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The prognostic value of soluble vascular cell adhesion molecules-1 (sVCAM-1) in children with septic shock.

Idham Jaya Ganda, Ikhsan Ali, St. Aizah Lawang, Dasril Daud

Departement of Pediatrics, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Abstract

Introduction: Septic shock is one of the major causes of mortality and morbidity in children all over the world. Septic shock is identified by endothelial dysfunction due to excessive stimulation of cytokines and chemical mediator. VCAM-1 is one of the adhesive molecules. VCAM-1 can predict the severity of the disease. This study aimed to identify sVCAM-1 as an outcome predictor (survival/non-survival) in children with sepsis.

Methods: This prospective cohort study was conducted in Pediatric Intensive Care Unit during February-June 2017. A total of 70 sepsis patients were included. The mean age in improved group was 6.38 years old and median was 4.6 years old, while in dying group was 4.87 and median 2.30 years old. Plasma specimens for sVCAM-1 were collected at admission, then the outcome of the patients were being followed. The diagnosis of septic shock is using the International Pediatric Sepsis Consensus 2005 criteria. Serum sVCAM-1 was measured using Enzyme Linked Immunosorbent Assay technique.

Results: The initial level of sVCAM-1 was significantly increased in both groups, but higher in the septic shock group. Cut off point ≥ 313 ng/ml for the sepsis patient becoming septic shock was obtained through the ROC, with sensitivity 100%, specificity 100%, positive predictive value 100%, negative predictive value 100% and Area under Curve (AUC) 1.

Conclusion: Initial level of sVCAM-1 can be used as an outcome predictor of sepsis patient in children and limit level ≥ 313 ng/ml is the most optimal cut off point as a prognostic value.

Keywords: sVCAM-1, Septic shock, Predictor.

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Introduction

Septic shock is a major health problem involving millions of people around the world. This disease is still a major cause of morbidity and mortality in children and neonates, along with multiple organ dysfunctions occurring in septic patients. Septic shock becom es a very complex clinical problem, occurring as a result of worsening sepsis. Proper treatment is needed to prevent septic shock and multiple organ dysfunctions [1].

The number of deaths due to septic shock depends on the initial site of infection, pathogenic bacteria, the presence of Multiorgan Dysfunction Syndrome (MODS) and host immune response. Bacterial sepsis that causes septic shock is a major cause of high rates of morbidity and mortality, especially in low birth weight infants [2]. In Indonesia, sepsis mortality is still extremely high at around 50-70%, if there is septic shock and multiple organ dysfunction of mortality becomes 80%. In RSCM FKUI Jakarta, the incidence of sepsis in patients treated in Pediatric Intensive Care Unit (PICU) from January 2009 to March 2010 was 19.3%, with approximately 54% mortality [3]. The incidence of sepsis at Pediatric Intensive Care Unit Makasar since January until December 2015 was 46% from 596 patients, patients with septic shock were 69% with mortality rates of 35%.

The host immune response, through the cellular and humoral immune system and the reticular endothelium system (RES), can prevent sepsis. This immune response produces an inflammatory cascade with highly toxic mediators including hormones, cytokines and enzymes. If this inflammatory cascade process is uncontrolled, SIRS occurs and may progress with cell, organ, and microcirculatory dysfunction. Tumor necrosis factor alpha (TNF-α) is a mediator of sepsis mainly in addition to some cytokines and other cells that are also involved. TNF-α is

thought to be an important mediator in the pathophysiology of septic shock [1,4].

The biological effect of TNF-α is to increase the expression of adhesion molecules on the vascular endothelial surface of intracellular adhesion molecules-1 (ICAM-1), vascular cell adhesion molecules-1 (VCAM-1), selectin and integrin ligand, also on the leukocyte surface of selectin ligand and integrin. The expression of such adhesion molecules will lead to endothelial activation and dysfunction characterized by increased permeability, vasodilation, and apoptosis. There is a relationship between high levels of VCAM-1 soluble and severe septic shock, as well as septic and dengue virus infection. The high levels of ICAM-1 and VCAM-1 in plasma are predictors of multiple organ failure (GOM) and death. Therefore, it is important to conduct research on adhesion molecules, one of which is VCAM-1, which is closely related to endothelial activation due to infection, to assess its role and its prognostic value in patients with septic shock [5].

Several studies have been conducted in the United States and Turkey. This study was a series of previous studies that sought the prognostic value of sVCAM-1 levels of sepsis in children with septic shock and non septic shock. Moreover, a study on intersection point of initial VCAM-1 levels among septic shock patients in children who died and improved has never been done before in South Sulawesi in particular and in Indonesia in general. So this study aims to determine the role of sVCAM-1 as a predictor to assess the outcome (death/improve) of children patients with septic shock.

Materials and Methods

This study was an observational studies which using prospective cohort method. The study variables consist of independent variable (sVCAM-1), dependent variable (outcome (improved or dead), intermediate variable (biological process happened in septic shock patient), random variable (gender), control variable (malnutrition, corticosteroid, trauma, burns, immune deficiency) and moderator variables (age and genetic).

The study was conducted in Pediatric Intensive Care Unit of DR. Wahidin sudirohusodo General Hospital, Makassar during February until June 2017. Blood sampling was analyzed at Laboratory Research Center of Hasanuddin University Hospital Makassar.

The population of the study was children with septic shock aged 1 month old to 18 years old who underwent hospitalization at Pediatric Intensive Care Unit (PICU) Makassar. The study sample was the entire possible population that met the inclusion and exclusion criteria.

Children aged 1 month-18 years old were diagnosed based on International Pediatric Sepsis Consensus 2005. The blood of the children who met the inclusion criteria were examined by using sVCAM-1. The age, sex, nutritional status, vital signs (blood pressure, pulse, breathing, temperature and consciousness), clinical symptoms and routine laboratory examination was also recorded. During the treatment, the subject was observed until the effect of sVCAM-1 was seen; either the patiens was improved or died. All the obtained data were recorded in the research data form and then grouped by destination and type and analysed by using univariate and bivariate analysis.

Univariate analysis was used to describe the characterization of the data, including sex, nutritional status, age, sVCAM-1 median value, and infection focus (respiratory, urinary tract, gastrointestinal, cardiovascular, etc). In bivariate analysis, Chi square test and Mann-Whitney test was chosen. Chi square test was used to compare prognostic factor variability (sex, nutritional status, age) and its outcome (dead/get better) in patients with septic shock, and Mann-Whitney test was used to compare sVCAM-1 median value on death group and improved group. ROC was made to set cut off point on diagnostic value of initial soluble serum sVCAM-1 and to further count sensitivity value, specificity, positive predictive value, and negative predictive value.

Results

Observational studies have been conducted with a prospective cohort approach to determine the role of sVCAM-1 as a predictor to assess the outcome (death/improve) of patients with septic shock in children. The study was conducted in Pediatric Care Unit Makassar which was implemented from February to 2017 until June 2017. Blood sampling was done at the Laboratory Research Center of Hasanuddin University Hospital Makassar.

During the study period, out of 70 patints with septic shock who met the inclusion criteria, 37 patients (52.8%) was died and 33 (47.2%) of was improved.

The relation between sex and the outcome of patients with septic shock showed that in the group of septic shock patient, the number of boys who died was 59.5% and 63.6%. In the septic shock group who improved, the number of girls 40.5% and 36.4%. Statistical analysis showed no significant difference in the distribution of sex between the two groups with p=0.720 (Table 1).

The relationship of nutritional status with outcome of death or improvement in septic shock patient showed that in group of septic shock patient who died, the number of well nourished status equal to 59.5% and under nourished equal to 40.5%. Patients with septic shock in improved

Table 1. *Relation of sex and septic shock patient outcome*

Sex	Septic Shock		Total
	Dying	Improving	
Male	22 (59.5%)	21 (63.6%)	43 (61.4%)
Female	15 (40.5%)	12 (36.4%)	27 (38.6%)
Total	37 (100%)	33 (100%)	70 (100%)

Chi-square X^2=0.121; df=1; p=0.720 (p>0.05)

group, the number of well nourished status was 54.5% and under nourished was 45.5%. Statistical analysis showed no significant difference in outcome to death or improved based on nutritional status with p=0.678 (Table 2).

The median age of patients with septic shock in the dying group was 2.3 years old with range 0.1-17.9 years old, while the median age in improved group was 4.6 years old with range 0.2-16.3 years old. Man age of dying group was 4.87 years old, while improving group was 6.38 years old. Mann Whitney test results showed that there was no significant difference between the two groups with p=0.153 (Table 3).

The mean value of baseline sVCAM-1 levels between the patients of sepsis and the resting confirmed sepsis showed that the initial sVCAM-1 level of septic shock patient had a median value of 428.14 ng/ml and a range of 318.55-882.38 ng/ml. While septic shock patients with improved result had a median value of 266.58 and a range of 97.94-312.46 ng/ml. Mann Whitney test results show that there is a very significant difference between the two groups with p=0.000 (p<0.001) (Table 4).

Table 2. *Relation of nutritional state with septic shock patient outcome*

Nutritional State	Septic Shock		Total
	Dying	Improving	
Good	22 (59.5%)	18 (54.5%)	40 (57.2%)
Less	15 (40.5%)	15 (45.5%)	30 (42.8%)
Total	37 (100%)	33 (100%)	70 (100%)

Chi square X^2=0.172; df=1; p=0.678 (p>0.05)

Table 3. *Mean age rate of septic shock patient in group that died and improved*

Age (year)	Septic Shock	
	Dying n=37	Improving n=33
Mean	4.87	6.38
Median	2.30	4.6
Standard of Deviation	5.25	5.34
Minimum-Maximum	0.10-17.90	0.20-16.30

Uji Mann Whitney p=0.153 (p>0.05)

Tabel 4*. Mean rate of early sVCAM-1 value in septic shock patient (improved and died)*

sVCAM-1 (ng/ml)	Septic Shock	
	Dying n=37	Improving n=33
Mean	446.24	257.06
Median	428.14	266.58
Standard of Deviation	121.95	48.58
Minimum-Maximum	318.55-882.38	97.94-312.46

Uji Mann Whitney p=0.000 (<0.001)

ROC values (Sensitivity, specificity, positive predictive value, negative predictive value & Area Under Curve (AUC) of each initial sVCAM-1 value indicate that the cutoff point ≥ 311 ng/ml has a sensitivity of 94.9%, specificity 100% A positive predictive value of 100%, a negative predictive value of 93.9%. At the cut point ≥ 312 ng/ml has a sensitivity value of 97.4%, 100% specificity, a positive predictive value of 100% and a negative predictive value of 93.9%. The initial cutoff sVCAM-1 ≥ 313 ng/ml to ≥ 318 ng/ml has the same value in terms of 100% sensitivity, 100% specificity, 100% positive prediction value, 100% negative predictive value. At the point of cutting ≥ 319 ng/ml has a sensitivity value of 100%, specificity 97.1%, positive predictive value 97.2% and 100% negative predictive value (Table 5).

To assess the best initial level of sVCAM-1 cutoff point in determining the outcome can be seen in the Receiver Operator Curve (Figure 1). There was significant relationship between sVCAM levels and clinical conditions (degree of awareness, leukocyte count and albumin levels (p 0.004 OR 4.75 (1.59-14.19), p 0.014 OR 2.32 (1.75-3.07), p 0.005 OR (1.52-11.71)) and no significant relationship between sVCAM levels and glucose levels (Table 6).

Discussion

Recently, based to studies by Watson and colleagues in the United States in children with severe sepsis (bacterial or fungal with at least one organ dysfunction) were reported >42,000 cases in 1995 with 10.3% mortality rates. Despite showing significant improvements in recent decades, severe sepsis is still the leading cause of death in children with >4,300 deaths each year (7% of all deaths in children) [6].

This study showed that inisial level of sVCAM-1 increased significantly in both groups of septic shock, but were higher in the deceased group. The cutting point ≥ 313 ng/ml until ≥ 318 ng/ml for patients with sepsis shock was declared through ROC, with 100% sensitivity, 100% specificity, 100% positive predictive value, 100% negative predictive value.

In this study, the relationship of sex with the outcome of patients with septic shock did not differ significantly with the value of p=0.720, which means sex is not a prognostic factor. Similar results were reported by Choudhary et al. [7] in a study conducted in India that there was no significant difference between patients with sepsis shock died and improved in children by sex with p=0.92. Ram Jat et al. [8], also reported the same result with p=0.464. Most researchers report women have better outcomes than males primarily on adult subjects due to sex hormone involvement.

Based on nutritional status, this study found no significant difference between patient with septic shock who died and who improved (p=678). Similarly, reported Delgado et al. [9], in Brazil also reported no significant difference between

Table 5. *ROC value (sensitivity, specificity, positive predictive value, negative predictive value, & area under curve (AUC)) from each early sVCAM-1 value*

sVCAM-1 (ng/ml)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Area Under Curve	P
≥ 311	94.9	100	100	93.9	0.970	0.00
≥ 312	97.4	100	100	93.9	0.985	0.00
≥ 313	100	100	100	100	1.000	0.00
≥ 314	100	100	100	100	1.000	0.00
≥ 315	100	100	100	100	1.000	0.00
≥ 316	100	100	100	100	1.000	0.00
≥ 317	100	100	100	100	1.000	0.00
≥ 318	100	100	100	100	1.000	0.00
≥ 319	100	97.1	97.2	100	0.959	0.00

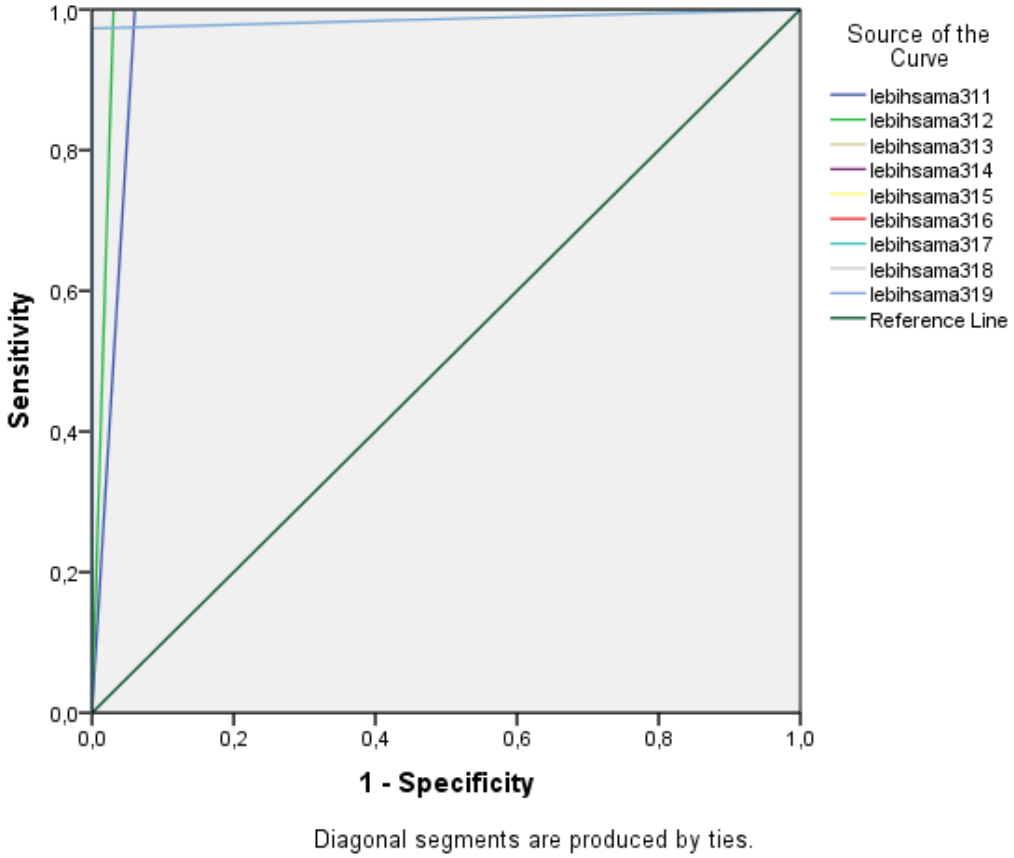

Figure 1. *ROC curve*

Table 6. *Relation of clinical condition and sVCAM*

Clinical Condition		sVCAM-1		P	OR (CI)
		≥ 313 ng/ml	<313 ng/ml		
GCS	8-Mar	19	6	0.004	4.75 (1.59-14.19)
	14-Sep	18	27	-	-
Lekosit	4000-10.000	0	5	0.014	2.32 (1.75-3.07)
	<4000 dan >10.000	37	28	-	-
Albumin	<3.5	28	14	0.005	4.22 (1.52-11.71)
	≥ 3.5	9	19	-	-
GDS	70-100	15	13	0.922	1.04 (0.40-2.73)
	<70 dan >100	22	20	-	-

the nutritional statuses of sepsis sufferers associated with mortality rate. Theoretically, the state of malnutrition causes changes in systemic function including reduced immune response, atrophy and increased permeability of the intestinal mucosal barrier that facilitates infection and translocation of germs. In this study, patients with malnutrition were not included.

Statistically, there were no significant differences in age between the two groups in patients with septic shock. It was similar to the research conducted by Ram Jat et al. [8] with p=0.586. Runtunuwu et al. [3] also reported that there was no significant difference between age and outcome of septic shock patient with p=0.387.

The focus of this study was respiratory infections, followed by central nervous system, gastrointestinal, urinary tract and cardiovascular infections. Possible infectious origins of sepsis were associated with the prevalence of childhood illness and national health statistics. According to Trihono [10], pneumonia is still the main cause of morbidity and mortality in infants. Every year more than 2 million children worldwide die from acute respiratory infections (ARI), especially pneumonia.

Choudhary et al. [7] reported that in India, the most common infections of children with septic shock were respiratory tract (32.4%), central nervous (16.9%), dengue (11.5%), gastrointestinal (4.7%) and urinary tract (1.4%). This is similar to a study conducted by Hofer et al. [11] in Germany, the top three infection focuses are respiratory infections, gastrointestinal tract infections and urinary tract infections.

The origin of the infection is also reported to play an important role in the outcome of septic shock. Septic shock sufferers from respiratory tract infections, gastrointestinal tract and central nervous system are reported to have higher mortality than urinary and soft-tissue infections. In this study, in patients with septic shock deaths found more respiratory infections (51.3%) with increased VCAM-1 levels compared with patients with improved sepsis.

In this study, the mean value of the initial sVCAM-1 level of septic shock in died group much higher than in improved group. Similar to previous study Shapiro et al. [4], in the United States, reported in addition there was an increase in sVCAM-1 levels in patients with septic shock compared with non-infectious control subjects with a $p<0.05$ score. Previous research has shown that generally VCAM-1 is expressed with low and undetectable values in healthy subjects. This study shows that baseline serum sVCAM-1 levels have increased since the onset of the disease. Pathogenic invasion of microorganisms and/or products will stimulate proinflammatory cytokines, in which case TNFα will stimulate the surface of endothelial cells to express VCAM-1. Leukocytes activate inflammatory mediators that bind to the VCAM-1 receptor on the surface of the endothelium and into the tissues to fight infection. Ongoing infections will lead to an imbalance between cytokines, in this case proinflammatory cytokines will continue to increase and along with these events the VCAM-1 adhesion molecule will also increase.

To evaluate sVCAM-1 levels increased or not, a point cut whose value far from normal values can be used to distinguish both groups (died and improved), so analysis is needed to determine the most optimal cut off point. Mann Whitney's results show that there is a very significant difference between the two groups with p=0.000. This occurs because at the early infection, leukocytes naturally with VCAM-1 have minimal role in leukocyte migration. The leukocyte cells entering the site of the lesion release the product and continue the process of inflammation [5].

VCAM-1 is an induced glycoprotein that is expressed during an inflammatory reaction. Upregulation on the surface of endothelial cells mediates leukocyte adhesion in the vascular endothelium. This process causes extravasation of leukocytes to the site of infection or injury. Therefore, VCAM-1 plays an important role in the development of organ injury in sepsis. Increased adhesion molecules have been found at various stages of the disease, especially infections and inflammation [12].

The limitation of this study is that serum sVCAM-1 test is not serialized until outcome due to serial examination can see the effect of therapy on the decrease of VCAM-1 level until outcome, while the strength of this research is prospective cohort design so that we can follow the effect of these prognostic factors simultaneously, as well as determining the initial cutoff point of sVCAM-1 as a prognostic factor using ROC and the study was conducted in the PICU Wahidin Sudirohusodo Hospital Makasssar which is the referral hospital of Eastern Indonesia so that the sample population could reflect Makassar city population in general.

Conclusion

The researchers concluded that the initial level of sVCAM-1 could be used as a prognostic factor in outcome (dying or improving) of patient with septic shock. The initial level of sVCAM-1 in patients with septic shock who died was higher than in patients who improved. The researchers suggest that further research involving other factors such as kinin and complemen systems which may also cause vasodilatation to be associated with septic shock outcome.

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Correspondence to:

Idham Jaya Ganda,
Departement of Pediatrics,
Faculty of Medicine,
Hasanuddin University,
Jl. Perintis Kemerdekaan Km. 11 Tamalanrea,
Makassar, 90245,
South Sulawesi,
Indonesia.
Tel: 62411-584461;
Fax: 62411-590629;
E-mail: hi_unhashospitalpediatrics@yahoo.com;
dhamjaya_spa@yahoo.com