Crit Care Shock (2019) 22:243-248

Eosinopenia as an indicator for organ dysfunction in sepsis patients

Syafri Kamsul Arif

Abstract

Sepsis is one of the most common causes of morbidity and mortality in intensive care unit (ICU).

***Objective*: To determine the possibility of eosinophil as indicator for organ dysfunctions in sepsis patients and septic shock patients in ICU.**

***Design*: Prospective.**

***Setting*: Intensive care unit (ICU) Wahidin Sudirohusodo Hospital, Makassar.**

***Participants*: Adult sepsis patients admitted to ICU from October to December 2018.**

***Measurement*: Eosinophils count and Sequential Organ Failure Assessment (SOFA) scores were assessed within 24 hours and after 72 hours after patients admitted in ICU. The patients were categorized into non- and organ dysfunction groups based on SOFA scores after 72 hours. Outcomes of the patients then evaluated at day 7.**

***Results*: Thirty four sepsis patients participated in the study. The mean of SOFA scores between non- and organ dysfunction groups were not different within 24 hours after admission but then showed a difference after 72 hours ($p=0.558$ and $p<0.001$, respectively). In contrast with non-organ dysfunction patients, after 72 hours the eosinophil count in organ dysfunction group decreased (from 0.51 to 0.15 cells/µl). There was a negative correlation between eosinophil count and SOFA scores at 72 hours ($p=0.043$; rho: -0.350). In discriminating non-organ dysfunction and organ dysfunction groups, the area under the receiver operating characteristic curve was 0.714. Eosinophils at 0.5 cells/µl (eosinopenia) yielded a sensitivity of 92.8%, a specificity of 66.6%, a positive predictive value of 92.8%, and a negative predictive value of 66,6%.**

***Conclusion*: Eosinopenia levels might be used as an indicator for organ dysfunction in critically ill patients, including sepsis patients, in area where laboratory facility is limited.**

Key words: Eosinopenia, sepsis, organ dysfunction, Makassar.

Introduction

According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) 2016, sepsis is defined as a life-threatening organ dysfunction caused by dysregulation of the host body's response to infection. (1) During sepsis, microbial infection or necrotic tissue releases high level of harmful substances, resulting in the activation of systemic immune response and excessive activation of immune cells.

A recent report from Center for Disease Control (CDC) estimated that sepsis affects around 1.5 million individuals in the United States annually. (2) A cohort study involved 25,375 patients in the United Stated and Europe reported the raw hospital mortality rates were 41.1% and 28.3%, respectively. (3) There is no published data reported the incidence as well as mortality rate of sepsis from Indonesia. However, Dharmais Cancer Hospital, a referral center for cancer, reported that 18.5% of patients admitted to this hospital between 2011 and 2012 had sepsis. (4)

Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs. Patients can be suspected

From Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine of Hasanuddin University, Makassar, Indonesia (Syafri Kamsul Arif).

Address for correspondence:
Syafri Kamsul Arif
Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine of Hasanuddin University, Makassar, Indonesia.
99 Syarif Al Qadri Street, Makassar, South Sulawesi, Indonesia
Tel: +62-811-462-0123
Email: syafrikarif@yahoo.com

of having an infection if systolic blood pressure ≤100 mmHg or respiratory rate ≥22/min. Septic shock is a subset of sepsis in underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Allegations of septic shock can be established if patient with sepsis has a persistent hypotension that requires vasopressors to maintain MAP≥65 mmHg and has a serum lactate level >2 mmol/l or 18 mg/dl. (1) Septic shock, which includes circulatory and metabolic dysfunction, is associated with higher mortality risk. (5)

Since there is dysregulation of the host body's response to infection exists during sepsis, systemic harmful condition such as hypotension, disturbed perfusion of the microcirculation, and direct tissue-toxicity, an organ failure may occur unpredictably. The failure of two or more vital organ systems is termed multi-organ dysfunction syndrome (MODS) and resembles a very critical condition associated with high morbidity and mortality. Various parameters and scoring systems have been investigated to diagnose, to estimate prognosis, to assess, and to monitor improvements and worsening of sepsis patients. (5) One parameter that is widely used in intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure is Sequential Organ Failure Assessment score (SOFA score). The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. (7) In clinical practice, organ dysfunction can be seen from an increase of two or more SOFA scores, which are associated with hospital mortality. (1) Worth to note that SOFA score was designed not to predict outcomes but to explain a series of complications in critically ill patients. In addition, assessment of SOFA score requires several laboratory measurements that might not be always available in remote hospitals.

Eosinophils are a variety of white blood cells and one of the immune system components in innate immunity. In normal individuals, eosinophils make up about 1-3% of white blood cells. (8) Under homeostasis, eosinophils are distributed in the blood, lung, thymus, uterus, adipose tissues, mammary gland, spleen, and the lamina propria of the gastrointestinal tract. (9) Eosinophilic functions include among other, movement to inflamed areas, trapping substances, killing cells, anti-parasitic and bactericidal activity, participating in immediate allergic reactions, and modulating inflammatory responses. These eosinophilic actions can be either helpful or harmful. (10) A low level of eosinophil is not usually considered a medical problem and sometimes the level can be zero. However, there are some conditions that can cause a low count of eosinophil or eosinopenia, for instance drunkenness and overproduction of cortisol. (11)

Acute infection is marked by reduction of the number of circulating eosinophil (12) and was utilized as a useful diagnostic sign for acute infection. (13) Eosinopenia is also reported as part of the normal response to stress (14) and is assumed that eosinopenia of acute infection is a secondary response to stress caused by the infection. (15) A study performed at medical ICU of Rabat University Hospital, Morocco reported that eosinophil counts among sepsis patients was significantly lower compared to the ones who have systemic inflammatory response syndrome (SIRS) without infection. The study concluded that eosinopenia can be used as a diagnostic marker of sepsis in newly admitted critically ill patients and was better diagnostic marker than CRP. (16)

This study was aimed to investigate the possibility to use a simple blood routine test, the eosinophils, to determine organ dysfunction in sepsis patients admitted to ICU.

Materials and methods

This prospective study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar, Indonesia from October-December 2018. All adult patients (surgery and non-surgery) that admitted in intensive care unit were involved in the study. Dr. Wahidin Sudirohusodo Hospital is the top referral hospital in South Sulawesi which received 150-250 critically ill patients annually. The study protocol was approved by the hospital ethics committee. Informed consent was not demanded because this observational has no any deviation from routine medical protocol.

Blood and SOFA scores collections

Blood collection for routine blood tests, including eosinophil count and for blood cultures were collected by using microtubes containing ethylenediamine tetraacetic acid anticoagulant as soon as patient arrived in the ICU. The white blood cell and eosinophil cell counts were performed by the Coulter (Gen·S) hematology analyzer (Beckman Coulter, Fullerton, CA, USA). SOFA scores (7) were assessed within 24 hours after admission. After 72 hours, laboratory test and SOFA score were reassessed. The results of blood cultures came out on day 5-7, and based on these results the patients were selected as study participants to undergo statistical analyses. The SOFA scores after 72 hours then were used to categorized the patient into non- and organ dysfunction groups.

Statistical analysis

Comparison of SOFA scores and eosinophil at 24 hours and 72 hours were tested using unpaired t-test. The Pearson correlation coefficient (*r*) was calculated to describe the quantitative relationships between SOFA scores and eosinophil. The best cut-off value was chosen using Younden's index. Receiver operating characteristic curves and the respective areas under the curves were calculated for eosinophil. The sensitivity, specificity, and positive and negative predictive value with 95% confidence intervals (CIs) were calculated at the best cut off value. Statistical analyses were carried out using SPSS for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Thirty four sepsis patients whose ages were ranged from 29 to 62 (mean 49.52) were involved in the study. The SOFA scores between organ dysfunction and non-organ dysfunction groups within 24 hours after admission were not different (p=0.558, 95% CI=-4.44 - 2.44), but then showed significant difference at 72 hours (p<0.001, 95 CI=-11.671- -5.044) (**Figure 1**).

Concerning the comparison between the organ dysfunction and non-organ dysfunction groups, the mean of eosinophil count within 24 hours was not different (p=0.102 and 95% CI=-0.768 - 072). Interestingly, after 72 hours the mean of eosinophil count between yielded significance (p=0.001, 95%CI=0.285-0,934), the mean in non- and organ dysfunction patients were 0.16 and 1.76 µl, respectively. The results of receiver operating characteristic curve analysis showed that area under the curve (AUC) of eosinophil levels by 0.714 with intervals of 0.402-1.000 and 95% significance. Diagnostic examination with AUC value of 0.714 or 71.4%, means that if there are 100 patients in the study, then as many as 71 patients will give the correct conclusion in determining whether there is a disease or not in that population. In this case, there were 71 out of 100 patients who could be correctly concluded to be included in the criteria for organ dysfunction based on an examination of increasing SOFA scores (**Figure 2**).

The best eosinophil cut off point to predict organ dysfunction was 0.5 cells/µl (eosinopenia) with a sensitivity 92.8% and specificity 66.6%. The positive and negative predictive value for cop 0.5 mm^3 were 92.8% and 66.6%, respectively, and the accuracy was 88.2% (**Table 1**). The correlation between eosinophil count and organ dysfunction (**Table 2**), as measured by SOFA scores, showed a significant negative correlation (Rho -0.350 and p< 0.05).

At day 7, some patients survived and others died. Based on this classification, we calculated the change of eosinophil counts and SOFA scores at day 1 and day 3. We found that there was a significant difference in eosinophil count as well as SOFA scores alterations between patients who died and survived (**Table 3**).

Discussion

It has been proved that the Sequential Organ Failure Assessment (SOFA) score is a simple and objective score that allows for calculation of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic). A study done in 248 patients in emergency department reported that SOFA scores associate positively with in-hospital mortality. They concluded that SOFA scores provided valuable information if applied to patients with severe sepsis with signs of hypoperfusion. (17) Similarly, a retrospective study done in maternal with related obstetric cause who were admitted to the maternal ICU in India found that SOFA scores were significantly higher in mother who did not survive compared to the ones who survived. (18) Both studies informed us that high SOFA scores related to the worst patient condition.

In the hospital where laboratory facility is limited, detection of organ dysfunction rapidly and specifically in order to fulfil SOFA scores component is not always available. A simple indicator of organ dysfunction among patient with sepsis in the wards or the ICU is needed in order to determine the management and progress of sepsis patients.

In the study of sepsis patient we conducted in Makassar, we found that eosinophil count 72 hours after patient admitted the ICU were significantly lower in the group of patients who died compared to the survive ones. From the calculation, we found that a cut off point by 0.5 cells/µl could detect sepsis patients who had experienced organ dysfunction. We also found a negative correlation between eosinophils counts and SOFA scores in our study (rho -0.350 and p=0.043), means that the lower eosinophil counts, the higher indication of organ dysfunction. In addition, data analysis using independent t-test showed that there was a statistically significant difference (p=0.001) between changes in eosinophil counts in patients who died and survived, the higher the decrease in eosinophils count, the more likely the patients will not survive on the seventh day.

Conclusions and recommendations

Overall, we concluded that eosinophils have sufficient sensitivity, specificity, and accuracy to determine the occurrence of organ dysfunction in sepsis patients. Since eosinophil measurement can be performed in hospital with limited facility, this finding might be useful for physician to decide the best management for patient with sepsis.

Acknowledgment

First, I would like to thank Primadonna for her valuable contribution in this study including patient selection, samples collection, and data analysis. I also would like to thank Sitti Wahyuni for reading and making significant corrections in this manuscript. This study was funded by Hasanuddin University.

Table 1. Sensitivity, specificity, positive, and negative predictive values as well as accuracy of different cut of eosinophil's count value in determining the occurrence of organ dysfunction among sepsis patients in ICU Wahidin Sudirohusodo Hospital, Makassar

Variable	Cut off point	Sensitivity (%) a/(a+c)	Specificity (%) d/(b+d)	PPV (%) a/(a+b)	NPV (%) d/(c+d)	Accuracy (%) a+d/(a+b+c+d)
Eosinophils (cells/µl)	0.0	55.5	33.3	83.3	18.2	41.2
	0.3	78.5	66.6	91.6	40.0	76.5
	0.5	92.8	66.6	92.8	66.6	88.2
	1.0	100	33.3	87.5	100	88.2

Legend: PPV=positive predictive values; NPV=negative predictive values.

Table 2. Correlation between eosinophil count and SOFA score in sepsis patients 72 h after admission in ICU Wahidin Sudirohusodo Hospital, Makassar

Variable	SOFA score	
	r	p value
Eosinophil level	-0.350	0.043

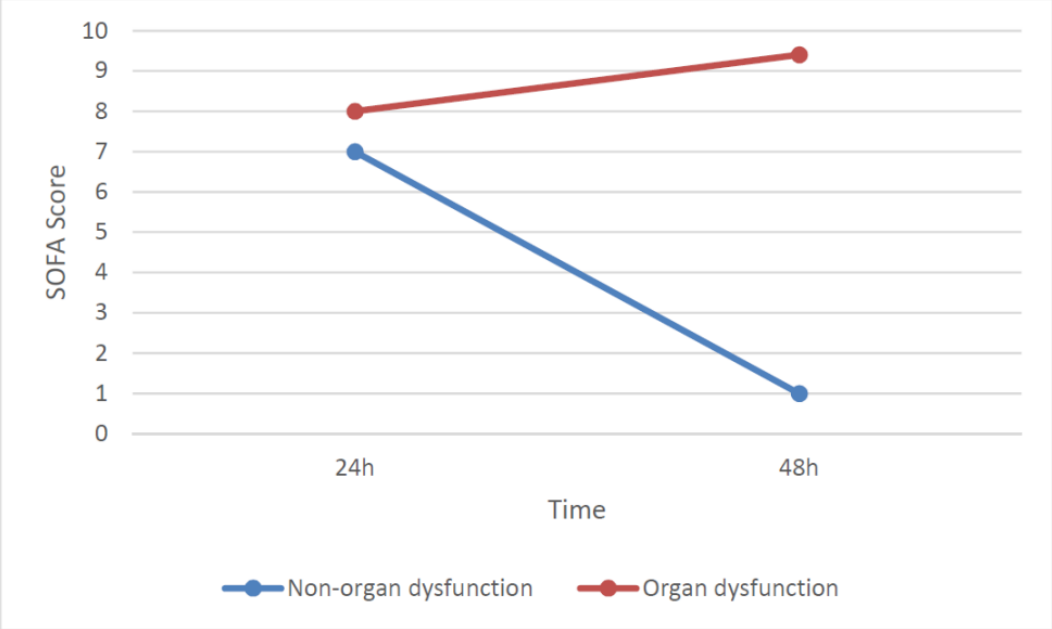
Legend: Pearson correlation test, $p<0.05$ means significant. SOFA=Sequential Organ Failure Assessment.

Table 3. The difference of eosinophil count and SOFA score alterations between dead and survived patients among sepsis patients in ICU Wahidin Sudirohusodo Hospital, Makassar

Alteration	Died (n=22)				Survived (n=12)				p
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Eosinophil count	0.46	0.59	-0.6	1.1	-0.3	0.55	-1.3	0.3	0.001
SOFA score	-2.36	1.7	-6	0,0	4.16	3.43	0,0	10	<0.001

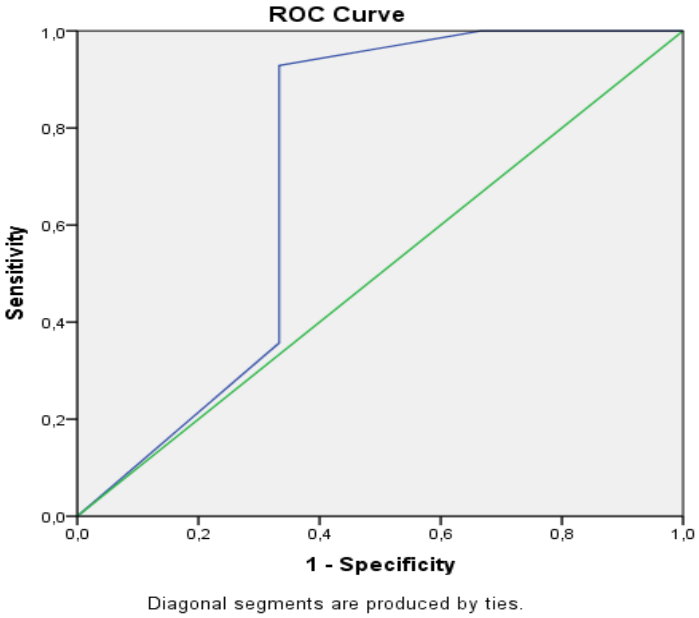
Legend: Unpaired t-test, +=decreased, -=increased. SOFA=Sequential Organ Failure Assessment.

Figure 1. The SOFA score at 24 hours and 72 hours after admission among sepsis patients in ICU Wahidin Sudirohusodo Hospital, Makassar



Legend: SOFA=Sequential Organ Failure Assessment.

Figure 2. ROC curve of eosinophil with the criteria of non- and organ dysfunction (based on SOFA score after 24 hours) among sepsis patients in ICU Wahidin Sudirohusodo Hospital, Makassar



Legend: ROC=Receiver operating characteristic; SOFA=Sequential Organ Failure Assessment.

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