Diagnostic Value of Mid Regional Proadrenomedullin as a Sepsis Biomarker in Pediatric Patients with Cancer-Related Chemotherapy

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Diagnostic Value of Mid Regional Proadrenomedullin as a Sepsis Biomarker in Pediatric Patients with Cancer-Related Chemotherapy

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Abstract

The aim of this study was to analyze the diagnostic value of mid regional proadrenomedullin as a sepsis biomarker in pediatric patients with cancer-related chemotherapy. This cross-sectional observational study was located in General Hospital Dr. Soetomo Surabaya from September until December 2020. International Pediatric Sepsis Consensus Conference criteria was used to define sepsis term on 2 study groups. Serum mid regional proadrenomedullin has been drawn from 60 subjects (41 in-ward pediatric patients) and measured on sandwich enzyme-linked immunosorbent assay from Elabscience® Human Mid Regional Proadrenomedullin. Humareader Single Plus® was used to measure the optical density. ROC analysis was used to find out cut off value, sensitivity, specificity, positive predictive value, negative predictive value, negative likelihood ratio, positive likelihood ratio, and accuracy, respectively. Statistics declared significant if $p<0.05$ (95% CI). Between groups, temperature and heart rate were statistically different ($p<0.001$; 95% CI). The median difference of mid regional proadrenomedullin between groups was significant ($p<0.05$; 95% CI). Cut off value 2,88 nmol/L, sensitivity 60.0%, specificity 56.67%, positive predictive value 58.06%, negative predictive value 58.62%, positive likelihood ratio 1.38, negative likelihood ratio 0.71 and diagnostic accuracy 59.33% was obtained while area under curve was 0.707, respectively. Sepsis in children with cancer –related chemotherapy has not well diagnosed by serum mid regional proadrenomedullin.

Keywords: *Cancer, chemotherapy, diagnostic, mid regional proadrenomedullin, pediatric, sepsis*

Introduction

Sepsis is a life-threatening organ dysfunction which caused by dysregulated body response upon an infection[1]. There are many causes of sepsis, which one is immunity cells decrement of quality either quantity. One of condition causing the decrement is cancer or malignancy. Pediatric patients on cancer-related chemotherapy have often been suffered from sepsis[2,3]. Blood culture, as a gold standard of sepsis diagnosis, has long turn-around time and low sensitivity[4]. Therefore, many criteria and diagnosis guidelines has been established for diagnosis of sepsis, which included clinical sign, symptoms, with addition of several laboratory parameters[5]. However, many biomarkers have been used by clinician to diagnose sepsis in their daily practice, e.g., C-reactive protein, procalcitonin and presepsin[6]. Their results were useful to decide giving empirical antibiotics[7].

Adrenomedullin is known as a vasoactive peptide that firstly found in pheochromocytoma

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tissue[8]. Previous research showed this molecule had several roles in sepsis pathophysiology. As a prognostic biomarker, it has shown high concordance with SOFA, pediatric SOFA and PELOD score[9,10]. Unfortunately, this peptide has short half-life, which only 22 minutes in circulation[8]. Therefore, researchers measured its equivalent molecule, mid regional proadrenomedullin, which both are originated from the same precursor, proadrenomedullin[11]. Mid regional proadrenomedullin had varied diagnostic value as a sepsis biomarker in childhood population. Angeletti *et al*. and Debiane *et al*. showed this peptide had remarkable diagnostic value as a sepsis biomarker on adult, otherwise Agnello *et al*., proved an unsignificant result[9,12,13]. Kesik *et al*. and Al Shuaibi *et al*. has proven the peptide showed high value as a pediatric sepsis biomarker of leukemia-related chemotherapy[14,15]. As we knew, there were no published study about mid regional proadrenomedullin as a sepsis biomarker in childhood with chemotherapy. The aim of this study was finding the diagnostic value of mid regional proadrenomedullin as sepsis biomarker in children with cancer-related chemotherapy.

Materials and Methods

This cross-sectional observational study enrolled 60 subjects from 41 patients into 2 groups: subjects with sign of sepsis as group 1, and subjects without sign of sepsis as group 2. We determined sepsis and non-sepsis according to IPSCC (International Pediatric Sepsis Consensus Conference) criteria[16]. All of the subjects were patients of the Pediatric Department of Soetomo General Hospital Surabaya, recruited from September 21 until December 30, 2020. The research population was 1 to 18-year-old children who have diagnosed with malignancy or cancer, who had informed consent been signed by their parents. The inclusion criteria for both groups were patients who had been diagnosed with cancer by hematology-oncology pediatrician based on bone marrow evaluation, radiology, or tissue biopsy. In addition, inclusion criteria for group 1 where subjects had at least 2 points on IPSCC criteria for SIRS, related to local infection they had suffered from. Subjects were willing to have their blood drawn for mid regional proadrenomedullin measurement and blood culture procedure. Exclusion criteria for both groups were impairment of renal function, diagnosed as pheochromocytoma, subjects transferred to the intensive care unit, and samples were hemolysis, lipemic or icteric. Subjects excluded if they declined or decided to drop out. Mid regional proadrenomedullin was measured at Immunology and Development Laboratory, Department of Clinical Pathology and Laboratory Medicine of Dr. Soetomo General Hospital Surabaya. A sandwich ELISA platform of human mid regional proadrenomedullin reagent kit from Elabscience® and ELISA reader Humareader® Single Plus were used. SPSS ver.17 was used to calculate sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy.

Results and Discussion

Moreover, this study enrolled patients which were distributed into 83 subjects from both groups. Because of hemolysis, renal impairment, pheochromocytoma, and later intensive care unit admission, there were remaining 60 subjects from 41 eligible patients, which were 30 samples in each group.

Table 1. General Characteristics.

Characteristics	Group		p value
	Group 1	Group 2	
Sex			0.605
Male	14 (46.7%)	17 (56.7%)	

***Cont...* Table 1. General Characteristics.**

Female	16 (53.3%)	13 (43.3%)	
Diagnosis			0.065
ALL	15 (50.0%)	22 (73.33%)	
AML	3 (10.0%)	0(0%)	
Lymphoma	8 (26.67%)	7 (23.33%)	
Neuroblastoma	1 (3.3%)	0 (0%)	
Retinoblastoma	3 (10%)	1 (3.3%)	
Age (year)	7 (1-15)	8 (1-16)	0.824
Axillar temperature (°C)	38.3 (38-39.1)	36.75 (36.2-37.4)	<0.001
Respiratory rate (per minute)	24.0 (18-28)	22 (18-28)	0.081
Heart rate (per minute)	100 (88-124)	92 (80-112)	<0.001
Leukocyte (per mm3)	3544.67-1365.61	4091.77±1029.74	0.085*
Immature granulocyte (%)	4 (3.0-8.0)	4 (3.0-6.0)	0.092
Neutrophil (per cmm)	667.83±266.08	776.03±179.57	0.102*
Body weight (kg)	22.83±10.07	24.63±8.13	0.449*
Body height (cm)	119.5 (18-156)	126 (75-160)	0.790
Sistolic pressure (mmHg)	90 (80-120)	100 (80-110)	0.070
Diastolic pressure (mmHg)	60 (50-80)	60 (50-70)	0.671

Note: data in table showed in median (min-max)

*data showed in mean±standard deviation.

In group 1, there were 7 subjects (23.33%) had suspect respiratory tract infection, 7 samples (23.33%) with gastrointestinal tract infection, 6 samples (20.00%) had urinary tract infection, 5 samples (16.67%) with skin infection, 3 samples (10.00%) had oral infection, and 2 samples (6.67%) had eye infection. There were 9 subjects (30%) had positive blood culture. Bacteria identification results were *Bacillus subtilis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella spp, Staphylococcus epidermidis, Staphylococcus haemolyticus* dan *Staphylococcus hominis*. There was no bacterial growth in Group 2.

The positivity of blood culture was 30%.

Table 2. Median Difference of Mid Regional Proadrenomedullin Level Between Groups.

Group	N	Median (min-max)	Unit	p Value
Group 1	0	0.194 (1.63-11.34)	nmol/L	0.006
Group 2	0	2.51 (1.01-5.09)	nmol/L	

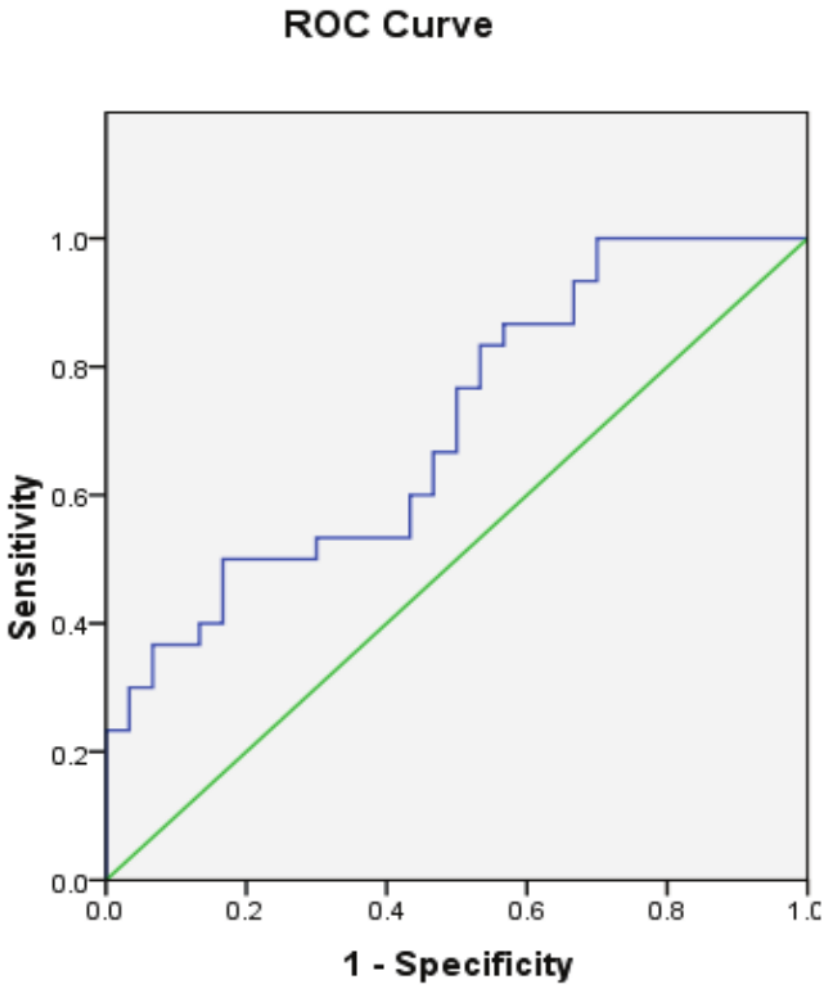

Figure 1. Receiver operating characteristics curve of this study.

ROC analysis showed area under curve 0.707 which p=0.006 (95% CI). It resulted some diagnostic parameters, they were cut off value, diagnostic sensitivity, diagnostic specificity, positive predictive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and diagnostic accuracy. Cut off value of present study was 2.88 nmol/L. This result may tally with Kesik *et al*. which had cut off value 2.90 nmol/L from their study[14]. Diagnostic sensitivity of this study was 60.00% (40.60-77.34%; 95%CI) and diagnostic specificity was 56.67% (37.43-74.54%; 95% CI). This result was similar with study by Ribalta *et al*., which results were 66.7% and 52.94%[17]. This study has PPV and NPV 58.06% (45.58-69.60%; 95% CI) and 58.62% (45.26-70.82%; 95% CI).

This study had LR+ 1.38 (0.84-2.29; 95% CI), that agreed with Ribalta *et al*. (2020) and 0.71 (0.41-1.21; 95% CI)[17]. The LR- of this study was 0.71 (0.41-1.21; 95% CI). Diagnostic accuracy of this study was 58.33% (44.88-70.93%; 95% CI). This result was similar to the study by Al-Shuaibi *et al*.[15]

Conclusion

In summary, this study has been conducted to analyze the diagnostic value of mid regional proadrenomedullin as a sepsis biomarker in pediatric patients with cancer-related chemotherapy. Although the AUC showed fair level at ROC, it is weak on sensitivity, specificity, PPV, NPV, LR+, LR- and diagnostic accuracy. This lacking value shows that sepsis in children with cancer-related chemotherapy is not well-diagnosed by serum mid regional proadrenomedullin level.

Conflict of Interest: The author declare that they have no conflict of interest.

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Ethical Approval: This study was approved by the Health Research Ethics Committee of Dr. Soetomo Regional General Hospital, Surabaya, Indonesia (approval number: 0067/KEPK/IX/2020).

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