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ORIGINAL PAPERS

Relationship Between CRP, Procalcitonin, I/T Ratio and The Incidence of Sepsis in Children

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Abstract

Background: Sepsis is body immune response due to infection. Sepsis is a medical emergency condition with high risk of mortality. WHO in 2018 stated that every year there were 2.9 million cases of death due to sepsis. Several markers can be used to support evidence of sepsis in children, such as C-Reactive Protein (CRP), Procalcitonin, and IT ratio. This study will assess 3 markers namely C-Reactive Protein, procalcitonin, and IT ratio that have not found in previous studies.

Aim: To analyse association between inflammatory parameters and the incidence of sepsis in children. Methods: This study is an observational analytic study with a cross-sectional approach that analyses the medical records of paediatric patients in the PICU of RSUP Dr. Kariadi, Semarang from January 2019 – August 2022. The data used are secondary data taken from medical records and then analysed descriptively for patient characteristics. The variables of this study were then analysed bivariate using the chi-square or fisher test then analysed multivariate by logistic regression analysis.

Result: Correlation between C-Reactive Protein levels, Procalcitonin, and IT ratio with the incidence of sepsis in children $p<0.001$ and nutritional status with incidence of sepsis in children p=0,011. The results of multivariate logistic regression analysis showed that the dominant significant variable was C-Reactive Protein with an OR value of 212.331 and $p<0.001$.

Conclusion: There is a significant association between inflammatory parameters (CRP, procalcitonin, and IT ratio) with the incidence of sepsis in children. C-Recative Protein is most dominant parameter for sepsis detection in children.

Keywords: Sepsis, CRP, Procalcitonin, IT Ratio, Child

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INTRODUCTION

WHO (World Health Organization) in 2010 stated that in developed countries, sepsis is the most common cause of death in intensive care units (ICU) and its incidence continues to increase from time to time. There are several conditions that cause the incidence of sepsis to frequently increase, such as malnutrition, poor hygiene and infection by germs.[1] WHO (World Health Organization) in 2018 show that every year there are approximately 2.9 million cases of death every year due to sepsis. Based on these figures, 44% of cases occur in children under 5 years.[2]

Sepsis is a state of the body immunological response to infection. Sepsis categorized as medical emergency because it can experience organ dysfunction which can lead to death. Organ dysfunction can be estimated using the Paediatric Logistic Organ Dysfunction score (PELOD-2), a person is suspected of having sepsis if they get PELOD-2 score ≥11 (if treated in a type A hospital) or ≥7 (if treated in a type B or C hospital).[3]

Sepsis can be diagnosed using anamnesis, the appearance of clinical symptoms, the presence of precipitating factors, and evidence from microbiological examination results indicating the pathogen causing the infection.[4] As supporting evidence of infection, there are several markers that can be used, one of which is procalcitonin which is a marker of specific severe bacterial infection and can differentiate sepsis from Systemic Inflammatory Response Syndrome (SIRS). The sensitivity of procalcitonin in assessing sepsis is up to 85% and the specificity is up to 91%.

Hematological changes such as the number of white blood cells and their components such as neutrophils and lymphocytes also occur in response to sepsis. For this reason, another parameter can be used to help diagnose infections that can lead to sepsis, namely the Immature to Total Neutrophil Ratio (I/T Ratio). The sensitivity of the I/T Ratio ranges from 60-90%.[5]

Apart from Procalcitonin (PCT) and I/T Ratio, there are other markers that become sensitive markers when someone has an infection, namely C-Reactive Protein (CRP). CRP is a widely observed as indicator of acute inflammation and also indicated as the basic, early measure for prognosis during intensive care unit (ICU) hospitalizations for septic cases [6].

During an infection or acute inflammation, CRP levels in the blood increase and its concentration can be measured, this increase can be seen 2 hours after infection and reaches a peak value at 48 hours.[7] Many indicators that can be assessed and the interrelatedness of the indicators certainly make these various markers important to know to determine the occurrence of infection in children who may develop sepsis.

Several previous studies have shown a significant correlation between CRP and prolactin on the incidence of sepsis in children. Wu *et al*, 2017 show that Combination of High-Sensitivity C-Reactive Protein, Procalcitonin and Pancreatic Stone serum is a sign promising and useful as clinical tool for classification risk of children with sepsis.[9] Previous study in Indonesia also stated that sepsis in children commonly find in male than female.[10] Among all of those studies, there is no study that talk about correlation between I/T ratio and sepsis. Most of them are analyse correlation between Neutrophile and Lymphocyte Ratio (NLR) and sepsis.

This study is different from previous studies because this study will assess 3 signs, namely CRP, procalcitonin, and I/T ratio with the incidence of sepsis in children where researchers have not found previous research that discusses and compares these three indicators simultaneously. The uniqueness of this study also lies in the use of National Medical Services (PNPK) criteria to determine the incidence of sepsis in patients.

METHOD

This research is an analytic observational study with a cross sectional approach. The selected sample is paediatric patients who are treated in the PICU of RSUP Dr. Kariadi Semarang in 2019-August 2022 with inclusion criteria for male and female gender, aged > 1 month -18 years, have medical records for examination of C-Reactive Protein (CRP), procalcitonin and I/T Ratio. Exclusion criteria of this study were patients with malignancy and patients with autoimmune. The independent variables in this study were CRP levels, procalcitonin, and I/T ratio. The dependent variable in this study was the incidence of sepsis in children. The confounding variable in this study was the nutritional status of children.

Collected data in this study will be processed using the Statistical Product and Service Solutions (SPSS) application version 25. First, each independent variable and the dependent variable are tested bivariately using the chi-square test. If the requirements for the chi-

square test are not met, namely having an expectation value of ≤5, the test used is Fisher's test. The confounding variable for the dependent variable was also tested bivariately. After that, if the variable tested bivariately has a p value <0.25, then the variable is entered into the multivariate analysis. The type of multivariate analysis used is logistic regression because the dependent variable in this study is a categorical variable.

This research was carried out after obtaining ethical clearance from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University with EC number No.188/EC/KEPK/FK-UNDIP/VI/2022 and research permits at RSUP Dr. Kariadi Semarang with the number DP.02.01/I.II/4952/2022.

RESULT

Total respondent in this study was 126 patients from RSUP Dr. Kariadi Semarang. Respondent data who met the inclusion and exclusion criteria was collected from medical records in Paediatric Intensive Care Unit (PICU).

Results of bivariate analysis of the relationship between CRP levels and the incidence of sepsis in children used the chi-square test and no Fisher's test was performed because there was no expected value of ≤5. This test shows that there is a significant relationship between CRP levels and the incidence of sepsis in children. This can be seen from the p value of <0.001 (<0.05) obtained from the SPSS processing output.

Bivariate analysis of the relationship between procalcitonin levels and the incidence of sepsis in children were carried out using the Fisher's test because it did not meet the requirements of the chi-square test, then based on this test the results obtained were a p value of <0.001 (<0.05) which was obtained from the SPSS processing output. The Fisher test did show significant results, but because in the procalcitonin variable test with the incidence of sepsis there was one cell that had a value of 0 so the results from the procalcitonin analysis could not be included in the logistic regression multivariate analysis because it did not meet the requirements of the chi-square test or fisher.

The results of bivariate analysis of the relationship between I/T ratio and the incidence of sepsis in children used the chi-square test and no Fisher's test was performed because there was no expected value of ≤5. This test shows that there is a significant relationship between I/T ratio and the incidence of sepsis in children. This can be seen from the p value of <0.001 (<0.05) obtained from the SPSS processing output (Table.1).

Relationship between nutritional status and the incidence of sepsis in children using the chi-square test showed that there was a significant relationship between nutritional status and the incidence of sepsis in children. This can be seen from the p value of 0.011 (<0.05) obtained from the SPSS processing output (Table.1).

Table 1. Results of Analysis of CRP Levels with Sepsis Incidence in Children

Sepsis Incidence in Children						
		Sepsis				
		Yes		No		P
		n	%	n	%	
CRP	≥2,05mg/L	42	82.4%	9	17.6%	
	<2,05mg/L	1	1.3%	74	98.7%	< 0.001
	Total	43	34.1%	83	65.9%	
		Sepsis				
		Yes		No		P
		n	%	n	%	
PCT	≥0.5 ng/mL	43	48.3%	46	51.7%	
	<0.5 ng/mL	0	0%	37	100%	< 0.001
	Total	43	34.1%	83	65.9%	
		Sepsis				
		Yes		No		P
		n	%	n	%	
IT Ratio	≥0.2	21	91.3%	2	8.7%	
	<0.2	22	21.4%	81	78.6%	< 0.001
	Total	43	34.1%	83	65.9%	
		Sepsis				
		Yes		No		P
		n	%	n	%	
Status Gizi	Malnutrition	13	50%	13	50%	
	Underweight	11	37.9%	18	62.1%	
	Normal	7	15.2%	39	84.8%	0.011
	Overweight	5	41.7%	7	58.3%	
	Obesity	7	53.8%	6	46.2%	
	Total	43	34.1%	83	65.9%	

Multivariate logistic regression test showed that the CRP level variable showed significant results with a P value <0.05 and was said to be a dominant factor influencing the incidence of sepsis in children with an exp(B) value or Odds Ratio (OR) = 212.331 which means that children with CRP levels ≥2.05 mg/L had a 212 times greater risk compared to children who had CRP levels <2.05 mg/L. Another variable, namely the IT ratio, showed insignificant results with a p value of more than 0.05, namely 0.054, and the nutritional status variable also showed insignificant results, with a p value of 1.065, so it can be concluded that the factor that greatly influenced the incidence of sepsis in children in this study was CRP (Table.2).

Table 2. Logistic Regression Test Results for Sepsis Incidence

Variable	p	OR	95% CI
Nutrition Status	0.803	1.065	0.649 – 1.749
CRP	0.000	212.331	25.444 – 1771.909
I/T Ratio	0.054	7.250	0.964 – 54.495

DISCUSSION

This research was conducted by recording and processing data from 126 data medical records of paediatric patients that fulfilled inclusion criteria in the PICU Dr. Kariadi Semarang from January 2019 to August 2022. This research focuses on discussing relationship between levels of C-Reactive Protein, procalcitonin and I/T ratio with sepsis in children. Sepsis can be interpreted as a setback event or life-threatening organ failure caused by dysregulation host response to infection.[10]

This study shows that of the 126 children in PICU, 43 children (34.1%) experienced sepsis with an average age of the child suffering from sepsis is 60 months and the average age of children who do not suffer sepsis is 44 months. Determination of the incidence of sepsis in this study using criteria Pediatric Logistic Organ Dysfunction (PELOD-2) with a minimum value of sepsis in type A hospital is ≥11 and in type B hospital is ≥7.6 RSUP Dr. Kariadi Semarang is a type A hospital so the data is classified as sepsis must have a minimum score equal to 11. The mean value PELOD-2 in 43 sepsis patients was 12.37, whereas in 83 patients without sepsis had an average value PELOD-2 was 2.81.

Correlation between CRP levels and sepsis in children

One of the main discussions of this research is to prove relationship between increased levels of C-Reactive Protein with increased incidence of sepsis in children in the PICU Dr. Kariadi Semarang where the incidence of sepsis is said occurs when the patient has a PELOD-2 value that is ≥11. C-Reactive Protein (CRP) levels in this study the authors divided it into categorical data with a cut-off of 2.05 taken from previous research CRP levels in this study were divided into categorical data with a cut-off of 2.05 which was taken from previous research.[11] The results of this study showed that of the 126 samples used, there were 51 data samples that had CRP values ≥2.05 mg/L of which 42 children (82.4%) had sepsis and 9 children (17.6%) did not suffer from sepsis. There were 75 children with a CRP <2.05 mg/L, with only 1 child (1.3%) suffering from sepsis and 74 children (98.7%) not suffering from sepsis.

The chi-square test for CRP levels on the incidence of sepsis in this child yielded a significant value, namely p <0.001. Regression test result show that OR=212,331 which means that children with CRP levels ≥2.05 mg/L have a risk of 212,331 times greater than children with CRP levels <2.05 mg/L and have confidence interval values between 25.4 – 1771.9.

The results of these data are in accordance with research by Lubis *et al* which explained that CRP is a biological marker that is sensitive to inflammatory responses and sepsis is a disease that is triggered by an infection and then causes an inflammatory reaction that leads to tissue damage.[1,11]

Correlation between Procalcitonin Levels and Sepsis in Children

This study used a cut-off point for procalcitonin levels of 0.5 ng/mL which is significant if a patient has a procalcitonin level ≥0.5 ng/mL then there is a risk of sepsis and vice versa if procalcitonin levels are seen <0.5 ng/mL then it does not lead to suspicion of sepsis. The results of the Fisher test for the relationship between procalcitonin levels and the incidence of sepsis in 126 samples showed that 43 children (48.3%) had sepsis according to PELOD-2 criteria and 46 children (51.7%) did not have sepsis, while 37 children (100%) had no sepsis in children who had procalcitonin levels below the cut-off. A value of 0 in the group of children with procalcitonin levels <0.5 ng/mL who suffer from sepsis makes this variable ineligible for Fisher's test so

that the authors cannot enter the results of these data into the multivariate test even though the bivariate test showed significant results, namely p <0.001.

Previous research revealed by Iankova *et al* that procalcitonin can be an indicator for initial indicator sepsis. Procalcitocin formation triggered by endotoxin from bacteria that be the cause of inflammation.[12,13] Procalcitonin was said by Vijayan *et al* to be very useful in marking a sepsis event. Microbes and their antigens activate various mediator anti-inflammatory in the septic body and stimulates immunological response. These anti-inflammatory mediators enter the blood circulation in various forms products that can be measured as indicators of inflammation. In particular, procalcitonin the increase can occur during a bacterial infection one of them at the event sepsis. It is assumed that the cytokines released during seossus and Bacterial lipopolysaccharide can affect liver and blood mononuclear cells peripheral to produce procalcitonin Procalcitonin is also said to be a good indicator of sepsis alone or combined with other examinations.[14] However, based on data and results of data processing obtained by the author, preferably procalcitonin not be the only indicator used to suspect sepsis and the results still have to be supported by other biological markers.

This is in accordance with the statement by Vijayan et al which is very useful in marking an event of sepsis. Microbes and their antigens activate various anti-inflammatory mediators in the septic body and stimulate the body's immunological response.[14]

Relationship of I/T Ratio with Sepsis Incidence in Children

Sepsis is one of the causes of mortality in children, therefore proper diagnosis is needed so that it can be resolved optimally. One of an indicator that can be seen in paediatric sepsis, especially neonates, is the I/T ratio. Immature to Total Neutrophil Ratio (I/T Ratio) is the measurement result of immature neutrophils are rod neutrophils divided by total rod and segment neutrophils. These immature neutrophils include blast cells, promyelocytes, and deep myelocytes one hundred manual neutrophil counts in blood smears.[15]

The cellular component of the fundamental body system is neutrophil. Especially in infants, the number of neutrophils can fluctuate. White blood cell count increased due to infection caused by the release of neutrophils into the blood flow. The released neutrophils are in the form of various types, both of which are immature and ripe. The time of infection and the incidence of sepsis is common time when such immature neutrophils are found inside blood so that the increase can be an indicator of the incidence of sepsis

According to Saboohi *et al*, cut off point I/T ratio that can be used as a reference for suspicion of sepsis is 0.2.[16] Result from this study showed that 23 children (18.3%) had grades I/T ratio ≥ 0.2 and 103 children (81.7%) had I/T ratio < 0.2. Distribution of this number is from 23 children, 21 children (91.3%) suffered from sepsis and 2 children (8.7%) did not suffer from sepsis. Children with an I/T ratio <0.2 are known as many as 22 children (21.4%) suffered from sepsis and the majority, namely 81 children (78.6%) did not suffer from sepsis.

The distribution of these characteristics after statistically tested obtained the results of (p<0.001) which means significant. Logistic regression analysis showed no significant correlation between I/T Ratio and Sepsis (p=0.054).

IT ratio has no dominant effect on this study even though the bivariate test has significant results.The significant results in the bivariate test are in line with the research by Saboohi *et al* that immature neutrophils can enter the blood circulation when the body is had an infection so that when the immature neutrophils were measured levels increase and cause the value of the I/T ratio also increases. I/T ratio too considered to have a fairly sensitive effect on sepsis with numbers sensitivity of 60-90%, but in diagnosing sepsis the I/T ratio is also a must assisted with clinical signs to establish a definite diagnosis

Relationship of Nutritional Status with Sepsis Incidence in Children

Nutritional status is one of the criteria that is often used to measure health status of children. Food and nutrition becoming one of the important factors that can affect immune system.[17] Based on previous studies, nutritional status was observed can be one of the factors that also influence the incidence of sepsis in child. Sepsis is a disease that is triggered by infection and Poor nutritional status can make the body more susceptible to infection due to immune system decline.[18]

Nutritional status in this study is not an independent variable but as confounding variable because it is suspected to have an effect on the incidence of sepsis in children. Nutritional status of children in the PICU Dr. Kariadi Semarang who entered into the sample divided into 5 categories namely malnutrition, undernutrition, good nutrition (normal), excess nutrition

(overweight) and obesity based on WHO anthro standard for infant and children. From 126 children who included in the study, after being tested by crosstab test the result was 26 children (20.6%) having malnutrition, 29 children (23%) in under nutrition category, 46 children (36.5%) with good nutrition or normal, 12 children (9.5%) are overweight and 13 children (10.3%) are obese. Nutritional status then also tested bivariately with the dependent variable, namely the incidence of sepsis then it is known that in 26 children with malnutrition, as many as 13 children (50%) had sepsis and the other 13 children (50%) did not have sepsis. Children with malnutrition namely 29 children, it was found that 11 children (37.9%) had sepsis and 18 children (62.1%) did not experience sepsis, other than that there were as many children with normal nutrition 7 children (15.2%) had sepsis and 39 children (84.8%) had no events sepsis as well as in children with more proven nutrition as many as 5 children (41.7%) sepsis and the remaining 7 children (58.3%) did not experience sepsis. Finally, children with obesity seen as many as 7 children (53.8%) had sepsis and 6 children (46.2%) did not have sepsis.

Chi-square result showed significant p value with 0.011 so that it can be said that in this study nutritional status has influence on the incidence of sepsis in children. Multivariate analysis of the logistic regression resulted in the conclusion that the p value was 0.803 (> 0.05), which means no nutritional status significant effect on the logistic regression multivariate test. Nutritional status perhaps can affect sepsis because sepsis is an infectious disease so the status Poor nutrition can make the body more susceptible to infection. Discussion this is in accordance with the explanation from Suminar, *et al* who said that the problem on nutrition can be part of the thing that causes infection. Malnutrition can worsen the resistance or immunity of a child's body against various diseases and the main one is infectious disease.[19]

The relationship between malnutrition and the incidence of sepsis is also supported by research from Hung, *et al* who stated that a correlation was found where there was immune system dysfunction that occurs in both patients with sepsis and with malnutrition so that a hypothesis is formed that nutritional insufficiency and immune dysfunction could have a synergistic effect in septic patients[20].

Nutritional status in this study is not an independent variable but a confounding variable. The results of Nutritional Status show that of the 126 children included in the study sample, after being tested by crosstab a number of 26 children (20.6%) were badly nourished, 29 children (23%) were undernourished, 46 children (36.5%) were well nourished or normal, 12 children (9.5%) were over nourished and 13 children (10.3%) were obese.

Nutritional status was also tested bivariately with the dependent variable, namely the incidence of sepsis. It was found that out of 26 children with severe malnutrition, 13 children (50%) had sepsis and 13 other children (50%) did not have sepsis. In children with malnutrition, namely 29 children, it was found that 11 children (37.9%) had sepsis and 18 children (62.1%) did not experience sepsis. In addition, in children with normal nutrition, 7 children (15.2%) had sepsis and 39 children (84.8%) did not experience sepsis. Similarly, in children with over nutrition, 5 children (41.7%) had sepsis and the remaining 7 children (58.3%) did not experience sepsis. children with obesity seen as many as 7 children (53.8%) had sepsis and 6 children (46.2%) did not have sepsis.

The results of the recap and processing of the data were then tested using the chi-square test and yielded a significant p-value of 0.011 (significant p <0.05) so that it can be said that in this study nutritional status had an influence on the incidence of sepsis in children. Malnutrition can worsen a child's resistance or immunity to various diseases and the main one is infectious disease.[21] The relationship between malnutrition and sepsis is also supported by research from Hung, *et al* which states that there is a correlation where there is immune system dysfunction that occurs in both patients with sepsis and patients with malnutrition so that a hypothesis is formed that nutritional insufficiency and immune dysfunction can have a synergistic effect on septic patients.

CONCLUSION

This study showed that there is a significant relationship between increased CRP, procalcitonin, I/T ratio and nutritional status with increased incidence of sepsis in children.

SUGGESTION

This study produced data on nutritional status which has a significant effect on the incidence of sepsis in children because there is a correlation between poor

nutritional status and immune system dysfunction that occurs in septic patients so that in subsequent studies nutritional status is included as an independent variable not as a confounder

Children who have an infection should have a complete CRP, procalcitonin and I/T ratio examination because it is hoped that this will make it easier to find out whether the child is at risk of experiencing sepsis or not

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