This study took 3 times a sample of patients with the aim of observing the body's response to therapy that has been given to patients whose main therapy research is surgery. From the observation of procalcitonin and CRP levels, the first test was obtained, namely before PCT surgery had a more significant relationship with PELOD score, in the first 24 hours, the CRP value had a more meaningful relationship with PELOD score, and at the third 24 hours it was obtained. CRP has a significant relationship with PELOD score. This is in line with the theory that procalcitonin is a sensitive biomarker of the inflammatory response and will increase in the early phase of infection. Bacterial polysaccharide cytokines

will react to trigger an immune response, in which procalcitonin is produced by thyroid cells and will increase rapidly in 2 to 6 hours. Meanwhile, CRP will cause a slower response than procalcitonin in the early phase. This is in line with the theory that CRP is useful in seeing the body's response to given therapy and its function as a marker for the diagnosis of sepsis is no better than procalcitonin. This is because the synthesis of CRP in the liver takes 24 to 48 hours from the start of the infection process. Thus, in early diagnosis of sepsis, procalcitonin has an advantage over CRP. Meanwhile, in the treatment process, to assess the body's response to our therapy, the value of CRP has an advantage over procalcitonin.

In the study also obtained the limit value of patients with PELOD value> 20, which means that they have a mortality risk of ≥ 50%, namely the procalcitonin value at the 9-12 level and the cCRP value at the 81.5-99 level. In my research, I took a range value based on the limit value of the first, second, and third sampling. This limit value will determine the probability of death for the patient.

In this study, it was also found that at the initial examination before surgery patients, patients with a procalcitonin value ≥10 would have a risk of death> 50% as much as 8.9 times compared to a procalcitonin value <10. While in the first 24 hours after surgery, patients with a CRP value ≥ 100 will have a risk of death> 50% greater 14.7x than a CRP value <100 and in the first 48 hours after surgery patients who have a CRP value ≥100 will have a 50% risk of death 8x greater than CRP value <100.

It has been observed that serum PCT and serum CRP levels increase the severity of sepsis and organ dysfunction which can also be used to identify patients at high risk for adverse outcomes. Biomarkers have proved a suitable method for predicting clinical outcomes in septic patients. PCT and CRP levels are generally measured in septic patients. PCT and CRP levels are associated with the severity of organ dysfunction, but the concentrations are still higher than during infection. This study shows a PCT value that correlates with CRP which can help us determine whether a patient has a septic process, determine the severity of the disease and see the therapeutic response we give to these patients. PCT and CRP determination could be the best tool for determining septic activity and prognosis rather than the parameters currently used. Persistently high plasma PCT concentrations, as well as decreased PCT within 24 hours, are associated with a significant increase in mortality in patients with severe sepsis and septic shock. The PELOD scoring system can be used to determine the likelihood of death of a patient in a pediatric intensive care unit.

Conclusion

There is a significant relationship between the relationship between PCT and CRP with PELOD Score

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