Original article

Absolute eosinophil count as a diagnostic and prognostic marker compared to C- reactive protein and Procalcitonin in patients with sepsis

Aneesh Puthiyedath Joy, Athira Bindu Murali*, Madhav Anantrao Joshi, Jafer Chalil Parambil

KIMS Al Shifa Super Speciality Hospital, Perinthalmanna, Malappuram, Kerala, 679322, India

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ABSTRACT

Objective: This study was undertaken to find out the usefulness of Absolute eosinophil count as a biomarker for sepsis, especially in Indian settings where cost constraints are the rule.**Methods:** A prospective observational study was carried out over a period of one year in KIMS Al Shifa Super Speciality Hospital which is a tertiary care referral hospital in Malabar region of Kerala. Patients admitted in the ICU with a diagnosis of Systemic Inflammatory Response Syndrome (SIRS) were included except those with hematological cancer, HIV infection, previous eosinophilia due to any cause, trauma patients or those on long term systemic steroids. Absolute eosinophil count estimation at time of admission, and on fifth day, were done manually using Neubauer counting chamber and confirmed using 5 part hematology analyzers ADVIA 2120 (Peroxidase method). The statistical analysis was carried out using the software, Statistical Software for Social Sciences 20.0.**Results:** The mean value of AEC in different categories of sepsis group was found to be significantly low in septic shock and refractory septic shock patients compared to other categories ($p = 0.04$), whereas CRP levels were significantly higher in all sepsis groups ($p < 0.001$). When the diagnostic performance of AEC, CRP and PCT were evaluated, Procalcitonin showed maximum sensitivity (89.5%) on day 1 with a cut off value of 0.5 mcg/L in diagnosing sepsis from SIRS patients. AEC shows maximum specificity (95.65%).**Conclusion:** It is concluded that Absolute eosinophil count below 50 cells/mm³ is a very specific but poorly sensitive indicator to differentiate sepsis from SIRS. A low value of eosinophil in SIRS patients should alert the physician regarding the possibility of severe sepsis and should direct treatment plan accordingly.

1. Introduction

Sepsis is a highly heterogeneous syndrome which is the net result of interactions between the host and the pathogen involving various biochemical mediators and cascades of inflammation. Sepsis Definitions Task Force in 2016 proposed the Third International Consensus Definitions specifying that sepsis is a dysregulated host response to infection that leads to acute organ dysfunction.¹ In 1991 the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) Consensus Conference defined sepsis as a Systemic Inflammatory Response Syndrome (SIRS) that has a proven or suspected microbial aetiology. The clinical expression varies, and several factors influence the severity like infectious aetiology, site of infection, genetic background, comorbidities, immune status, age, time to initiation of treatment and appropriate treatment.²

The usefulness of various biomarkers has been studied in the diagnosis of sepsis. To be clinically useful, a sepsis biomarker needs to

provide information additional to that already available from established clinical assessments (e.g. history and examination) and investigations [e.g. white cell count (WCC)]. To do this, it needs to be able to differentiate accurately, bacterial infection from non-infective causes of SIRS, and be available in a timely and cost-effective manner. The utility of a biomarker is potentially further enhanced if it can indicate the severity of infection and is able to act as a guide to the effectiveness of therapy.³ The need for a good biomarker is again emphasized by the fact that, a 1 h delay in diagnosis and initiation of antimicrobials increases the mortality up to five folds.⁴ The available biomarkers include CRP, Procalcitonin interleukin-6 (IL-6), triggering receptor expressed on myeloid cells-1 (TREM-1) etc. Among these biomarkers Procalcitonin (PCT) and CRP has been the most studied and, in some countries, is now being included in routine clinical practice and guideline recommendations.⁵ Adequate and detailed studies on eosinopenia as a marker of sepsis are lacking. Routinely, eosinophils do not attract much attention as far as sepsis is concerned. Neutrophils and

* Corresponding author.

E-mail address: bm.athira@gmail.com (A.B. Murali).<https://doi.org/10.1016/j.cegh.2019.12.017>

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platelets get all the attention. CRP and Procalcitonin are considered more reliable, after multiple studies have established that overall, these parameters are useful in diagnosing and prognosticating sepsis.

However the main drawback is their cost effectiveness. The availability of these tests is limited to urban areas mainly; peripheral areas need to send samples to large laboratories which also entails considerable delay. Therefore a cheaper, simpler and faster biomarker which is reliable, if available, will lead to faster diagnosis and thereby earlier treatment of sepsis. It is here that eosinophil count in sepsis becomes important since even the simplest laboratory and technician can perform the count at a very low cost. Therefore this study assumes importance.

Eosinopenia is proposed as one potential biomarker in sepsis by different studies which have showed that eosinophil counts are low in infection and sepsis.^{6,7} As the eosinophil count is already measured in routine clinical investigations, it would entail no additional costs. If comparable sensitivity and specificity could be demonstrated with established markers like Procalcitonin and CRP to diagnose and prognosticate sepsis, eosinophil count could be a very useful tool for clinician's at least in the group of patients with low socioeconomic status.⁴ Hence, this study was undertaken to find out the usefulness of Absolute eosinophil count as a biomarker for sepsis, especially in Indian settings where cost constraints are the rule. Additionally the prevalence of parasitic infestations very common in India and AEC as a marker of sepsis was tested in this setting. In addition, we analyzed the reliability of these biomarkers to predict mortality cohort in patients with sepsis.

2. Materials and methods

2.1. Study site and design

A prospective observational study was carried out over a period of one year during 2017–2018 in KIMS Al Shifa Super Speciality Hospital which is a tertiary care referral hospital in Malabar region of Kerala. The study was initiated with prior approval from the Hospital Ethics Committee and written informed consents were obtained from the patients or their relatives before enrolling the patient into the study. Male and female patients above 18 years of age, admitted in the ICU with a diagnosis of Systemic Inflammatory Response Syndrome (SIRS) were included. Patients excluded in this study were those on long term steroids because steroids directly affect eosinophil count, hematological cancer patients since several cancers affect eosinophil count directly or indirectly, people infected with HIV since infection affects the marrow and any patient with previous history of eosinophilia or eosinopenia.

Baseline data of all the participants were collected which included the clinical and laboratory parameters.

The patients were then classified into one of the two groups: SIRS without Sepsis and SIRS with sepsis as per the old American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) Consensus Conference and 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. SIRS with sepsis group was further classified as sepsis, severe sepsis, septic shock^{2,8} and refractory septic shock. Refractory septic shock was defined as Septic shock that lasts for > 1 h and does not respond to fluid or pressor administration.⁴ This classification was further reviewed after obtaining the final diagnosis.

Each patient was evaluated with respect to their age, sex, principal diagnosis, vital signs and comorbid conditions like diabetes mellitus, hypertension, chronic kidney disease (CKD), chronic liver disease, coronary artery disease (CAD), stroke, chronic obstructive pulmonary disease (COPD) and malignancy. The white blood cell count, the absolute eosinophil cell count, the CRP level and the procalcitonin levels were systematically recorded on admission to the ICU for all patients and on day 5 for the survivors.

Blood samples were obtained by venipuncture on admission. Blood cultures were taken if a patient's body temperature exceeded 38.3 °C

(101 °F), if a patient has clinical signs of severe sepsis, or if there was a need for vasopressor therapy for suspected septic shock. Other cultures including urine, cerebrospinal fluid, and respiratory secretions (including a sputum specimen for Gram stain) were obtained according to the clinical circumstance and optimally before antibiotics were given. Empirical antibiotic treatment was based on the presumptive diagnosis when bacteriological results became available, antibiotics were modified according to the pathogen isolated and the antimicrobial susceptibility test results.

Absolute eosinophil count estimation at time of admission, and on fifth day, was done manually using Neubauer counting chamber and confirmed using 5 part hematology analyzers ADVIA 2120 (Peroxidase method). Lower limit of detection was 10/mm³. C-Reactive Protein Levels estimation was based on latex enhanced turbidimetric immuno assay. Measurement range is 1–200 mg/L and Serum Procalcitonin assay (B.R.A.H.M.S) was performed using an automated test performed on Vidas, by ELFA (Enzyme Linked Fluorescent Assay) method. The assay principle combines a one step immune-assay sandwich method with a final fluorescent detection. Measurement range is 0.05–200 ng/mL was based on Enzyme-linked fluorescence assay technique.

2.2. Statistical analysis

The statistical analysis were carried out using the software, Statistical Software for Social Sciences 20.0. The data on patients' categorical variables such as gender, comorbid conditions etc. were expressed as frequencies and percentages. Data would be presented as mean + standard deviation or as median (inter quartile range) after testing the normality of the data using Kolmogorov Smirnov test. The comparison of categorical variables between the clinical outcomes was carried out using chi-square test or Fisher's exact test. The comparison between the three groups was carried out using the one way ANOVA or Kruskal – Wallis test. A p value < 0.05 was considered as statistically significant. Sensitivity, specificity, PPV and NPV were calculated for AEC, CRP and procalcitonin. Area under ROC curve was also calculated for the variables.

3. Results

The minimum sample size was estimated as 62 based on specificity of 91%, 1.96 at 5% level of significance. 71 Patients who fulfilled the criteria for SIRS were enrolled in the study, out of which 43 were males and 28 were females. The majority of the patients were above the age of 60 years. The mean age of the population was 61 ± 18.15 years. 48 patients (67.7%) were having SIRS with sepsis and 23 patients (32.4%) were having SIRS without Sepsis. 15.5% of patients were fulfilling 2 SIRS criteria, 45% were having 3 SIRS criteria and 39.4% fulfilled all the 4 SIRS criteria. Even though sepsis group and no-sepsis group were almost equal in number of patients with 2 and 3 SIRS criteria, number of patients fulfilling all the 4 SIRS criteria was significantly higher in sepsis group. (89.28% in sepsis group and 10.71% in no-sepsis group.) The patients in the sepsis group were again categorized according to severity of sepsis into Sepsis (16.6%), Severe sepsis (20.8%), Septic shock (43.7%) and Refractory septic shock (18.7%). Diabetes mellitus was found to be the most common co morbidity among the study subjects which was present in 32.8% of patients followed by Hypertension (21%), CAD (13.4%) and CKD (10.9). Regarding aetiology of sepsis, UTI was the most prevailing (33%) while Pneumonia ranked second (23%). In 17% of cases a definite diagnosis on source of infection could not be made. 47.92% of patients showed culture positivity. Blood culture positivity was only 14.5%. The mortality rate of the study sample was found to be 32.4%. The mortality rate among SIRS without sepsis was identified as 39.1%, whereas, the same among sepsis group was appraised as 29.17%. The mortality was around 90% in refractory septic shock patients. The mean age in non survivors and survived is around 60 and increased mortality is not seen with age in patients with sepsis

Table 1
Mean value of AEC in different categories of sepsis group.

AEC 1	N	Mean	Std. Deviation	F	P-value (one-way ANOVA)
SIRS No Sepsis	23	208.26	126.515	2.59	0.04
SIRS Sepsis	9	155.56	115.338		
Severe Sepsis	9	179.50	105.871		
Septic Shock	21	132.86	96.288		
Refractory Septic Shock	9	88.89	45.399		
Total	71	160.50	111.373		

($p = 0.09$) and SIRS group without sepsis ($p = 0.27$).

It was found that the mean value of CRP on day 1 was significantly greater in sepsis group compared to no sepsis group ($p < 0.001$) and mean value of AEC on day 1 was significantly lower in sepsis group than no Sepsis group ($p = 0.01$) in independent *t*-test. The median value of Serum Procalcitonin in no sepsis group was 0.9 and in sepsis group was 10 which showed significant difference with $p < 0.001$ on analysis using Mann-Whitney *U* test.

The mean value of AEC in different categories of sepsis group was analysed using one-way ANOVA and was found to be significantly low in septic shock and refractory septic shock patients compared to other categories ($p = 0.04$) (Table 1), whereas CRP levels were significantly higher in all sepsis groups ($p < 0.001$). The value of serum Procalcitonin on day 1 is significantly increased with grade of sepsis with $P < 0.001$ in Kruskal Wallis test. The mean and median value of Procalcitonin and CRP is significantly low on day 5 compared to day 1 in patients who survived. The mean value of AEC is higher on day 5 than day 1 ($p = 0.001$).

When the diagnostic performance of AEC, CRP and PCT were evaluated, Procalcitonin showed maximum sensitivity (89.5%) on day 1 with a cut off value of 0.5 micg/L in diagnosing sepsis from SIRS patients. AEC shows maximum specificity (95.65%). AEC has got maximum positive likelihood ratio also (4.79) [Table 2]. ROC curves were also used to illustrate the diagnostic performance [Figs. 1 and 2]. Area under the curve was maximum with CRP (0.82) and minimum for AEC (0.689) in diagnosing sepsis from SIRS patients.

Correlation of various factors with outcome was assessed and it was found that there was no significant correlation between age and 5th day mortality. Spearman Correlation was used to identify correlation between survival and values of PCT, AEC and CRP on day 1. There found to be no significant correlation as the *p* values were greater than 0.05 (Table 3).

4. Discussion

This prospective observational study included 71 patients with a clinical diagnosis of SIRS, as defined by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) Consensus Conference.^{2,8} Out of the 71 patients, 43 were males and 28 were females. The study population was an older group with mean age of 61. Majority of patients in sepsis group were critically ill with 44% in septic shock and 19% in refractory septic shock. The overall mortality

Table 2
Diagnostic performance of AEC, CRP and serum Procalcitonin on day 1.

	CRP day 1	AEC Day 1	PCT Day 1 (0.5 cut-off)	PCT Day 1 (2 cut-off)
Sensitivity	72.92	20.8	89.58	83.33
Specificity	82.61	95.65	34.78	56.52
Positive predictive value	89.74	90.91	74.14	80.0
Negative predictive value	59.38	36.67	61.54	61.90
Positive likelihood ratio	4.19	4.79	1.37	1.92

in study subjects was 32.4% and in sepsis group was 29.2%. The 5 day mortality in SIRS group with sepsis was 39.1%. Mortality was very high in patients with septic shock and refractory septic shock. The high mortality rate in the study group may be due to critical nature of study group, older age. The high mortality of SIRS without sepsis may be due to the critical nature of disease.

The mortality in sepsis is correlated to severity and ranges from 18% to 56% in various studies done previously. In a study by Martin et al.,⁹ the mortality was 18% which was lower than the present study and a study by Grozdanovski et al.,¹⁰ showed higher mortality rate, that was 51.6%. In a study conducted by Jain et al.¹¹ in a tertiary care hospital in India, the mortality was found to be 43% which was comparable to the current study. Diabetes mellitus which was present in 39% of patients appeared to be the most common comorbidity in all subsets of population followed by hypertension which accounted for 25%. There was no statistical difference in distribution of comorbidities in SIRS group and sepsis group. Urinary tract infection and community acquired pneumonia constituted the majority of cases of sepsis which were 33% and 23% respectively. This finding was consistent with the study by Shaaban et al.,⁷ in which infections related to pneumonia were 39% and urinary tract infections were 29%. In SIRS without sepsis group the common causes were acute coronary syndrome, pulmonary edema, acute pancreatitis, COPD & bronchial asthma exacerbation. The studies of Shaaban et al.⁷ and Abidi et al.⁶ also have similar aetiology in SIRS patients without infection group. In the present study the total culture positivity in sepsis patients was 47% whereas in Shaaban's study⁷ it was 61%. In the present study blood culture positivity was only 14.5% however in Jose Garnacho-Montero's study¹² it was 30%. The lower blood culture positivity in present study may be attributed to prior antibiotic treatment in another hospital before being referred to our hospital. Severe sepsis (sepsis with any organ dysfunction) was seen in 19% of cases and 44% patients had septic shock and 19% had refractory septic shock. The mortality was 89.9% in patients with refractory septic shock which was 30% in Abidi et al.'s study⁶ and 71.4% in Grozdanovski et al.'s study.¹⁰

The mean value of CRP and AEC on day 1 in total study group were 79.3 mg/L and 160 cells/mm³ respectively. The median value of procalcitonin was 3.8 (0.56–29.84). The mean and median values of CRP and procalcitonin on day 1 were significantly greater in SIRS with sepsis group than SIRS without sepsis. The value of absolute eosinophil count was significantly lower in SIRS with sepsis group. The studies by Abidi et al.⁶ and Shaaban et al.⁷ showed similar results but the mean value of eosinophil count was lower compared to the present study in all groups. Very low eosinophil counts, even zero/mm³ were observed in their studies but in the present study it was above 80/mm³ in all groups. However studies by Savitskiy A¹³ and EB Moura¹⁴ showed higher mean values of eosinophil counts which was in accordance with the current study. The mean value of absolute eosinophil count was the lowest in refractory septic shock and lower in septic shock which was statistically significant. These findings are in agreement with Abidi's study⁶ but with a higher mean value of AEC. Median Procalcitonin levels were the highest for refractory septic shock patients followed by septic shock patients and the lowest in severe sepsis patients. It was also higher in SIRS with uncomplicated sepsis than non sepsis group. This observation is in accordance with the previous studies on procalcitonin in sepsis by Brunkhorst et al.¹⁵ and Al-Nawas et al.¹⁶

CRP also showed similar trends and was increasing with severity of sepsis same as noted by Abidi's study.⁶ The same cut off values as in previous studies by Shaaban et al.⁷ and Abidi et al.⁶ were used for the present study. At a cut off value of 50 cells/mm³, AEC yielded a sensitivity of 20.8% and specificity of 95.65% with a positive predictive value of 90.9% and negative predictive value of 36.67% in diagnosing sepsis from SIRS. A higher cut off value of 100/mm³ was used in Savitskiy's study¹³ but showed similar results. In the present study higher cut off values were not used because the ranges of eosinophils are normally between 40 and 440/mm³. In this study a value of CRP above

Fig. 1. Receiver Operating Characteristic (ROC) curve for CRP and Procalcitonin on day 1.

70 mg/L yielded better sensitivity and specificity. Procalcitonin which is said to be the most promising biomarker of sepsis had sensitivity and specificity of 89.5% and 34.7% respectively with a cut off of 0.5 µg/L. A cut off of 2 microgm/L as used in some studies has sensitivity and specificity of 83.3 and 56.5 respectively. This poor diagnostic performance of procalcitonin in current study was in accordance with a large

Table 3
Correlation between PCT CRP and AEC on day 1 with outcome.

		PCT Day 1	AEC Day 1	CRP Day 1
Outcome	Correlation coefficient	−0.084	0.144	0.015
	P-value	0.484	0.230	0.898

Fig. 2. Receiver Operating Characteristic (ROC) curve for AEC on day 1.

meta analysis of 18 studies which assessed the ability of procalcitonin to identify sepsis from SIRS patients and found that Procalcitonin has only 71% of sensitivity and specificity.¹⁷ The importance of present study relies in this fact that a very costly investigation like procalcitonin is yielding low diagnostic performance only and hence there is obviously a scope for a cheap biomarker with comparable or even less accuracy.

Area under ROC curve were 0.68 (95% confidence interval 0.56–0.82) for AEC, 0.76 (95% confidence interval 0.64–0.88) for procalcitonin and 0.82 (95% confidence interval 0.72–0.94) for CRP. In the present study CRP seemed to be the most promising biomarker at a cut off value of 70 mg/dL.¹⁸ Vanderschueren et al.'s study¹⁸ also proved that extremely high CRP above 50 mg/dL has very high diagnostic ability for bacterial infection. In the present study AEC below 50 cells/mm³ was found to have very high specificity and positive predictive value for sepsis but very poor sensitivity and negative predictive value. The chance of higher eosinophil counts in population exposed to multiple tropical parasites could be a possible explanation for higher eosinophil counts noted in all study groups. In this context the normal AEC range in the population has to be determined. Still a low eosinophil count during a routine screening can alert the physician regarding the possibility of severe sepsis. In the present study there was no significant difference in age between survivors and non survivors. This may be because of the reason that severe sepsis even in lower age group causes higher chance of mortality. Absolute eosinophil count was observed to be lower in non survivors than those who survived after 5 days (p value 0.07). But no correlation was found between eosinophil count and outcome which is consistent with the findings of study by Escobar-Valdivia and Merino.¹⁹ AEC on day 5 is significantly higher in survivors than on day 1. Neither Procalcitonin nor CRP showed any prognostic value in this study.

The following facts strengthen the present study. There was a diverse patient population with a variety of ICU diagnoses in the study sample. Similar to Abidi's⁶ and Shaaban's⁷ studies, it was a real-life study. In addition we were able to compare eosinophil count with the more accepted procalcitonin which was not done in previous studies.

The study has some limitations also. One is the small sample size. Secondly, the investigators were not blinded from the results. Thirdly, severity scores like APACHE 2 and SOFA score were not assessed. Finally, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3)¹ was released only during the concluding time of our study hence could not be incorporated.

Further studies are required in assessing the normal range of eosinophils in tropical setting and for better cut offs in sepsis. Procalcitonin and CRP are better markers of sepsis, but they are not ideal markers and their diagnostic performance should be reassessed in large multi centric studies.

5. Conclusion

It is found that Absolute eosinophil count below 50 cells/mm³ is a very specific but poorly sensitive indicator to differentiate sepsis from SIRS. It should be noted that a normal eosinophil count does not rule out sepsis and the role of Eosinopenia as an indicator of mortality seems

to be doubtful. However it can be stated that an increase in AEC and a corresponding decrease in CRP and Procalcitonin may indicate an improvement in sepsis process. Overall it is concluded that, a low value of eosinophil in SIRS patients should alert the physician regarding the possibility of severe sepsis and should direct treatment plan accordingly.

Declaration of competing interest

The authors have none to declare.

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