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Eosinopenia as a Diagnostic Marker of Sepsis in Critically Ill Patients

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ABSTRACT

Background: sepsis refers to the presence of a serious infection that correlates with systemic and uncontrolled immune activation. Few studies had analyzed eosinophil count as a prognostic marker of outcome in patients with infection. Eosinopenia is an interesting biomarker because the eosinophil count is always measured in clinical practice and the additional costs would therefore be negligible.**The aim of this wrk:** this studyaimed to test the value of eosinopenia in the diagnosis of sepsis in critically ill patients admitted to ICUs. **Patients and Methods:** this prospective observational, randomized study was conducted on 50 adult critically ill patients who were admitted to ICU of Ahmed Maher Teaching Hospitalin the period from March 2017to July 2017. They either had sepsis on admission or not. An informed written consent was obtained from patients and/or relatives before starting this study. **Inclusion criteria** were patients more than 18 years old and less than 60 years that were critically ill either in sepsis or not. **Exclusion criteria** were patients less than 18 years old and more than 60 years old, patient or relatives who refused to be included in this study, those with hematological cancer, HIV infection, bronchial asthma and other atopic disorders like hay fever, atopic dermatitis and allergic conjunctivitis and increased levels of eosinophil count as part of any parasitic infection or trauma patients. **Results:** comparison between infected and non-infected studied patients was statistically significant as regard variables of SOFA score, APACHE II score at admission, TLC and Eosinophil count at admission (p-value<0.05). There were no statistical significant differences as regard length of ICU stay (p>0.05). Multivariate regression analysis showed statistically significant differences and was independent predictors for infection as follow: total leucocytic count, eosinophil count at admission and SOFA score. The AUC for eosinophil count to predict was 95% with optimal cut off value was 50 cells/mm^3 with a sensitivity of 92.85% and specificity of 93.33% with P value <0.001.**Conclusion:** the result of the present study revealed that eosinophil counts was <50 cells/mm3 at admission time to ICU was a predictor for diagnosis of sepsis in critically ill patients. However, eosinophil counts at admission time to ICU were not a specific indicator of mortality. **Recommendations:** eosinophil counts are cheap and easily accessible test can be used to guide for sepsis diagnosis and treatment.Larger studies are needed to determine the prognostic value of this test and establish better cutoff values.

Keywords: eosinopenia, sepsis, critical patients, adult.

INTRODUCTION

Sepsis refers to presence of a serious infection that correlates with systemic and uncontrolled immune activation [(1)]. Patients die as a result of organ failure as the disease elicits an exacerbated and damaging immune response with approximately 250,000 cases leading to fatalities in the USA annually [(2)].Owing to the broad and vague definition of sepsis along with its various manifestations and severity levels in different patient populations, a definitive biomarker that can aid in therapeutic strategies could be difficult to scertain. More than 100 different molecules have been suggested as useful biomarkers of sepsis [(3)].The international sepsis forum colloquium on biomarkers of sepsis was convened in 2005 to develop a systematic framework for the identification and validation of biomarkers of sepsis [(4)].The diagnosis of sepsis is difficult, particularly in the ICU where signs of sepsis may be present in absence of a real infection [(5)].The effort of many investigating groups has been to find a reliable marker to discriminate the inflammatory response to infection from other types of inflammation. Gold standards for the diagnosis of infection do not exist, but procalcitonin is known to be among the most promising sepsis markers in critically ill patients and is capable of complementing clinical signs and routine laboratory variables that are suggestive of sepsis[(6)].Several biomarkers, such as C-reactive protein and procalcitonin,have been used to indicate bacterial infection. These biomarkers could also provide prognostic information in distincting infectious processes and in patients with sepsis[(7)].

A study analyzed eosinophil count as a prognostic marker of outcome in patients with infection, but its utility as a marker of outcome in patients with bacteremia was unknown[(8)].

A study used eosinophil counts, specifically eosinopenia, as a marker of infection [(9)]and as an indicator of bacteremia, but theresults were controversial.Eosinopenia would be an interesting biomarker because the eosinophil

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count is always measured in clinical practice and the additional costs would therefore be negligible[10].A study performed in an emergency department demonstrated that profound eosinopenia is very specific for sepsis, and it was suggested that it may become a helpful tool in daily practice [11].The eosinophil count has been revisited in recent decades, especially eosinopenia; [;;p some authors consider a criterion of SIRS. There is no precise cut-off value in the literature to define eosinopenia, with different authors reporting values ranging from <40/mm3 [12] to <50/mm^3[13].

Aim of the Work

The aim of this study was to test the value of Eosinopenia in the diagnosis of sepsis in critically ill patients admitted to ICUs.

Patients and Methods

This study was a prospective observational, randomized double blinded single-center study, it was conducted on 50 adult critically ill patients who were admitted to ICU of Ahmed Maher Teaching Hospital in the period of March 2017 to July 2017either they had sepsis on admission or not.An informed written consent was obtained from patients and/or relatives before starting this study.

Primary outcome measure:

Test the value of esinopenia in diagnosis of sepsis in critically ill patients.

Secondary outcome measures:

Morbidity and mortality and effect of early diagnosis of sepsis on length of ICU stay.

Inclusion Criteria

All patients weremore than 18 years old and less than 60 years old that were critically ill either in sepsis or not.

Exclusion Criteria

- Patients less than 18 years old and more than 60 years old.
- Patient or relatives who refused to be included in this study.
- Those with hematological cancer.
- HIV infection.
- Bronchial asthma and other atopic disorders like hay fever, atopic dermatitis and allergic conjunctivitis.
- Increased levels of eosinophil count as part of any parasitic infection.

The diagnosis of SIRS, severe sepsis and septic shock was established according to the definitions of the American College of Chest Physicians consensus conference [14]. All patients received standard supportive treatment following recommendations of the surviving sepsis campaign released in 2008 [15].

S**epsis diagnosis** requires the presence of infection (which can be proven or suspected) and 2 or more of the following criteria:

- Hypotension (systolic blood pressure < 90 mm Hg or fallen by >40 mmHg from baseline, mean arterial pressure < 70 mm Hg).
- Mottled skin.
- Decreased capillary refill of nail beds or skin.
- Fever> 38.3 degrees C, or 101 degrees F.
- Hypothermia< 36 degrees C core temperature (<96.8 degrees F).
- Heart rate > 90 bpm.
- Tachypnea.
- Change in mental status.
- Acute drop in urine output (<0.5 ml/kg/hr for at least 2 hours despite fluid resuscitation, or about 35 ml/hour for a 70 kg person).
- Significant edema or positive fluid balance (>20 mL/kg over 24 hours).
- Absent bowel sounds (ileus).
- Eosinophils counts under40 cells/mm3.
- Lactate> 1 mmol /L.
- Arterial hypoxemia (PaO2 / FiO2< 300).
- White blood cell count > 12,000 or less than 4,000, or with >10% "bands" (immature forms).
- Elevated C-reactive protein in serum (according to lab's cutoffs).
- Elevated procalcitonin in serum (according to lab).
- Creatinine increase > 0.5 mg/dL.
- INR> 1.5 or APTT> 60 seconds.
- Platelet count < 100,000.
- High bilirubin (total bilirubin > 4 mg/dl).
- Hyperglycemia (>140 mg/dL) in someone without diabetes.

Study design:

All patients were subjected to the followings:

1. Full history: including personal data, special habits as smoking, co-morbidities as diabetes, hypertension, renal impairment or cardiac disease.
2. Hemodynamic monitoring: Daily hemodynamic monitoring of the patients:
   - Arterial blood pressure
   - Heart rate
   - Respiratory rate
   - Temperature
   - Urine output
   - CVP measurement
3. Daily clinical examination: daily full clinical examination
4. Lab profile: Routine laboratory investigations on day of admission and during stay in ICU:
   - Liver function tests.
   - Coagulation profile.
   - Kidney function tests.

- Blood gases
- Cultures & sensitivity according to source of sepsis
- CBC: The eosinophil counts were performed by automated analyzer.

5. Radiological
   - CXR, some patients underwent Ct chest, abd. U/S & Echo
6. Early Goal directed therapy will be initiated for all patients:
   - Early empirical broad spectrum antibiotics
   - Maintain mean blood pressure > 65 MMHG
   - Maintaining CVP 8-12 CMH2O
   - Maintaining UOP 0.5-1 ml/kg/hour
7. Patients data were collected as regard
   - Causes of admission.
   - Eosinophil count for patients on admission to ICU.
   - Infection Data
   - Infection site (pulmonary, genitourinary, abdomen and surgical wound).
   - Pathogenic Bacteria (Gram +ve,-ve Bacteria and fungi)detected by cultures from (blood,urine, sputum and wound swap)
   - Morbidity and Mortality.
   - Length of ICU Stay.
8. Scoring System: at ICU admission, severity of the illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, considering the worst data point for the first 24 hours in the ICU [(16)]. Failure of organs and severity of multiple organ dysfunction syndromes was assessed by the Sequential Organ Failure Assessment (SOFA) scale [(17)].

Table 1: acute physiology and chronic health evaluation II score [(18)]

A- Glasgow Coma Scale	B - Age Points	C- Chronic Health Points	
Eyes open 4 - spontaneously 3 - to verbal 2 - to painfulstimul 1 - no response **Verbal** 5 - oriented 4 - disoriented and talks 3 –in appropriate words 2 in comprehensible Sounds 1 - no response **Motor** 6 - response to verbal command 5 - localizes to pain 4 - withdraws to pain 3 – de corticate 2 – de cerebrate 1 - no response	Age points <44 0 45-54 2 55-64 3 65-74 5 >75 6	Liver Cardiovascular Pulmonary Kidney Immune If any of the 5 CHE categories is answered with yes give +5 points for non-operative or emergency post-operative patients ▪ Cirrhosis with portal hypertension or encephalopathy ▪ Class IV angina or at rest or with minimal self-care activities ▪ Chronic hypoxemia or hypercapnia ▪ polycytaemia of pulmonary hypertension >40mmHg ▪ Chronic peritoneal or hemodyalys ▪ Immunecompromised host	**Apache-II Score** (sum of A+B+C) A APS points + B Age points + C Chronic Health Points

Table 2:SOFA score[17]

Variable	SOFA Score				
	0	1	2	3	4
Respiratory PaO_2/FiO_2 mmHg	> 400	< 400	< 300	< 200✵	100✵
Coagulation Platelets x 103/µL#	> 150	< 150	< 100	< 50	< 20
Liver Billirubin, mg/dL#	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mmHg	Dop< 5 or dob (any dose) §	Dop> 5, epi< 0.1, Or norepi < 0.1§	Dop> 15, epi> 0.1, or norepi > 0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	< 6
Renal Creatinine, mg/dL or urine output, mL/d‖	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9 or < 500	> 5.0 or < 200

* Norepi Indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and FiO2, fraction of inspired oxygen. ✵Values are with respiratory support. # To convert bilirubin from mg/dL to µmol/L, multiply by 17.1. § Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).

To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

Sample size justification:

MedCalc® version 12.3.0.0 program was used for calculations of sample size, statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%**,**According to a previous study [13],showed that the Non infection versus infection of Eosinophils at <50 cells/mm3 yielded a sensitivity of 85% (95% CI, 71% to 86%), a specificity of 91% (95% CI, 79% to 96%), a positive likelihood ratio of 9.12 (95% CI, 3.9 to 21), and a negative likelihood ratio of 0.21(95% CI, 0.15 to 0.31), also SIRS versus infection Eosinophils at <40 cells/mm^3 yielded a sensitivity of 85% (95% CI, 71% to 86%), a specificity of 80% (95% CI, 55% to 93%), a positive likelihood ratio of 4 (95% CI, 1.65 to 9.65), and a negative likelihood ratio of 0.25 (95% CI, 0.17 to 0.36), So it can be relied upon in this study, based on this assumption, sample size was calculated according to these values produced a minimal samples size of 48 cases were enough to find such a difference. Assuming a drop-out ratio of 5%, the sample size will be 50 cases.

Statistical analysis

The collected data were tabulated and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 22.0.

Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) minimum and maximum of the range and for numerical non parametric data as median and 1^{st}& 3^{rd} inter-quartile range, while they were done for categorical data as number and percentage. Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non-parametric data. Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.Inferential analyses were done for qualitative data using Chi square test for independent groups. The level of

significance was taken at P value <0.050 is significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance. **The study was approved by the Ethics Board of Ain Shams University.**

RESULTS

This was a prospective randomized double blinded study that was conducted in Ahmed Maher Teaching Hospital. Fifty patients were included in this study and an informed written consent was obtained from patients and /or relatives. All patients were adults, more than 18 years old, admitted to ICU either had sepsis on admission or not in the period fromMarch2017toJuly2017.

Table 3: baseline characteristics of studied patients.

Baseline Characteristics of Study Patients	n (%) 50	MEAN ± SD
Age (years)		**50.38 ± 5.35**
Male	27(54%)	
Female	23(46%)	
Risk factors		
Smoking	18(36%)	
Dyslipidemia	16(32%)	
DM	30(60%)	
Hypertension	34(66%)	
Admission category		
Medical	42 (84%)	
Surgical	8(16%)	
Infection group		
Infected	28(56%)	
Non-infected	22(44%)	

Table 3 showed that 50 patients were included in this study, their ages with a mean of 58.38±13.35years. 27 patients (54%) were males and 23 patients (46%) were females. The most frequent risk factors were hypertension (66%) followed by diabetes (60%) beside other risk factors as smoking and dyslipidemia. The patients were admitted post-surgical interventions 8 (16%) or for medical reasons 42 (84%).

Table 4:comorbidities characteristics of the studied patients

Comorbidities	n	%
Past history of IHD	18	36%
history of cerbrovascular stroke (CVS)	6	12%
COPD or chest diseases	6	12%
Urinary	7	14%
Liver diseases	1	2%
Autoimmune diseases	1	2%

In **table 4** comorbidities in the studied patients were mostly IHD 36% thenrenal diseases14%, COPD or chest diseases12%, old CVS 12%. The least Comorbidities were liver diseases 2.2% and autoimmune diseases 2.2%.

Table 5: source of infection in the infected patients

Source of infection	n=28	%
Abdominal	3	10.7%
Respiratory	14	50%
Urinary	5	17.9%
Skin and soft tissues	1	3.57%
Mixed	4	14.28%
Others	1	3.57%

In **table 5** sources of infection in the infected patients were mostly respiratory 50% then renal 17.9%, mixed 14.28% and abdominal diseases10.7%. The least sources of infection were skin and soft tissues 3.57% and others (infection from central venous line)3.57%.

Table 6: means of total leucocytic count and Eosinophil count at admission in the studied patients

Variable	Mean	standard deviation
Total leucocytic count	14.73	±8.10
Eosinophil count	84.26	±32.26

In **table 6** means of total leucocytic count and Eosinophil count at admission were 14.73±8.10 and 84.26±32.26 respectively.

Table 7: **positive cultures in the studied patients**

Positive cultures	n=28	%
Gram +ve only	3	10.71%
Gram –ve only	11	39.28%
Polymicrobial	12	42.85%
No growth	2	7.14%

In **table 7** infection in the studied patients were gram -ve only 11(39.28%) and polymicrobial 12(42.85%). The least were gram +ve only 3(10.71%). No growth was in 2 cases 7.14%.

Table 8: **types of organisms in culture-positive infected patients**

Types of organisms		Frequency (%)
Gram-positive	Staphylococcus aureus	10.71%
	MRSA	3.57%
	Staph. epidermidis	3.57%
	Strept. pneumoniae	7.14%
	Enterococcus	3.57%
	Others	3.57%
Gram-negative	Pseudomonas species	14.28%
	Escherichia coli	21.42%
	Klebsiella species	25%
	Proteus mirabilis	7.14%
	Acinetobacter species	16.52%
	Enterobacter	3.57%
	H. Influenzae	7.14%
	Others	3.57%
Fungi	Candida	3.57%

In **table 8** in gram positive bacteria, *Staphylococcus aureus* and *Strept. pneumonia* were more prevalent (10.7% and 7.142% respectively. In gram negative bacteria, *Escherichia coli* and *Klebsiella* species were more prevalent (25% and 21% respectively). *Pseudomonas* species, *Proteus mirabilis,Acinetobacter* species, *H. influenzae*, *Enterobacter* and others were 14.28%, 7.14%, 16.52%, 3.57%, 7.14% and 3.57% respectively. Fungal infection was caused by candida in 3.57% patients.

Table 9: **follow-up parameters in ICU in the infected patients**

Follow-up parameters in ICU		Mean± SD	n=28 %
SOFA score at admission (Points)		6.94±3.67	
Mean SOFA score during study period		8.72±5.41	
APACHE II score at admission (Points)		18.08±10.17	
Length of ICU stay (days)		9.52±5.007	
Outcome in ICU	*Survival*		21(75%)
	Mortality		7(25%)

In **table 9** mean of SOFA score at admission was 6.94±3.67 (Points). Mean SOFA score during study period 8.72±5.41. Mean of APACHE II score at admission was 18.08±10.17 (Points). Mean length of ICU stay was 9.52±5.007 (days). Outcome of infected patients in ICU was 21(75%) survived patients and 7(25%) non survived patients.

Table 10: **follow-up parameters in ICU in the non-infected patients**

Follow-up parameters in ICU		Mean ± SD	n=22 %
SOFA score at admission (Points)		4.27±2.81	
Mean SOFA score during study period		6.27±3.51	
APACHE II score at admission (Points)		14.01±10.17	
Length of ICU stay (days)		10.41±4.02	
Outcome in ICU	*Survival*		17(77%)
	Mortality		5(22%)

In **table 10** mean of SOFA score at admission was 4.27±2.81 (Points). Mean SOFA score during study period 6.27±3.51. Mean of APACHE II score at admission was 14.01±10.17 (Points). Mean length of ICU stay was 10.41±4.02 (days). Outcome of non-infected patients in ICU was 17(77%) survived patients and 5(22%) non survived patients.

Table 11:**comparison between infected and non-infected studied patients**

Baseline Characteristics of Study Patients	n=50	Infected n=28	Non- Infected n=22	P-value
		Mean ±SD or n %	Mean ±SD or n %	
Age (years)		53.38 ±4.32	55.31±2.94	0.33
Gender				
Female	23(46%)	12(42.9%)	11(50%)	0.61
Male	27(54%)	16(57.1%)	11(50%)	
Risk factors				
Smoking	18(36%)	9(32.1%)	9(40.9%)	0.52
Dyslipidemia	16(32%)	10(35.7%)	6(27.3%)	0.52
DM	30(60%)	18(64.3%)	121(54.5%)	0.48
Hypertension	33(66%)	20(71.4%)	13(59.1%)	0.36
Comorbidities				
≥2 comorbidities	16(32%)	9(32.1%)	7(31.8%)	0.98
Admission category				
Medical	42(84%)	26(92.9%)	16(72.7%)	0.054
Surgical	8(16%)	2(7.14%)	6(27.27%)	0.065
Mortality	12(24%)	7(25%)	5(22.7%)	0.85

In **table 11** comparison between infected and non-infected of the studied patients as regard variables of demographic, risk factors, ≥2 comorbidities, admission category or mortality showed that there was no statistical significant difference between them (p>0.05).

Table 12: comparison between infected and non-infected as regard scores, leucocytic, eosinophilic count and ICU length of stay in the studied patients

Clinical characteristics of Study patients	Infected n=28	Non- infected n=22	P-value
	Mean ±SD or n %	Mean ±SD or n %	
Total leucocytic count ($x10^3$)	20.48±5.96	7.41±2.75	**<0.001***
Eosinophil count	48.32±10.31	130.0±40.55	**0.001***
SOFA score at admission	9.53±2.45	3.63±1.81	**<0.001***
APACHE II score at admission	21.39±5.15	13.86±2.81	**0.008***
Length of ICU stay (days)	9.92±5.53	8.04±3.83	**0.18**

In **table 11**comparison between infected and non-infected groups of the studied patients was statistically significant as regard variables of SOFA score, APACHE II score at admission, TLC andEosinophil count at admission (p-value<0.05). There were no statistical significant differences as regard length of ICU stay (p>0.05).

Table 13: multivariate regression analysis as regard mortality in ICU

Clinical Parameters	Odd's ratio	P-value
Total Leucocytic Count	31.62	<0.001
Eosinophil	28.13	<0.001
APACHII score (points)	6.88	0.009
SOFA score (points)	32.44	<0.001

In **table 13** multivariate regression analysis of several variables in this study shows statistically significant differences and were independent predictors for infection as follow: Total Leucocytic Count (Odd's ratio =31.6) and (p<0.001),Eosinophil count at admission (Odd's ratio =28.13, p <0.001), APACHII score (Odd's ratio =6.88, p=0.009), and SOFA score (Odd's ratio =32.44, p<0.001).

Table 14: ROC curve for eosinophil count in the studied patients

	Cutoff value	AUC	CI	Sensitivity	Specificity	P-value
Eosinophil count	50	0.95	0.876- 1.00	92.85	93.33	<0.001*

Receiver operator characteristic (ROC) curve was calculated for eosinophil count in the studied patients as a predictor for infection. The area under the curve (AUC) for eosinophil count to predict was 95% with confidence interval (CI: 0.876- 1.00). The optimal cut off value was 50 cells with a sensitivity of 92.85% and specificity of 93.33% with P value <0.001.

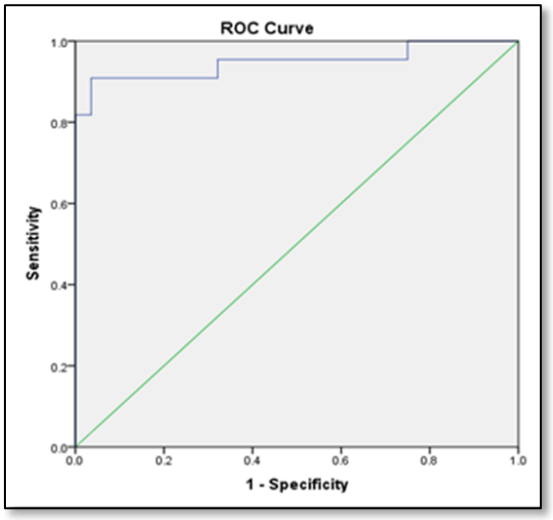

Fig.5: ROC curve for eosinophil count among the studied patients in ICU

Table 15: ROC curve for eosinophil count for mortality prediction in the infected patients

	Cutoff value	AUC	CI	Sensitivity	Specificity	P-value
Eosinophil count	50	0.439	0. 239-0. 639	54.85	58.33	0.52

In **table 12** receiver operator characteristic (ROC) curve was calculated for eosinophil count in the studied patients as a predictor for mortality but it was non-significant (AUC=0.439, p>0.05).

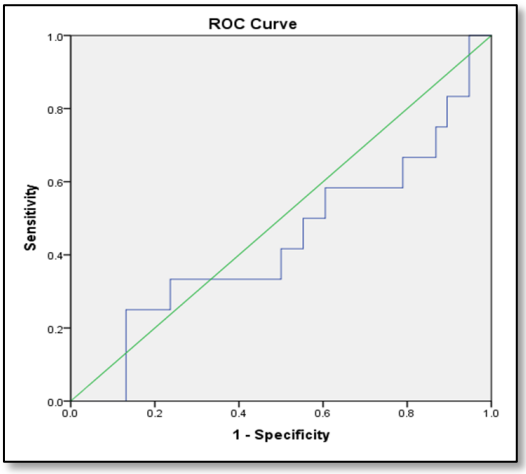

Fig. 6: ROC curve for eosinophil count for mortality prediction in the infected patients

DISCUSSION

The early diagnosis of sepsis plays an integral role in the morbidity and mortality of patients admitted to the intensivecare unit (ICU) because it ensures the early administration of antibiotics therapy. The clinical parameters that make upthe sepsis syndrome are not specific and frequently overlap with the clinical presentation of a systemic inflammatoryresponse syndrome (SIRS) secondary to other noninfectiouscauses [(19)]. Acute infection can cause eosinopenia through several mechanisms, such as peripheral sequestration of eosinophils in inflammatory sites, suppression of the emergence of mature eosinophils from the bone marrow and suppression of eosinophil production [(20)]. Acute stress also involves eosinopenia, which is mediated by adrenal glucocorticoids and epinephrine. Severe, stressful conditions in the ICU are directly linked to mortality [(21)]. An early diagnosis of sepsis before receiving the results of microbial culture would certainly facilitate the choice of antibiotic therapy and reduce the patient mortality[(22)].

This study was conducted to achieve our aim that was to test the value of eosinopenia in the diagnosis of sepsis in critically ill patients admitted to ICUs. In this study, 50 patients were included and were adults more than 18 years old, admitted to ICU either had sepsis on admission or not.Their ages were with a mean of 50.38 ± 5.35 years. 27 patients (54%) were males and 23 patients (46%) were females. The most frequent risk factors were hypertension (66%) followed by diabetes (60%) beside other risk factors as smoking and dyslipidemia. The patients were admitted for postsurgical interventions were 8 (16%) or for medical reasons were 42 (84%). Demographic data in our study were similar to those data recorded in study of **Zanon*et al*.**[(23)]who found that mean age was 60.7± 18.6 years and 56.8% of the patients were older than 60 years, 55.5% were men.**Furuta*et al*.**[(24)]found that the average age of the population in their study was 54.5±20 years. There were no significant differences regarding age or gender with our findings. That show average age of the population 50.38±5.35.

Regarding the risk factors, **Wang *et al*.**[(25)]stated that the risk of incidence of sepsis was higher among older individuals. While, both current and past history of tobacco use were associated with increased sepsis risk. Also, **Mayr *et al*.**[(26)]reported that most of the risk factors of severe sepsis were, age, male gender, black race and increased burden of chronic health conditions.Also, they found that the incidence of severe sepsis increases disproportionately in older adults and more than half of severe sepsis cases occur in adults over 65y of age.In this study, comorbidities in the studied patients were mostly IHD 36% thenrenal diseases14%, COPD or chest diseases12% and old CVS 12%. The least comorbidities were liver diseases 2.2% and autoimmune diseases 2.2%. These finding are similar to those conditions included in the study of **Wang *et al*.**[(25)]who showed a significant association between these factors and the incidence of sepsis. Chronic lung disease and chronic kidney disease resulted in increased risk of sepsis (p=0.001).

Mayr *et al*.[(26)]reported that severe sepsis is more likely to occur in individuals with chronic obstructive pulmonary disease, cancer, chronic renal and liver disease and diabetes. Other risk factors included residence in long-term care facilities, malnutrition, use of immune-suppressive medications and prosthetic devices. In the current study, sources of infection in the infected patients were mostly respiratory50%then

urinary 17.9%, mixed 14.28% and abdominal diseases10.7%. The least sources of infection were skin and soft tissues 3.57%and others (infection from central venous line)3.57%. **Zanon *et al*.** [23]in their study found that the most frequent sites of infection were the lungs (71.6%), of all study patients.

Similarly, **Esper *et al.*** [27]found that respiratory tract infections, particularly pneumonia, are the most common site of infectionand associated with the highest mortality. Men are particularly prone to develop pneumonia, [28] while genitourinary infections are more common among women [29]. In this study, infections in the studied patients with Gram –ve were only in 11 patient (39.28%) and Polymicrobial in 12 patient (42.85%). The least were Gram +ve only 3(10.71%). No growth was in 2 cases7.14%.Gram positive bacteria, *Staphylococcusaureus* and *Streptococcuspneumonia* were more prevalent (10.7% and 7.142% respectively). In gram negative bacteria, *Escherichia coli* and *Klebsiella* species were more prevalent (25% and 21% respectively). *Pseudomonas* species, *Proteus mirabilis*, *Acinetobacter* species,*H. influenzae*, *Enterobacter* and others were 14.28%, 7.14%, 16.52%, 3.57%, 7.14% and 3.57%respectively. Fungal infection was caused by candida in 3.57% patients.

Zanon *et al.* [23]revealed in their study thatthe most frequent pathogens were gram-negativebacilli (*Escherichia coli*,*Pseudomonas aeruginosa*,*Enterobacterspand Acinetobactersp*) in 53.2%of the cases, while gram-positive cocci (Coagulase-negative*Staphylococcus* and *Staphylococcusaureus*) were detected in 42.7%.More than one pathogen was identified in 2.8% of thecases and fungi, in 1.3% of cases.In the study performed by **Vincent *et al.*** [30]patterns of infecting predominant organisms were *Staphylococcus aureus* (20.5%), Pseudomonas species (19.9%), *Enterobacteriacae* (mainly *E. coli*, 16.0%) and fungi (19%). *Acinetobacter* was involved in 9% of all infections, with significant variation of infection rates across different regions (3.7% in North America vs. 19.2% in Asia).

In **Huang *et al*.** [31]study, out of 269 patients showed microbiological results, Gram-negative bacteria, Gram-positivebacteria and fungi were isolated in 65%, 25%, and 10% of thesevere sepsis patients. The most prevalent species were *Klebsiellapneumoniae* (8.6%), *Escherichiacoli* (6.0%), *Acinetobacterbaumannii* (5.6%), *Pseudomonas aeruginosa* (5.4%)and *Enterococcus* species (4.5%). In this study, mean of APACHE II score at admission was 18.08±10.17 (Points) in all study patient however it was 21.39±5.15 in septic patient in comparison to 13.86±2.81 (P 0.008) in non-septic patient. Mean length of ICU stay was 9.52±5.007 (days) the mean length of ICU stay in septic patients was 9.92±5.53 day in comparison to 8.04±3.83 (P 0.18) in non septic patient.

Outcome of infected patients in ICU was 21(75%) survived patients and 7(25%) non survived patients in comparison to 22.7% mortality in non septic patients.Studies in Europe and the US with patients with sepsis reported general mortality ratesthat ranged from 13.5% to 53.6%[32].

The Scripture Observe Apply Pray (SOAP) study[33], conducted in198 ICU patients in Europe, found a mortality rate of 32.2%for severe sepsis and of 54.1% for septic shock.Brazilian studies reported mortality rates of 11.3%for non-infectious SIRS, of 16.7% to 33.9% for sepsis,34.4% to 46.9% for severe sepsis, and 52.2% to 65.3% for septic shock [34].

Ferreira *et al*. [35]reported that the mean SOFA score in survivors was 3.48±2.238 and in non-survivors was 8.9±3.45 and the difference was statistically significant.

In the current study, comparison between infected and non-infected studied patients revealed thatthere were statistically significant differences as regards SOFA score, APACHE II score at admission, TLC andEosinophil count at admission (p-value<0.05). There were no statistical significant differences as regards length of ICU stay (p>0.05). Multivariate regression analysis of several variables in this study showed statistically significant differences and was independent predictors for infection as follow: Total Leucocytic Count (Odd's ratio =31.6) and (p<0.001), Eosinophil Count at admission (Odd's ratio =28.13, p<0.001), APACHII score (Odd's ratio =6.88, p=0.009), and SOFA score (Odd's ratio =32.44, p <0.001).Receiver operator characteristic (ROC) curve was calculated for eosinophil count, the area under the curve (AUC) for eosinophil count to predict was 95% with confidence interval (CI: 0.876- 1.00). The optimal cut off value was 50 cells with a sensitivity of 92.85% and specificity of 93.33% with P value <0.001.

The previous findings of eosinophil count in our study were similar to many studies as**Abidi*et al*.** [36]who found that an AUROC of 0.89 (95% CI 0.83–0.94) foran eosinophil count cut-off of 50 cells/mm3, performed onadmission, to differentiate between non-infected and infectedpatients in a medical intensive care unit in Morocco.Also,**Shaaban *et al.*** [6]showed a strong

relationship between bacterial infection and eosinopenia suggesting that eosinopenia could differentiate between sepsis and noninfectious inflammation response, difficult to differentiate clinically. Studies by**Lopez de Toro *et al*.**[37]and**Gil *et al*.**[12]suggested that eosinopenia can bea marker of bacterial infection in patients with sepsis.

The findings of the **Abidi *et al*.**[36]study were (80% sensitivity and 80% specificity) for cutoff value 40cells/cu.mm.Anotherprospective observational study by**Hota and Reddy**[38]consisting of 50 patients with SIRS and sepsis on admission were studied. They found that eosinophil count was an effective prognostic marker of sepsis with low cost.The cut off value was taken as 40cells/cu.mm. Fifty eight percent of the cases were below the cut off value and the rest of the cases were above the cut of value, i.e., 42%. Sensitivity and specificity of eosinophil count in comparison to the result of the present study which revealed 92.85% and 93.33% respectively.

On the contrary, **Moura *et al*.**[39] in their study found that eosinopenia was not a good early diagnostic marker forsepsis in this population.At a cut-off value of 100 cells/mm^3, the eosinophil count yielded a sensitivity of 35%, a specificity of 71%. The differencesbetween the results of that study and the current study may be due to higher cut-off value that used in our study.

Setterberg *et al*.[40]reported that eosinopenia is not a valuable marker for infection. This might be due to the inclusion of different patient groups in the noninfectious category as compared to our study. Also, several literaturesshowed conflicting results when studying eosinopenia as a biomarker for diagnosing infection. **Smithson *et al*.**[9]showed no correlation between eosinopenia and infections.

Holland *et al*.[8] analyzed eosinophil count on admission in 66patients with exacerbation of chronic obstructive pulmonarydisease and found that mortality was significantlyhigher in patients with eosinopenia at baseline than in those withnormal eosinophil values (17.4% versus 2.4%, respectively). They suggested that eosinophil count could be a useful markerof severity and prognosis independently of other, routinely usedindicators. In patients with bacteremia, such as those included inthe present study, the initial eosinophil count did not allow patientoutcome to be predicted.

In our findings, receiver operator characteristic (ROC) curve was calculated for eosinophil count in the studied patients as a predictor for mortality but it was non-significant (AUC=0.439, p>0.05). In consistent withEscobar-Valdivia et al.[42]in 2015 in a retrospectivedesign study, including an unselected population ofcritically ill patients found an increased frequency of sepsis inthe group of non-survivors, but they did not find a difference in eosinophil count at ICUadmission between survivor and non-survivor patientswith sepsis; the value of this analysis is limited due to alow number of patients included (77 patient).

On the contrary, **Abidi *et al*.**[36]evaluated eosinopenia as an early marker ofmortality in critically ill patients, a high percentage of who hadinfection.In the multivariate analysis, eosinopenia was a predictorof mortality at 28 days. The difference between the results of Abidi et al.[36]study & the present study may be attributed to small sample size and lack of serial follow up of eosinophil count.

Eosinophils for long have been found to beplaying a role in acute infections. A distinctcharacteristic of the eosinophil is to initiate a hostresponse to acute infection. The initial response toacute inflammation includes a rapid drop incirculating eosinophils and an accumulation ofeosinophils at the peripheral inflammatory site,alongwith inhibition of release of eosinophils from thebone marrow. The responses of eosinophils have beenvariable in infection, bacteremia and SystemicInflammatory Response Syndrome[43].Eosinophils normally account for only 1-3% of bloodleucocytes. The Absolute Eosinophil Count (AEC) values range between 40-440/cmm. As this is a wide range this series adopted theaverage of the range as the cut off below which thevalue was termed as eosinopeniabut values less than40/cmm was termed as severe eosinopenia. Theeosinophils in the body are normally well regulated[44].

The causative mechanisms that control eosinopenia inacute infections, involve mediation by glucocorticoidsand adrenaline. The initial eosinopenic response seen,in acute infections is the culmination of a peripheralsequestration of circulating eosinophils. A part of thissequestration can be attributed to the migration ofeosinophils into the inflammatory site itself, inresponse to the chemotactic substances released duringacute inflammation. The major chemotactic substancesinclude C5a and fibrin fragments that have beendetected in the peripheral circulation during acuteinflammatory states [20].Eosinopenia is an easy but often ignoredmarker of acute infection. Various animal models have suggested thesignificance of eosinopenia and infection. Animalmodels suggest that eosinopenia is aresponse to theacute inflammatory process rather than a response to aspecific pathogen [20]. Though

eosinopenia has areasonable specificity as a marker of bloodstreaminfection in adult patients, these results strengthen the fact that the presenceof eosinopenia can be as an inexpensive alert forbloodstream infections [(45)].

The present study has some limitations such as : small sample size, we did not take into account the percentage of eosinophils with respect to total leukocyte count and the study was conductedat a single center.

Conclusion

The result of the present study revealed that eosinophil counts <50 cells/mm3 at admission time to ICU was apredictor for diagnosis of sepsis in critically ill patients. However,eosinophil counts at admission time to ICU were not a specific indicator of mortality.

RECOMMENDATIONS

1- Eosinophil counts are cheap and easily accessible test can be used to guide for sepsis diagnosis and treatment.
2- Larger studies are needed to determine the prognostic value of this test and establish better cutoff values.

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