Eosinopenia As a Marker of Sepsis in Intensive Care Unit Patients

Suraiya Begum[1], Sheuly Ferdousi[2], Reba Das[3]

Abstract:

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

Objective: *This study was done to evaluate eosinopenia as a marker of sepsis in intensive care unit patients.*

Materials and Methods: *This cross sectional study was carried out in the Department of Clinical Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka . AEC was done by automated cell counter and rechecked manually microscopically.*

Observations and Results: *In this study 74 suspected case of sepsis were enrolled from intensive care unit, BSMMU, Dhaka. To evaluate the usefulness of AEC for predicting significant sepsis the area under the ROC curve was analyzed. The area under ROC curve was 0.765 in current study. At the cut off valve of AEC < 40 cell/cu mm, the sensitivity and specificity of AEC for diagnosis of sepsis was 72.5% and 61.8% respectively.*

Conclusion: *This present data revealed that decreased absolute eosinophil count was significantly associated with sepsis. So eosinopenia may be a reliable marker for early diagnosis of sepsis.*

Introduction:

Sepsis is one of most common causes of mortality and morbidity in the intensive care unit[1]. Despite continuing advances in diagnosis and treatment, sepsis remains one of the important causes of higher mortality and morbidity. Early diagnosis of sepsis plays an integral role in the morbidity and mortality of patients admitted to the intensive care unit[2].

Sepsis is a systemic inflammatory response to infection, manifested by two or more of the following condition as a result of infection: Temperature >38^{0}c or < 36^{0}c, Heart rate >90 beats/min, Respiratory rate > 20 breaths/min and white cell count >12,000/cu mm,<4000/cu mm, or >10% immature (band) forms[1,3].

Sepsis was documented more than 35% of patients during their ICU stay[4]. The hospital mortality ranged from 16.9% for non-infected patients to 53.6% for patients who had infection at ICU. An estimated 7,50,000 cases of sepsis occur annually in the United States and the mortality rate is about 30%. The incidence will increase by 1.5 per year[5].

Normal eosinophil count is 40-400 cells/cu mm of blood[6]. Eosinopenia refers to a reduction in the normal number of circulating eosinophils[7]. The level of eosinophils is normally tightly regulated[1]. Eosinophil production is regulated by IL-3, IL-5 and granulocyte macrophage colony stimulating factor (GM-CSF). Without these cytokines, eosinophil can not survive. These cytokines are

1. Clinical Pathologist, Department of Clinical Pathology, Sir Salimullah Medical College Mitford Hospital, Dhaka

2. Associate Professor, Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

3. Lecturer, Department of Pathology, Sir Salimullah Medical College, Dhaka.

Address of Correspondence: Dr. Suraiya Begum, Clinical Pathologist, Department of Clinical Pathology, Sir Salimullah Medical College Mitford Hospital, Dhaka. E-mail: drripa74@gmail.com ORCID: 0000-0001-5853-7140

not significantly activated in patients with sepsis. It is believed to be main mechanism of eosinopenia is sepsis[8]. Eosinopenia during infection is also enhanced by chemotactic substance such as C5a[9]. This substance causes migration of eosinophils into the inflammatory site[10]. Chemotactic factor (C 5a) causes a brief non specific granulocytopenia followed by a prolong eosinopenic-neutrophilic response. So eosinopenia caused by migration of these cells from the vascular space, inhibition of bone marrow release and eventual decrease in marrow production[11].

Sepsis and non-infectious systemic inflammatory response syndrome (SIRS) produce very similar clinical feature[2]. Therapy and outcome differ greatly between patient with and those without sepsis. The widespread use of antibiotics for all such patients is likely to increase antibiotic resistance and toxicity[12]. The definitive diagnosis of sepsis is made by a positive culture, which requires a minimum of 48-72 hours[13]. As the culture procedure is costly and longer time required, other tests in the diagnosis of sepsis are required[4]. Several markers like C-reactive protein, procalcitonin, lactate, Interleukin-1 (IL-1), Inter leukin-6 (IL-6), Tumor necroting factor (TNF), triggering receptor expressed on myeloid cells-1 (TREM-1) etc have been reported to predict sepsis[9]. Most of these markers are expensive, not easily accessible to clinicians, less sensitive and not ideal for early diagnosis of sepsis. Among these markers, eosinopenia shows more diagnostic sensitivity and specificity. Among these markers blood eosinophil count is simple, easy, quick, less expensive and reliable marker of sepsis[9]. It is a part of complete blood count which is done as routine laboratory test. It reduces widespread use of antibiotic, mortality and sepsis related complications and shorten the hospital stay. So this study was carried out to evaluate the diagnostic sensitivity of eosinopenia for detection of sepsis in ICU patients.

Materials and methods:
This cross sectional study was carried out at the Department of Clinical Pathology in collaboration with Department of Anesthesia, Analgesia and Intensive care Medicine and Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2012 to February 2013. Study population was 74 patients selected from intensive care unit, BSMMU, according to inclusion criteria. Suspected cases of sepsis and adult age group were included in the study. Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU, Dhaka. 2ml blood was collected for CBC including AEC which was done by automated cell counter and rechecked manually microscopically. Single set of culture was done for each patients. All data were recorded systematically in a preform data collection sheet and expressed as mean ± standard deviation (SD), t-test, Z test, Chi-square test. ROC curve and the respective area under curves was calculated for eosinophils. Sensitivity, specificity were calculated at the best cut off value. Statistical analysis was done by using statistical package for social science SPSS 17.0. P value <0.05 was considered as significant.

Result:
In this study, 74 patients were divided into two group according to blood culture findings. Out of 74 patients, 34 patients were considered as proven sepsis by blood culture as infection group. The rest 40 patients were considered by blood culture as non infection group. Suspected case of sepsis and adult age group were included in the study. The mean ± SD of AEC was found 18.3±11.4 cells/cu mm in infection group and 145.0±57.7 cells/cu mm in non-infection group. In infection group AEC was lower than non-infection group. The result was statistically highly significant (p<0.001). To evaluate the usefulness of AEC for predicting significant infection the area under the ROC curve was analyzed. The area under the ROC curve was 0.765 in current study. In receiver-operating characteristic (ROC) curve the cut-off value of AEC < 40 cell/cu mm. At this cut-off value the sensitivity and specificity of AEC in diagnosing infection were found to be 72.5% and 61.8% respectively. These findings were statistically significant (P < 0.001).

Figure 1 shows blood culture was positive in 34 patients 46% which indicate infection group and negative in 40 patients (54%) which indicate non infection group.
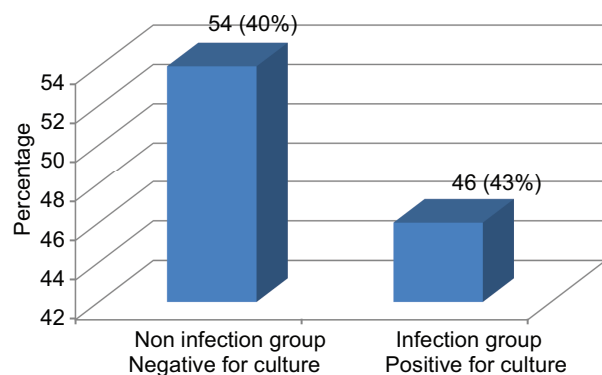
Fig.-1. *Bar diagram showing distribution of bacterial growth in study patients (n=74).*

Table I shows the AEC of the study patients. AEC <40 cells/cumm was found 25(73.5%) in infection group and 13(32.5%) in non infection group. AEC >40 cells/cumm was found 9(26.5%) in infection group and 27(67.5%) in non infection group. The mean AEC was found 18.3±11.4 cells/cumm in infection group and 145.0±57.7 cells/cumm in non infection group. The difference was statistically significant (P<0.05) between two groups.

Table I: Distribution of the study populations according to Absolute Eosinophil Count (AEC) (n=74)

AEC (cell/cumm)	Infection group (n=34)		Non infection group (n=40)		*p* value
	n	%	n	%	
<40	25	73.5	13	32.5	
>40	9	26.5	27	67.5	
Mean± SD	18.3±11.4		145.0±57.7		0.001

P value reached from unpaired t-test.
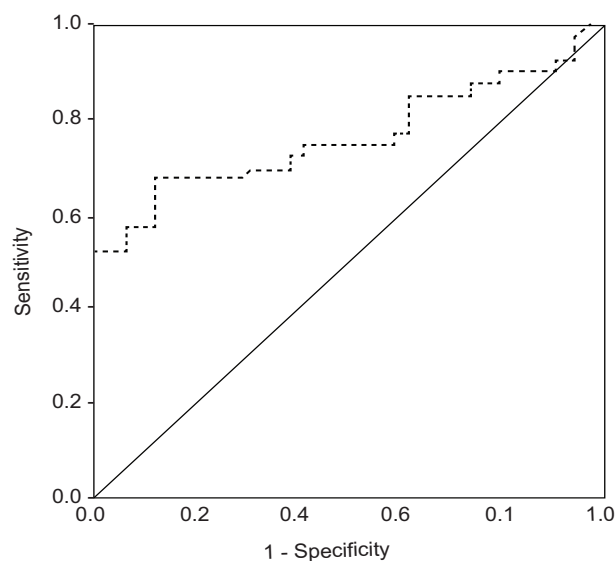
Fig.-2: *Receiver-operating characteristic (ROC) curve of AEC for prediction of infection*

Receiver-operating characteristic (ROC) curve of Absolute Eosinophil Count (AEC) for prediction of infection

The area under the receiver-operating characteristic (ROC) curves for the infection predictors is depicted in the following table. Based on the ROC curves AEC had the best area under curve. ROC were constructed using AEC of the patients with infection, which gave a AEC cut off value of (<40 cells/cu mm) as the value with a best combination of sensitivity and specificity for infection. At this AEC cut-off value of <40 cells/cu mm, the sensitivity and specificity of AEC in infection was found to be 72.5% and 61.8%, respectively (Table 1I and Fig 2). These findings were statistically significant (P< 0.001).

Table II: Receiver-operating characteristic (ROC) curve of AEC for prediction of infection.

	Cut off value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval(CI)	
						Lower bound	Upper bound
AEC	<40	72.5	61.8	0.765	0.001s	0.653	0.877

Discussion:

This cross sectional study was carried out to evaluated absolute eosinophil count for early diagnosis of sepsis compared with gold standard blood culture.

In our study mean age was found 54.7±13.4 year in infection group and 44.9±18.4 years in non infection group. The mean age was statistically significant(p less than 0.001) between two groups in unpaired t-test which indicates sepsis was associated with increased in age. Majority of patients were aged belonged to 31 to 50 years in non infection group and 51-70 years in infection group. Similar findings were found in other studies done by Wibrow et al[8], Shaban et al[9], Moura et al[14]. According to their study mean age was 62 years, 68 years and 58 years respectively. All of them found that sepsis was positively correlated with age. These findings were consistent with our study.

Analysis of sex distribution showed that out of 34 sepsis patients 27(79.4%) were male and 7(20.6%) were female. Predominance of male patients of sepsis was found in other studies done by Abidi et al[1], Abidi et al[1] showed that 58%sepsis patients were male and 42% were female. From the study of Ho et al (2009) 59% sepsis patients were male and 41% were female. These findings were nearly consistent with our study. Though exact reason for this male predominance is not known, it is probably due to the fact that the factors regulating the synthesis of gamma globulin are situated on the X chromosome. Male has only one X chromosome and is less immunologically protected than females[15].

In this study mean value of AEC was 18±11.4 cells/ cu mm in infection group and 145±57.4 cells/ cu mm in non infection group. The mean AEC difference was statistically significant (p less than 0.001) between two groups which indicates sepsis was associated with decreased eosinophil count. Similar findings were observed in the study done by Abidi et al[1], Shaban et al[9], Kadir et al[16], Gil et al[17], From the study of Kadir et al[16], mean AEC were 23±46 cells/ cu mm in sepsis and 143±101 cells/ cu mm in patients without sepsis. This finding was similar to our study. In previous study the sensitivity of eosinopenia in sepsis patient had a resonable range of variation. Our study showed

sensitivity 75.5% which was consistent with the study of Abdi et al[1]. From the study of Abidi et al[1], Bayram el al[13], Lopez et al[19], Gil et al[17], sensitivity was 71%, 61.4%, 64.8%, 64% respectively. These result were nearly consistent with our study. The present study has also defined the specificity of eosinopenia in sepsis patients. Our study showed specificity of eosinopenia for diagnosis of sepsis was 61.8% which was consistent with the study of Shaban et al[9]. According to their observation specificity was 65%. From the study of Lopez et al[19], Moura et al[14] specificity was 70.9%, 71% respectively. These results were nearly consistent with our study. The area under ROC curve for the sepsis was depicted in our study. The area under receiver operating characteristic curve was 0.765 in current study. This is similar to the observation of the study done by Shaban et al (2010) which was 0.72. Considering the sensitivity specificity, this study implies that eosinopenia is reliable as a diagnostic tool for sepsis.

The level of eosinophils in the body is normally tightly regulated[1]. Eosinophil production is regulated by IL-3, IL-5 and granulocyte macrophage colony stimulating factor. Without these cytokines, eosinophil can not survive. These cytokines are not significantly activated in patients with sepsis. It is believed to be main mechanism of eosinopenia in sepsis[8].

Conclusion:

The result from our study support that AEC is significantly lower in patients with sepsis. Eosinopenia may be a useful marker to distinguish the infected from non infected patients. An early diagnosis of sepsis is made by absolute eosinophil count that can be obtained from routine laboratory test (Complete blood Count) which is simple, quick, cost effective and readily available. In our study eosinopenia provide an effective guideline to make decision regarding judicious use of antibiotic therapy which will be life saving and minimize the risk of emergence of resistant organism due to misuse of antibiotics.

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