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Research Article

Validity of Eosinopenia in Bacterial Sepsis Patients Based On Sepsis-3 Consensus Criteria

Uji Validitas Eosinopenia Pada Pasien Sepsis Bakterialis Berdasarkan Kriteria Konsensus Sepsis-3

Adrian Suhendra[1*], Ida Parwati[2], Adhi K Sugianli[2]
[1]Department of Clinical Pathology, Faculty of Medicine, Maranatha Christian University
Jl. Prof. drg. Surya Sumantri, M.P.H. 65, Bandung, 40164, West Java, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine Padjadjaran University / Hasan Sadikin General Hospital
Jl. Pasteur 38, Bandung, Jawa Barat, 40161, Indonesia
**Penulis korespondensi*
Email: suhendraadriansppk@gmail.com

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Abstract

Sepsis remains a major global healthcare problem, indicate as most frequently cause of morbidity and mortality worldwide. The last consensus of sepsis in 2016 defined sepsis as life threatening organ dysfunction caused by a dysregulated host response to infection. Dysfunction of organs can be represented by Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score. Score2 points or more consequent to the infection. Nowadays, there is ideal biomarkers of sepsis such as procalcitonin (PCT). However, the use of that markers in developing countries are hardly accessible. Eosinopenia is an prepossess biomarker because eosinophil count is always measured in daily practice and considered as a forgotten marker. The study purpose is to determine the validity of absolute eosinopenia in bacterial sepsis patients. This study is a descriptive observational study, collecting 118 patient's medical record data from the past, diagnosed as sepsis using consensus criteria of Sepsis-3 between January 1st 2018–December 31st 2019. Eosinopenia validity test in sepsis patients showed 92.7% specificity and 71.4% sensitivity. This study also showed significant differences of absolute eosinophil count between positive sepsis patients and negative group with p value <0.001. Eosinopenia had high specificity so it could be used as a marker of diagnostic in septic patients.

Keywords: *eosinopenia; sepsis; sepsis-3 consensus criteria*

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Abstrak

Sepsis sampai saat ini masih menjadi masalah kesehatan besar karena merupakan penyebab tersering meningkatnya angka kesakitan dan kematian di seluruh dunia. Berdasarkan konsensus sepsis tahun 2016, sepsis didefinisikan sebagai disfungsi organ yang mengancam nyawa dan disebabkan oleh disregulasi respons tubuh terhadap infeksi. Disfungsi organ dapat diidentifikasi dengan adanya skor SOFA. Skor SOFA2 poin atau lebih konsekuen dengan adanya infeksi. Saat ini telah ada penanda biologis sepsis yang mendekati ideal seperti Pro-Calcitonin, tetapi terdapat kendala dalam penggunaan penanda biologis ini terutama di negara berkembang karena ketersediaan pemeriksaan yang terbatas. Eosinopenia merupakan penanda biologis yang menarik karena hitung eosinofil merupakan pemeriksaan yang selalu dilakukan pada praktik klinis dan sering dianggap penanda yang dilupakan. Tujuan penelitian ini adalah menguji validitas eosinopenia absolut pada pasien sepsis. Penelitian ini adalah penelitian deskriptif observasional dengan pengambilan data dilakukan secara retrospektif dengan menelusuri catatan rekam medik 118 pasien yang didiagnosis sebagai sepsis dengan menggunakan kriteria konsensus Sepsis-3 periode 1 Januari 2018–31 Desember 2019. Hasil uji validitas eosinopenia pada pasien sepsis menunjukkan spesifisitas 92,7% dan sensitivitas 71,4%. Hasil penelitian juga menunjukkan terdapat perbedaan bermakna hasil hitung eosinofil absolut antara kelompok pasien sepsis positif dan negatif dengan nilai p<0,001. Simpulan, eosinopenia mempunyai spesifisitas tinggi sehingga dapat digunakan sebagai penanda diagnostik pada sepsis.

Kata kunci: eosinopenia; kriteria konsensus sepsis-3; sepsis

Introduction

Sepsis is a syndrome results from a complicated interaction between infectious agents and the host. It is characterized by the multiple pathway activation, including of pro-inflammatory and anti-inflammatory responses, along with noninflammatory pathways such as coagulation, metabolic, cardiovascular, neuronal, autonomic and hormonal.[1,2] The pathobiology and management of sepsis is highly developed suggesting the need for reconsideration. In 2016, The Third International Consensus for Sepsis (Sepsis-3) agreed to release a new definition for sepsis and septic shock. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. Septic shock defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Sepsis is caused by many organisms including bacteria, viruses and fungi, each with its own mechanism of action. Bacteria have been shown to be the most widely pathogen of sepsis among patients with detected pathogens, while sepsis caused by viruses and fungi are underdiagnosed worldwide.[3,4]

More than 100 different molecules have been suggested as useful biomarkers of sepsis.[5] Unfortunately, until now, the availability of infection markers that have high validity has not been found. An ideal infection marker would be highly sensitive and specific, easy to perform, rapid, cheap, and related to prognosis and disease severity.[6,7]

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The gold standard for infection diagnosis is still microbiological culture but has several limitations such as time required to produce result and lack of sensitivity. Several infection markers, such as procalcitonin, presepsin and C-reactive protein considered as the most ideal and currently considered the most frequently used markers. The disadvantages of these tests are usually costly and this combined with microbiological culture that takes minimal 72 hours for the result to be attained, making these parameters not ideal for diagnosis of sepsis.[7-12]

Eosinopenia or reduction in the number of circulating eosinophils is an old inflammatory marker of acute infection. It was first reported in 1893 by Zappert and was utilized during the 19th century as a diagnostic test of infection.[13] Eosinopenia is an prepossess biomarker because it always measured in daily practice and therefore the extra costs could be avoided but now eosinopenia considerable as a forgotten marker. The eosinophil response to an acute infections was described as result of rapid and massive eosinophils peripheral sequestration in peripheral blood and related to production of stress related chemotactic factors as a secondary response to infection-induced stress .[6,7] Eosinophils are multifunctional leucocytes implicated in the pathogenesis of numerous infection processes. The function of eosinophils is primarily associated with their contribution to host defence against parasitic infection in which eosinophilia would be found. Eosinopenia will be found in bacterial, viral, and fungal infections with different mechanisms of action.[14] This study purpose is to determine the validity of absolute eosinopenia in bacterial sepsis patients based on Sepsis-3 consensus criteria.

Methods

Study design and setting

A retrospective study taken from patient's medical record with the diagnosis of sepsis based on ICD-10-CM A41 was performed of all adult inpatient admitted to Internal Medicine Department/Intensive Care Unit of Siloam Hospital Purwakarta and Siloam Hospital Bekasi Sepanjangjaya with sepsis between January 1st 2018 and December 31st 2019. Subjects above 18 years old, with sepsis diagnosis based on Sepsis-3 consensus criteria, had blood culture for bacteria taken 2 times from 2 different sites within the first 24 hours and before administration of antibiotics, with WBC count >10.000 cells/mm^3 and >70% neutrophils in differential count (bacterial sepsis) were included.[10] Subject with hematological malignancy, immunosuppressive state, autoimmune and parasite disease, and history of atopic disease were excluded from this study since those circumstances would affect eosinophils count. The research has been approved by the Hasan Sadikin General Hospital Bandung' ethics committee on February 18th 2020 No: LB.02.01/X.6.5/43/2020.

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Data collection and definitions

From the patient's medical record, we evaluated their principal diagnosis, gender, age, site of infection, and laboratory data: eosinophil count, WBC count, neutrophil percentage, and blood culture result. According to latest consensus criteria of Sepsis (Sepsis-3) as a new gold standard for sepsis diagnose, patients were catagorized as having sepsis or not at the first evaluation. The diagnosis of sepsis based on SOFA score of 2 or more can be seen in Table 1.[1] Eosinopenia defined if the absolute eosinophil count with fluorescent flowcytometry method is ≤ 50 cells/mm^3.[5-7] The validity of eosinopenia were assessed by comparing the count of eosinophil cell between bacterial sepsis patients and non-bacterial sepsis patients at the time of evaluate.

Statistical analyses

Prior to statistical analyses, for numerical data, the normality of distribution data was tested using one sample Kolmogorov-Smirnov test. Parametric (independent t test) used if the data is normally distributed and data are presented as mean ± standard deviation. A nonparametric (Mann-Whitney test) used if the data is not normally distributed and data are presented as median and 1st& 3rd interquartile range.

Table 1 Sequential Organ Failure Assessment Score[1]

	Score				
Human System	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FIO_2, mmHg (kPa)	≥400(53.3)	<400(53.3)	<300(40)	<200(26.7) with respiratory support	<100(13.3) with respiratory support
Coagulation					
Platelets, $x10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System					
Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal					
Creatinine,mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine output,mL/d				<500	<200

F_{IO2}: *fraction of inspired oxygen*; MAP: *mean arterial pressure*; PaO_2: *partial pressure of oxygen*

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The sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), likelihood ratio (+)/(-) were calculated based on the respective cut-off point of eosinophil count (50 cells/mm^3). A *P* value <0.05 is considered significant, otherwise is non significant. The collected data were statistically analyzed using SPSS program for Windows, software version 25.0.

Results

Study Population

During the period of the study, 141 patients were diagnosed by clinician as sepsis, and 23 patients were excluded because of WBC count was normal (n = 12), no neutrophilia (n = 9), has asthma bronchial (n = 2), on corticosteroid therapy (n = 1) and has reactive anti-HIV (n = 1). The remaining 118 patients enrolled in the study were categorized by SOFA score into 65.3% (n = 77) patients with SOFA score ≥2 and 34.7% (n = 41) patients with SOFA score <2. The patients included and excluded from the study are presented in Figure 1.

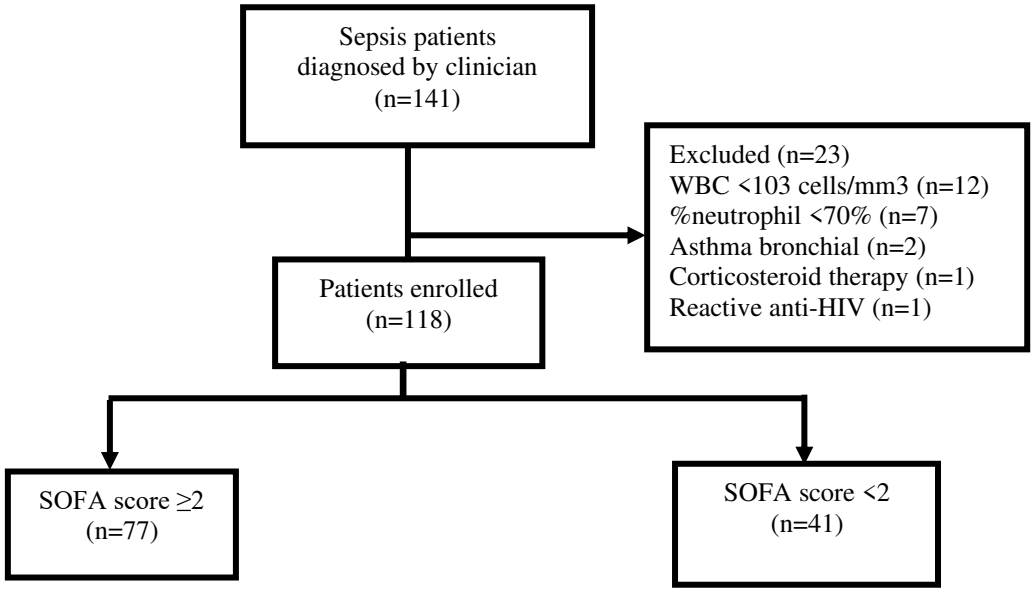

Figure 1 Flow Chart of Study Population

The gender of enrolled subjects is almost equal with age ranging from 40-60 years old. The most sources of infection on both SOFA score of 2 or more and SOFA score less than 2 subjects are respiratory tracts. The median eosinophil count in the SOFA score ≥2 group and SOFA score <2 group was 40 cells/mm^3 and 140 cells/mm^3 respectively. There were significant differences in the eosinophil count between the different groups (Mann-Whitney test, $p < 0.001$).

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The median WBC count was 16,230 cells/mm^3 in the SOFA score ≥2 group (range; 10,360-36,270 cells/mm^3) and 10,960 cells/mm^3 in the SOFA score <2 group (range; 10,020-18,220 cells/mm^3). Patient characteristics were presented and comparable in Table 2.

From 77 patients with SOFA score ≥2 only 31 (40.3%) subjects with positive result of blood cultures; Gram positive bacteria 9 (29.03%) isolates and Gram negative bacteria 22 (70.97%) isolates. Various causative agents of sepsis in study subjects was presented in Figure 2.

Table 2 The Patient Characteristics, Site of Infection, WBC, Neutrophil and Eosinophil Count

	SOFA						p value
	Score ≥2 (n=77)			Score <2 (n=41)			
	n	%	Median (Range)	n	%	Median (Range)	
Gender							0.334*
Male	38	49.4		16	39.0		
Female	39	50.6		25	61.0		
Age (Years)							0.152**
18-29	1	1.3		3	7.3		
30-39	11	14.3		8	19.5		
40-49	22	28.6		16	39.0		
50-59	29	37.7		9	22.0		
60-69	11	14.3		4	9.8		
70-79	2	2.6		1	2.4		
80-89	1	1.3		0	0.0		
Site of Infection							0.598**
Respiratory	40	51.95		24	58.53		
Genitourinary	15	19.48		10	24.39		
Abdomen	6	7.79		1	2.44		
Skin and Soft Tissues	5	6.49		1	2.44		
Others	11	14.29		5	12.20		
WBC count (cells/mm^3)			16,230 (10,360-36,270)			10,960 (10,020-18,220)	< 0.001***
Neutrophil (%)			77.8 (70.0-94.0)			73.1 (70.0-84.4)	< 0.001***
Eosinophil count (cells/mm^3)			40 (10-210)			140 (40-250)	< 0.001***

**) Fisher's exact test*
***) chi square test*
****) Mann Whitney U Test*

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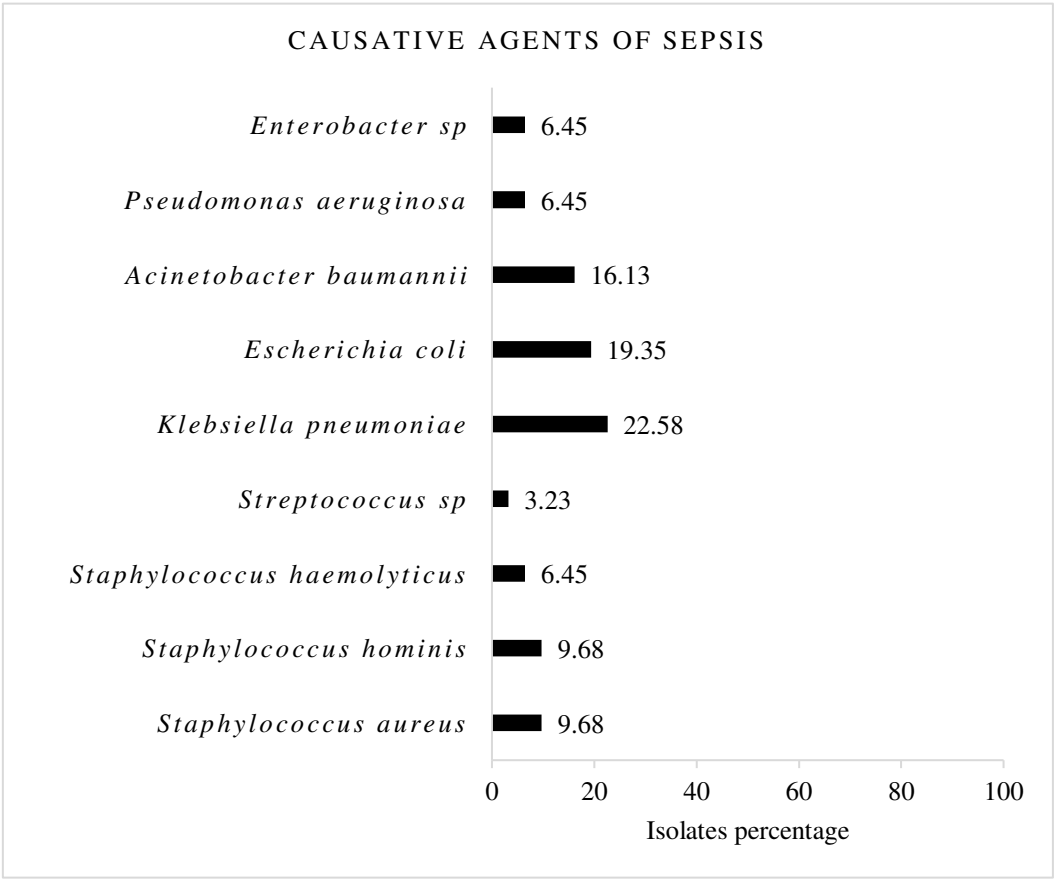

Figure 2 Causative Agents of Sepsis with SOFA score ≥2

Validity of Eosinopenia

The eosinopenia produced a sensitivity of 71.4%, specificity of 92.7%, PPV of 94.8%, NPV of 63.3%, LR (+) of 9.8, and LR (-) of 0.3, at cut-off value of ≤ 50 cells/mm^3 as shown on Table 3.

Table 3 Validity of Eosinopenia in Bacterial Sepsis Patients based on Sepsis-3 Consensus Criteria

Validity	Value
Sensitivity	71.4%
Specificity	92.7%
PPV	94.8%
NPV	63.3%
LR (+)	9.8
LR (-)	0.3

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Discussion

The present study is one of earliest research to determine the usefulness of eosinopenia in bacterial sepsis patients based on latest consensus criteria of sepsis (Sepsis-3). Results study show the higher specificity and PPV than sensitivity and NPV of eosinopenia in bacterial sepsis diagnosis based on Sepsis-3 consensus criteria. The result of this study is similar to previous studies from Salem, Abidi, Shaaban, Luhulima, Sipayung and Gil which stated that there were differences between absolute eosinophil counts in sepsis and non-sepsis patients with absolute eosinophil counts varying between 8-72 cells/mm^3, sensitivity ranges from 64-97.4% and specificity ranges from 65-100%, respectively. Therefore, eosinopenia may represent an excellent marker for the diagnosis of bacterial sepsis.[5-7,11,12,15]

The study by Gil in 2003 showed that sepsis was strongly correlated with an eosinophil count <40 cells/mm^3 and WBC count >10,000 cells/mm^3 with specificity and PPV of 100% and related to bacterial infectious diseases.[15] Abidi's study in 2008 showed that eosinopenia (cut-off value of ≤ 50 cells/mm^3) could be used as sepsis marker in patients hospitalized in the ICU with a sensitivity of 80% and specificity of 91%.[6] Shaaban et al in 2010 also certified the usefulness of eosinopenia in sepsis patients and concluded that eosinopenia with cut-off value of ≤ 50 cells/mm^3 has a sensitivity of 81% and specificity of 65%.[7]

Eosinophils reference range account for 1-3% of leucocytes, and the upper limit of the normal range is 400 cells/mm3.[16] The level of eosinophils in the body is usually tightly regulated. It has been hypothesized that several mechanism controlling eosinopenia in acute infection including acute stress mediated by adrenal glucocorticosteroids and epinephrine. The initial eosinopenia response in infection is believed to be secondary to rapid peripheral sequestration and migration of the circulating eosinophils to the site of infection. This process is stimulated by the production of cytokines and other chemotactic substances (C5A and fibrin fragments) that released into the peripheral blood during the acute stages of inflammatory.[17] The release of cytokines will also involve mediation by adrenal glucocorticosteroids. Increases of glucocorticoids inhibit the synthesis of eosinophil and also inhibit the release of mature eosinophils from bone marrow by inhibition of IL-5.[6,7,14,17,18]

Eosinopenia can be used to assist and guide clinicians in their decisions regarding early diagnosis of sepsis and appropriate use of antibiotics before receiving microbial culture results that could impact and reduce morbidity and mortality in newly hospitalized bacterial sepsis patients especially in developing countries and also will reduce the increasing problem of antibiotic resistance. As a cheap and always measured test, eosinopenia offers a higher reliability than other hematology markers of infection such as leucocytosis and neutrophilia.[4-6,19] In acute

infection, the eosinophils demonstrated a persistent eosinopenia. The neutrophils although dropping immediately, rose to normal levels within 20-60 minutes then proceeded to significant elevations. This variable range of neutrophils (also leucocytes since 50-80% of leucocytes is neutrophils) makes eosinopenia a more reliable marker especially in early stage of acute infection.[17]

Our study is one of earliest research to suggest the usefulness of eosinopenia in bacterial sepsis patients based on latest consensus criteria of sepsis (Sepsis-3) that already been used in clinical practise to diagnose sepsis. The difference in validity test results found in several studies is probably due to the renewal of consensus criteria and changes in the definition of sepsis continuously causing the approach to the sepsis population to be varied. The limitation of this study is that we used medical record data based on ICD diagnosis code of sepsis as main diagnosis and search keywords, thus allowing bias in the screening process in patients that sepsis is not categorized as the main diagnosis. Finally, microbiologically documented bacterial infections only in 40.3% of cases. This low percentage is similar with results from previous studies ranging from 30-50%.[20]

Conclusion

Eosinopenia has a good validity with high specificity using the latest consensus criteria of sepsis (Sepsis-3), therefore eosinopenia in bacterial sepsis patients can be used as a new gold standard for diagnosis marker of sepsis.

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