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Absolute Eosinophil Count as a Marker for Sepsis Diagnosis

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ABSTRACT

Eosinopenia, defined as low number of absolute eosinophil count, was used to support the diagnosis of sepsis in several studies by differentiating infection from non-infection cases. However, the results between studies were not consistent. This study was used to determine whether the eosinopenia served to distinguish sepsis from non-sepsis. A prospective cohort study was conducted on adult patients in the Intensive Care Unit (ICU) of Royal Taruma Hospital, Jakarta. Subjects were included in the sepsis group if they met the sepsis criteria (Surviving Sepsis Campaign). Within the study period from May 2016 to November 2016, there were 35 subjects recruited. From those, 17 subjects were diagnosed with sepsis. From statistical analysis with cut-off point of absolute eosinophil count <50 cells/uL, no significant difference was found in the proportion of subjects with eosinopenia between sepsis and non-sepsis. After the cut off point was changed into ≤90 cells/uL, we found significant difference of proportion of subjects with eosinopenia between sepsis and non-sepsis, with 70.6% sensitivity, 66.7% specificity, and area under the ROC curve (AUC) 0.314 (95%CI 0.134 to 0.494). In conclusion, the present study found an association between eosinopenia with the diagnosis of sepsis. However, considering the low sensitivity and specificity, our study did not recommend the use of absolute eosinophil count as single diagnostic tool.

Keywords: *Eosinopenia, Absolute eosinophil count, Sepsis, Marker, Diagnosis.*

1. BACKGROUND

Sepsis is considered a major cause of health loss. Mortality from sepsis is much higher than that from acute coronary syndrome or stroke. Roughly the mortality was 30% in sepsis and 80% in septic shock. These data were retrieved from an epidemiologic study on sepsis between 1980 to 2008 in four countries – United States, Brazil, United Kingdom and Australia. The incidence of sepsis from the study was around 22 to 240 cases per 100,000 population, severe sepsis was 13 to 300 cases per 100,000 population and 11 septic shock cases per 100,000 population. To date, there has not been any large scale study of sepsis epidemiology from developing countries.[1] From an observational study of severe sepsis and septic shock in Cipto Mangunkusumo Hospital, Jakarta, in 2021-2013, sepsis mortality was around similar, it was 61%.[2] It is noted that diagnosis and treatment delay contribute to the high mortality of sepsis.

The diagnosis of sepsis constantly encounters some important issues. Diagnosis of sepsis based on clinical findings leads to high false positive rate. Forty three percent of the patients diagnosed with sepsis on admission – using systemic inflammatory response syndrome (SIRS) criteria with suspected infection – later turned to be non-infection cases.[3] Various biological marker including procalcitonin, adrenomodulin, C-reactive protein (CRP), procalcitonin and interleukin (IL)-6 were examined to support the diagnosis and stratify the risk in sepsis.[4] However, those latter markers are relatively costly and not readily available in the peripheral laboratories. In addition, blood culture, the gold standard for sepsis

diagnosis, requires several days for the result and the positivity rate is low, only 20% in sepsis.[5]

Prompt diagnosis and comprehensive management in sepsis will improve the survival significantly.[6] A simple, quick, and low-cost diagnostic tool will facilitate early diagnosis and, therefore, immediate treatment in sepsis.

Absolute eosinophil count is an uncomplicated and effortless laboratory examination which is performed routinely. We sampled it from the peripheral blood and performed the check as part of the leukocyte counting. The result is relatively quick and can be executed in peripheral laboratories. Previous studies has used eosinophil count for diagnosis, risk stratification[7-9] and prognostic marker in sepsis[10,11].

After all, the use of eosinophil count examination for diagnostic marker in sepsis is still inconclusive. According to some studies, eosinophil count was neither specific for diagnosis or stratification of sepsis.[12] To clarify the previous results, another study with more precise methods and recruitment has to be conducted. Should eosinophil count be proven to support sepsis diagnosis, it might be used as a screening tool to rule out sepsis from non-infection cases.

This study aims to investigate whether eosinopenia, measured from absolute eosinophil count from the peripheral blood, can differentiate sepsis from non-sepsis.

2. METHODS

A prospective cohort study was conducted in the ICU of Royal Taruma Hospital, Jakarta, from May to November 2016. Subjects were recruited consecutively. The recruitment criteria were patients age ≥18 years admitted to the ICU. Subjects were excluded if died or discharged within 24 hours after admitted, had parasitic infection, asthma, atopic dermatitis, leukemia, lymphoma, autoimmune disease, Cushing syndrome or on long term steroid use.

Independent variable in this study was eosinopenia and the dependent variable was the diagnosis of sepsis. Eosinopenia was defined as absolute eosinophil count <50 cells/µL on admission. It was sampled from subjects' peripheral blood. Sepsis was diagnosed using Surviving Sepsis Campaign Criteria 2012, that is suspected or proven infection with minimum two of the following criteria: body temperature >38.3ºC or <36.0ºC, heart rate >90 beats/minute, respiratory rate >20 breaths/minute, altered mental status, significant edema or positive fluid balance (>20 mL/kg over 24 hour), plasma glucose >140 mg/dL in the absence of diabetes, leukocyte count >12,000/µL or <4,000/µL or immature forms >10%, CRP level >2 standard deviation (SD) and procalcitonin level >2 SD.[13]

Leukocyte and differential counting, collected from peripheral blood, were performed with Advia 2021i (Siemens) using flow cytometry technique. Absolute eosinophil count was calculated by multiplying the percentage of eosinophil retrieved from the machine counting with the total leukocyte count.

Along with the blood cell counting, we also measured procalcitonin level, hs-CRP (high-sensitivity C-reactive protein) level and blood culture. Procalcitonin was measured with VIDAS PC (Biomerieux) using sandwich immunoassay technique and fluorescent detection; hs-CRP was measured with Dimension XL 200 using turbidimetry technique; and blood culture was analyzed using Vitex 2 Compact.

According to the absolute eosinophil count level, subjects were grouped into eosinopenic and non-eosinopenic. Subjects without infection or with focal infection were grouped into non-septic while subjects with sepsis, severe sepsis and septic shock were grouped into sepsis. Statistical analysis was performed using SPSS version 23.0.

This study has been approved by Universitas Tarumanagar Faculty of Medicine and ethical committee of Royal Taruma Hospital. We did not request any consent from the patients or the guardian since this study was categorized into low and negligible risk study. There was no additional or invasive procedure related to this study.

3. RESULTS

Within the study period, 35 subjects had been recruited. Table 1 described the characteristics of the subjects.

Table 1. Subjects' characteristics

Characteristics	
Sex	
• Male (%)	26/35 (74.3)
• Female (%)	9/35 (25.7)
Infection on admission* (%)	27/35 (77.1)
Source of infection on admission	
• Respiratory tract (%)	22/27 (81.5)
• Skin and soft tissue (%)	3/27 (11.1)
• Urinary tract (%)	2/27 (7.4)
Sepsis on admission (%)	17/ 35 (48.6)
Positive blood culture in sepsis (%)	7/17 (41.2)
Length of hospital stay (days)	10 (3-43)
Length of ICU stay (days)	4 (1-31)
Died	
• In-hospital (%)	5/35 (14.3)
• Within the first 3 day (%)	1/5 (20)

* Clinically diagnosed or confirmed infection

Table 2 showed the mean or median of the absolute eosinophil count, procalcitonin and hs-CRP on recruitment in sepsis and non-sepsis groups.

Table 2. Eosinophil count, procalcitonin and hs-CRP levels in sepsis and non-sepsis groups

Parameter	Total n = 35	Sepsis n = 17	Non-Sepsis n = 18	p[a]
Absolute eosinophil count (cells/µL)	114.5 ± 91.24	129.7 ± 89.47	100.1 ± 93.08	NA
Procalcitonin (ng/mL)	0.53 (0.05-200)	6.8 (0.07-200)	0.12 (0.05-31.02)	0.000*
hs-CRP (mg/L)	23.18 (0.98-355.8)	49.49 (2.69-355.8)	15.5 (0.98-211.46)	0.007*

[a] Mann-Whitney U test; * p <0.05; NA not applicable

Five out of 17 subjects with sepsis had eosinopenia on admission while in non-sepsis group, 6 out of 18 subjects had eosinopenia. From chi-square testing, we found no difference in the proportion of eosinopenic subjects between sepsis and non-sepsis on admission day (p = 0.803). For this analysis, we used absolute eosinophil count <50 cells/µL as the cut off of eosinopenia.

To find the preferred cut off of eosinophil count to differentiate sepsis from non-sepsis, receiver operating characteristic (ROC) analysis was performed. Using absolute eosinophil count ≤90 cells/µL, we found significant association between eosinopenia and sepsis diagnosis on admission (p = 0.028). Table 3 demonstrated the number of subjects with eosinopenia using the new cut off.

Table 3. Subjects with eosinopenia (absolute eosinophil count ≤ 90 cells/µL) in sepsis and non-sepsis groups

Eosinopenia	Sepsis	Non-Sepsis
Yes	5	12
No	12	6

Using eosinophil count ≤90 cells/µL as a cut off to determinate sepsis from non-sepsis, we yielded sensitivity of 70.6%, specificity of 66.7%, area under the ROC curve (AUC) of 0.314 (95%CI 0.134-0.494), positive predictive value (PPV) of 29.4%, and negative predictive value (NPV) of 33.3%. In comparison, the AUC of procalcitonin and hs-CRP to determine sepsis from non-sepsis on ICU admission in this study were 0.833 (95%CI 0.7-.966) and 0.761 (95%CI 0.601-0.922), respectively.

4. DISCUSSION

According to the pathophysiology, and supported by previous studies, eosinopenia might occur as a response from acute inflammation as in sepsis.[9,14-17] However, this study showed that the mean of absolute eosinophil count in sepsis was higher than that in non-sepsis patients (Table 2). This trend was in contrary to the procalcitonin and hs-CRP levels. Both levels were increased significantly in sepsis compared to non-sepsis patients. The use of both markers to establish the diagnosis of sepsis on admission might explain the significant differences between groups.

The absolute eosinophil count demonstrated differences between groups after a new cut off from the analysis was applied. The new cut off of eosinopenia to determine sepsis in this study was different from the study of Abidi et al which used <50 cells/µL as cut off to diagnose sepsis.[7] Several other studies had various cut off points for eosinopenia but the values were all below 100 cells/µL.

Some studies demonstrated the significance of absolute eosinophil count to support the diagnosis of sepsis. Luhulima et al studied absolute eosinophil count as compared to procalcitonin as a marker of sepsis in 61 patients admitted with SIRS manifestation. With the cut off of 50 cells/µL the absolute eosinophil count could be used as sepsis marker.[18] Abidi et al conducted a prospective cohort study to 177 ICU patients. With the cut off of <50 cells/µL, eosinopenia managed to differentiate sepsis from non-sepsis patients with the AUC of 0.89 (95%CI 0.83-0.94). The AUC of eosinopenia to determine SIRS from infection was 0.84 (95%CI 0.74-0.94).[7] A case control study by Wibrow et al in West

Australia to 352 adult patients compared eosinophil count with CRP, total leukocyte and neutrophil count. Subjects were grouped into those with positive and negative blood culture. The median of eosinophil count was significantly lower in subjects with positive blood culture. The AUCs of absolute eosinophil count, total leukocyte, neutrophil count and CRP were 0.349, 0.569, 0.615, and 0.689, respectively. The study suggested that eosinopenia can be used as early detection of bacteremia. Therefore, those patients deserved further check to confirm sepsis.[19]

The sensitivity and specificity of the absolute eosinophil count in our study were about similar compared to the other studies. Most of the studies showed better sensitivity with lower specificity. This indicates that eosinopenia was more for screening tool for sepsis diagnosis.[9,18,19] Even though statistically the eosinopenia in this study was significant as sepsis marker, the low AUC suggests that eosinopenia *per se* was not an ideal marker for diagnosing sepsis. Compared to other sepsis markers, i.e., procalcitonin and hs-CRP, the AUC of eosinopenia to diagnose sepsis was low. To add, the mean of the eosinophil count was not even lower in sepsis group. The PPV and NPV were also low. Therefore, we do not suggest using eosinopenia as a single diagnostic tool. Eosinopenia could be an alternative diagnostic tool in the remote area where the other marker of sepsis could not be checked or costly.

Several studies did not suggest eosinopenia as marker of sepsis. Those studies compared the eosinophil count with the other sepsis markers, those were procalcitonin, CRP and circulating-free DNA (cf-DNA). The studies summarized that the absolute eosinophil count could not differentiate infection from non-infection and sepsis from non-sepsis.[8,20-23]

Our study has some advantages. The result managed to show the significance of eosinopenia as diagnostic marker in sepsis. The cut off was about similar with the previous studies. To add, this study was conducted in the ICU in which sepsis management protocol was strictly applied, the blood checks were more extensive and the timing of the sample collection was prompt.

There were some limitations in this study. Firstly, diagnosis of sepsis ideally was established on admission. However, in some subjects, the diagnosis was established after a few days on hospitalization. In consequence, patients' development during hospital stays and previous laboratory results could potentially bias the sepsis diagnosis. Secondly, we did not stratify the severity of sepsis in the analysis. It is possible that stratifying the severity may give different degree of eosinopenia. Thirdly, we did not make any model to combine the eosinopenia with the other marker for sepsis. It would be interesting to learn whether including eosinopenia into any established model of sepsis marker would increase the predictive value of sepsis diagnosis.

In conclusion, there was an association between eosinopenia and the diagnosis of sepsis on admission. The cut off of eosinopenia was ≤90 cells/μL. However, this study did not recommend using eosinopenia as a single diagnostic tool to diagnose sepsis.

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