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ORIGINAL RESEARCH ARTICLE

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Eosinophil count: a predictor of in-hospital mortality in a cohort of cirrhosis patients with sepsis

K. V. Anoop*, Krishnadas Devadas and Jijo Varghese

Abstract

Background: Declining eosinophil count has recently been associated with sepsis. Thus, absolute eosinophil count (AEC) can be used as a marker of the severity of sepsis, which helps in the early identification of high-risk patients, and better management can be offered to such patients. The aim of this study was to assess whether AEC at the time of ICU admission can be used as a predictor of in-hospital mortality in cirrhotics with sepsis.

Results: This was a retrospective study which was conducted in 105 cirrhotic patients admitted with sepsis in the Department of Gastroenterology, Medical College Trivandrum, from May 2014 to October 2014. Every consecutive patient with cirrhosis and sepsis (defined as systemic inflammatory response syndrome (SIRS) and the presence of infections) admitted to the ICU/high dependency unit was recruited for the study. Among the various parameters analyzed, model for end-stage liver disease (MELD) score, Child-Pugh Turcot (CTP) score, albumin levels, total count, *C-reactive protein* (CRP), *erythrocyte sedimentation rate* (ESR), alanine aminotransferase (ALT), bilirubin, creatinine, urea, and absolute eosinophil count were statistically significant in predicting in-hospital mortality. The AUROC of AEC was plotted and found to be 0.881, which was better than other parameters for predicting in-hospital mortality. The cutoff of AEC by Youden's index was 110 cells/cumm (sensitivity 91.3%, specificity 89%, positive predictive value 87.5%, and negative predictive value 93%) to predict in-hospital mortality. The AUROC of MELD was 0.78 with a cutoff of > 24 (sensitivity 89%, specificity 74.6%, positive predictive value 73%, and negative predictive value 89%) to predict the mortality. The odds ratio for predicting mortality was highest for absolute eosinophil count (92.75) followed by MELD (24.57), total count (20.475), CTP (10), and the presence of SIRS (9.08).

Conclusion: In critically ill cirrhosis patients with sepsis, AEC < 110 cells/cumm can predict in-hospital mortality.

Keywords: Cirrhosis, Eosinophil, Sepsis, Infection, Mortality

Background

Eosinophil is a granulocyte with acidophilic granules and plays an important role in inflammation and infection. The eosinophils are mainly activated by IL-5 [1]. At the time of acute sepsis, there will be an increased level of cytokines and chemotatic factors [1]. It results in margination and sequestration of eosinophils into the tissues and can result in a decrease in circulatory eosinophils [1]. In tissues, these eosinophils form eosinophil extracellular traps (EET), which are mitochondrial DNA secreted by eosinphils [1]. These DNA are sticky, and eosinophils bind to these traps, get activated and degranulated, and can result in the killing of pathogenic organisms. Eosinophils do not have the capability to phagocyte pathogen. In short, they are incapable of intracellular killing pathogens.

The decrease in eosinophil count that accompanies many acute infections was first mentioned by Ehrlich in 1880 and was well described by Zappert in 1893 [2]. What

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we are postulating is that the eosinophil count in circulation at the time of acute infection can predict the severity of sepsis. The more the severity of sepsis, the more will be the cytokine and chemokine production and can result in more eosinophil sequestration into the tissues from the blood. In short, eosinophil count in sepsis can predict in-hospital mortality. As cirrhotic patients are more prone to infection and can have a detrimental course following the infection, early identification of high-risk patients is important in predicting poor prognosis and better management can be offered to such patients, so that in-hospital mortality can be reduced. Numerous biomarkers have been evaluated to predict the mortality in sepsis in cirrhotic patients, but none has been proven to be entirely useful. Other markers frequently used are CRP and procalcitonin. Procalcitonin has been considered to have a higher potential in diagnosing sepsis than CRP and thereby the mortality. Another novel marker which is being used is the circulating cell-free DNA (cf-DNA), which is believed to be released from the apoptotic cells [3].

Methods

The aim of this study was to assess whether absolute eosinophil count (AEC) at the time of ICU admission can be used as a predictor of in-hospital mortality in cirrhosis patients with sepsis. This was a retrospective study which was conducted in the Department of Medical Gastroenterology, Medical College Thiruvananthapuram. Every consecutive patient with cirrhosis and sepsis admitted to the ICU/high dependency unit was recruited for the study. All patients with features of SIRS and the presence of infections were diagnosed with sepsis. SIRS was defined according to the definition provided by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [4]. Infection was documented by demonstrating an organism, either by culture or microscopy, from a clinical focus like the blood, sputum, urine, ascitic fluid, synovial fluid, abscess, and pleural fluid.

The following patients were excluded from the study:

1. Patients who died within 24 h of hospital admission
2. Patients who had malignancy
3. Patients who had chances of high absolute eosinophil count due to pulmonary illness like bronchial asthma and allergic pulmonary disease
4. Patients who had documented allergic disorders in the past
5. Patients with autoimmune disorders in the past
6. Patients with acute on chronic liver failure
7. Patients with no absolute eosinophil count done at the time of admission

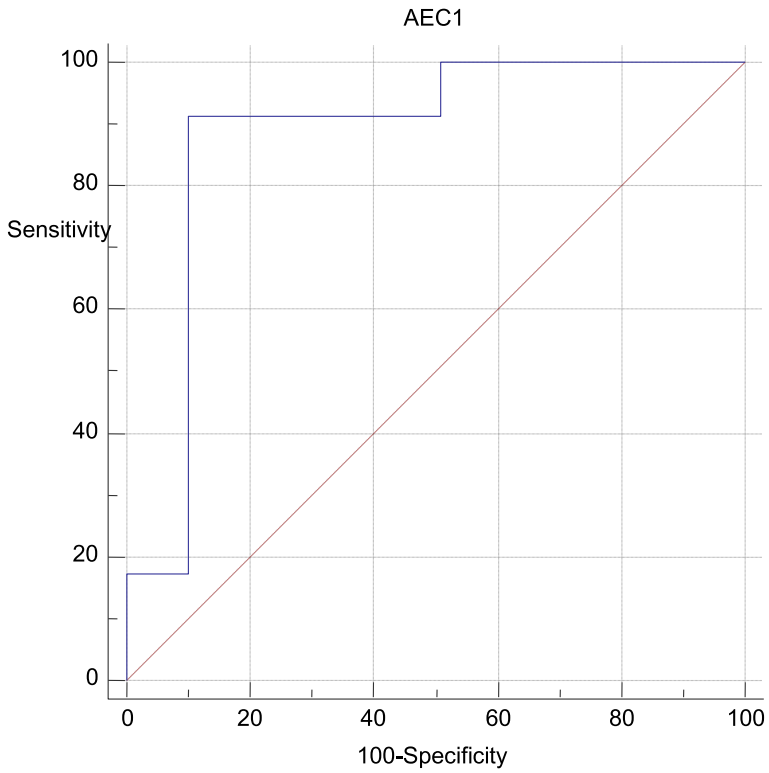

Fig. 1 Algorithm showing patient selection and exclusion

An algorithm is shown below showing how the patients were selected and excluded from the study (Fig. 1).

On the day of ICU admission, complete blood count was measured using XN-1000 Symex 5-part differential hematology analyzer, and differential count of 100 leukocytes was obtained by the Romanowsky method using Leishman stain. The differential count for eosinophil obtained in percentage was multiplied to total count resulting in absolute eosinophil count, and patients were followed up for in-hospital mortality. The study was submitted to and approved by the institutional ethics committee with ID no. A2/SBMR/02/2019/MCT held on 09/04/2019.

Table 1 Etiology of chronic liver disease among study population

Etiology	Dead	Alive	Total
AIH	3	3	6
HCV	3	7	10
Ethanol	17	23	40
HBV	9	3	12
NASH	14	21	35
WILSON	0	2	2
Total	46	59	105

Statistical analysis

All the data were analyzed by the SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA). The receiver operating characteristic (ROC) curves were obtained for various parameters to predict in-hospital mortality. Sensitivity, specificity, and positive and negative predictive values were calculated for specified cutoff values. Differences with a P value < 0.05 were considered as statistically significant.

Results

A total of 105 patients were enrolled for the study. Patients with sepsis having absolute eosinophil count at the time of admission were taken up for the study. Out of the study population, 81 were males (77.1%) and 24 were females (22.9%). Fifteen patients were having Child B cirrhosis (14.2%), and 90 patients belonged to Child C cirrhosis (85.8%). Among the various etiologies of cirrhosis, we had alcohol (40) cases, NAFLD (non-alcoholic fatty liver disease) (35) cases, hepatitis B virus (HBV) (12) cases, hepatitis C virus (HCV) (10) cases, and other (8) cases as shown in Table 1.

Among the study population, the most common source of sepsis was spontaneous bacterial peritonitis (SBP) (38 cases) followed by lower respiratory tract infection (LRTI) (28 cases), cellulitis (11 cases), urinary tract

Table 2 Sources of sepsis among the study population

Site of infection	Dead		Alive		Total	
	N	%	*N*	%	*N*	%
Cellulitis	5	45.5	6	54.5	11	100.0%
Liver abscess	0	0.0	2	100.0	2	100.0%
LRTI	12	42.9	16	57.1	28	100.0%
LRTI/SBP	3	100.0	0	0.0	3	100.0%
SBE	0	0.0	6	100.0	6	100.0%
SBP	23	60.5	15	39.5	38	100.0%
Septic arthritis	0	0.0	3	100.0	3	100.0%
Unknown	0	0.0	5	100.0	5	100.0%
UTI	3	33.3	6	66.7	9	100.0%
Total	46	43.8	59	56.2	105	100.0

Table 3 SIRS among the study population

SIRS	Dead		Alive		Total		χ^2	df	*P*
	N	%	*N*	%	*N*	%			
Yes	41	59.4	28	40.6	69	100.0	19.923	1	< 0.001
No	5	13.9	31	86.1	36	100.0			
Total	46	43.8	59	56.2	105	100.0			

Table 4 Statistical analysis of various variables in predicting mortality

	Outcome				*t*	*P*
	Dead		Alive			
	Mean	sd	Mean	sd		
Age	53.04	13.83	52.76	11.54	0.11	0.910
MELD score	30.67	8.74	23.29	6.20	5.06	< 0.001
Hemoglobin	10.26	1.77	10.42	1.14	− 0.56	0.574
Total count	16,758.04	7220.09	9063.39	4730.87	6.58	< 0.001
AEC	101.74	54.59	251.97	86.75	− 10.26	< 0.001
CRP	38.20	31.47	41.14	58.08	− 0.23	0.816
Bilirubin	10.34	11.58	4.92	2.77	3.47	0.001
AST	71.65	76.38	59.32	29.96	1.13	0.259
ALT	49.41	18.24	36.14	19.55	3.56	0.001
ALP	100.41	28.68	92.20	21.67	1.67	0.098
S. creatinine	1.80	0.68	1.50	7.52	− 2.51	0.014
B urea	55.02	32.02	29.42	16.47	5.31	< 0.001
NA+	126.24	8.93	128.97	5.39	− 1.94	0.055
Albumin	2.65	0.26	2.83	0.26	3.50	0.001
K+	3.93	0.45	3.89	0.30	0.58	0.563
Ca++	7.88	0.61	8.18	0.85	− 1.74	0.086

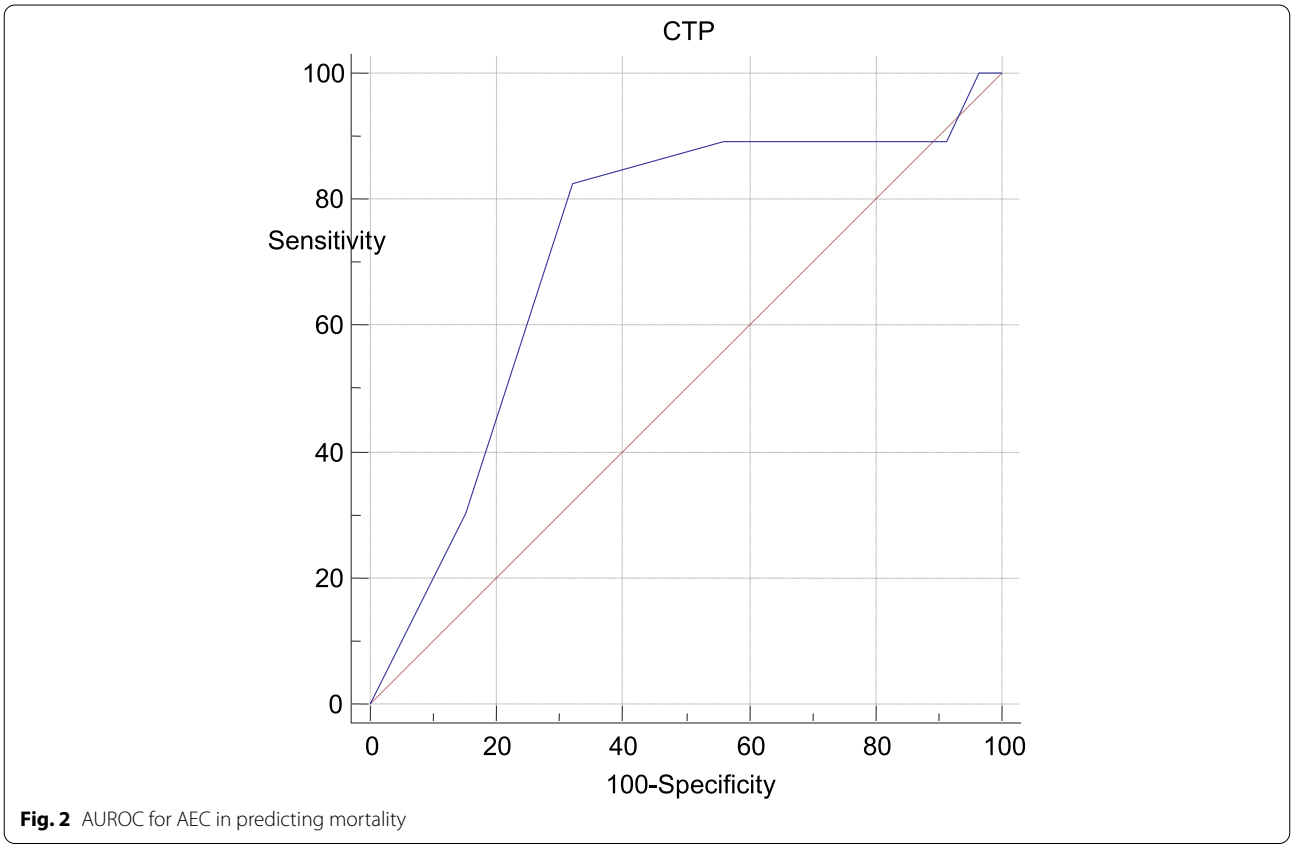

Fig. 2 AUROC for AEC in predicting mortality

infection (UTI) (9 cases), spontaneous bacterial empyema (SBE) (6 cases), unknown source (5 cases), septic arthritis (3 cases), LRTI + SBP (3 cases), and liver abscess (2 cases) as shown in Table 2. Among the various etiologies, the highest percentage of mortality was seen in LRTI+ SBP (100%) followed by SBP (60.5%).

Among the study population, SIRS was seen in 69 cases (65.7%). Among the dead patients, SIRS was seen in 41 (89.1%), and among those patients who survived, SIRS was seen in 5 (13.9%). By the chi-square test, SIRS was statistically significant in predicting mortality in cirrhosis patients with sepsis as shown in Table 3. Among the various variables analyzed, MELD score, CTP score, albumin levels, total count, ALT, bilirubin, creatinine, blood urea, SIRS, and absolute eosinophil count (AEC) were statistically significant in predicting the mortality as shown in Table 4.

The absolute eosinophil count at the time of admission was analyzed for predicting in-hospital mortality. The AUROC was plotted (Fig. 2), and the area under the curve was 0.881. The cutoff of AEC by Youden's index was found to be 110 cells/cumm in predicting the mortality (sensitivity 91.3% and specificity 89%, positive predictive value 87.5%, and negative predictive value 93%). The AUROC curve of AEC was 0.881 compared to 0.722 for CTP (Fig. 3) with a cutoff > 12, 0.784 for MELD (Fig. 4) with a cutoff > 24, 0.73 for albumin with a cutoff < 2.6 and 0.82 for total count with a cutoff > 9100.

The odds ratio for predicting mortality was highest for absolute eosinophil count (92.75) followed by MELD (24.57), total count (20.475), CTP (10), and the presence of SIRS (9.08), as shown in Table 5.

Discussion

Cirrhosis patients are prone to numerous infections and subsequent sepsis. They are more prone to develop severe sepsis because of their immunocompromised state. Early detection of a bad prognosis can result in better hospital care and more intensive treatment. Margination and sequestration of eosinophil under the influence of chemotactic agents are well known, and as the milieu of chemotactic agents and chemokines increases, there will be a proportional increase in sequestration of eosinophil into the tissues from the circulation. As more eosinophils get sequestrated, there will be increased eosinophilic protein in tissue, and we postulate that this can result in decreased EET formation and widespread organ damage and mortality. Thus, eosinophil count can be an indirect predictor of severe sepsis and mortality. The eosinophil

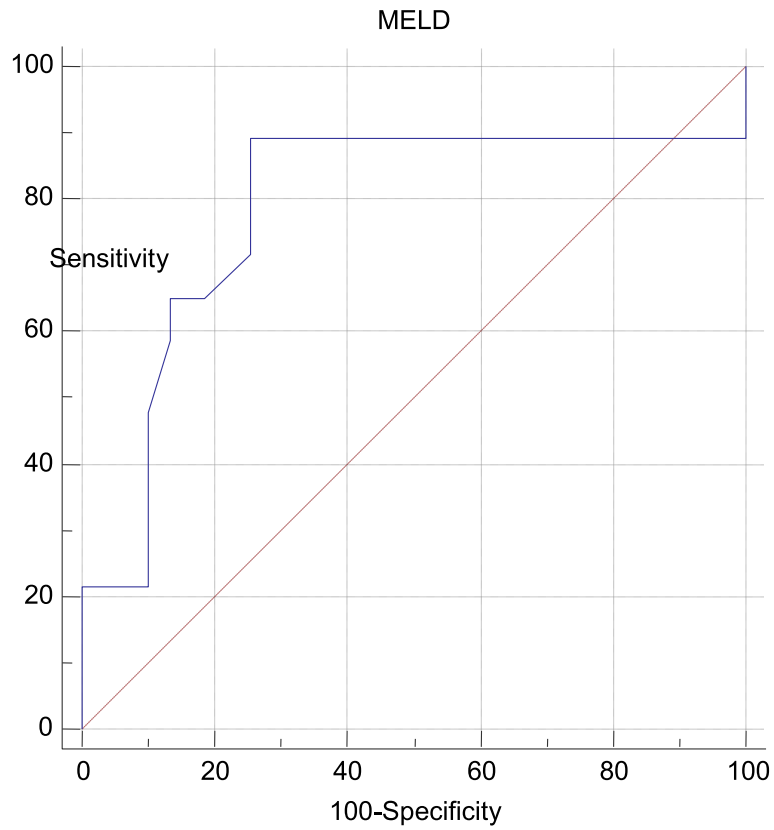

Fig. 3 AUROC for CTP in predicting mortality

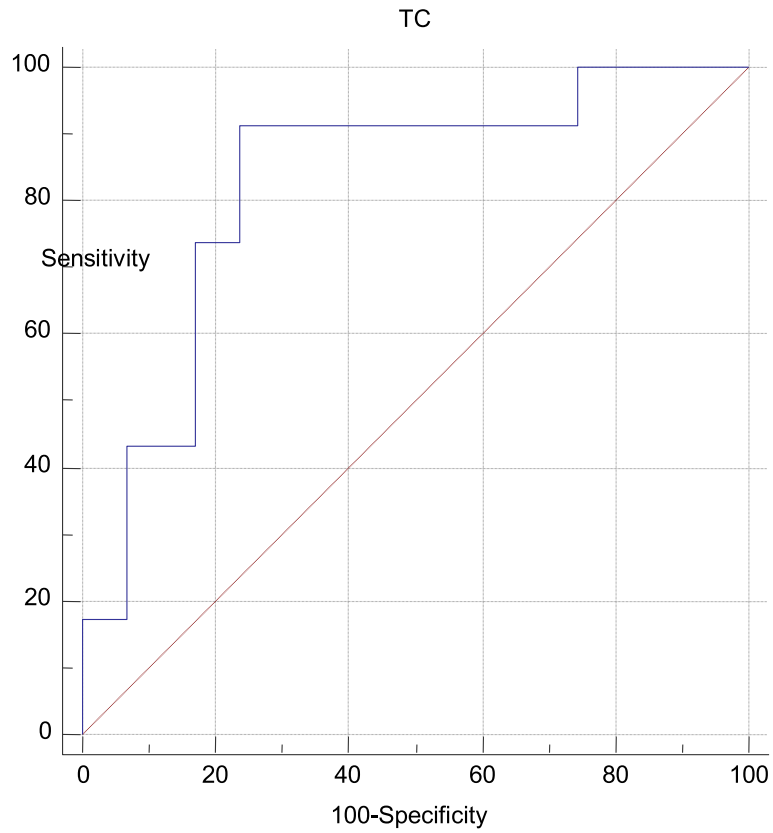

Fig. 4 AUROC for MELD in predicting mortality

count can be measured, and AEC is a cheap marker when compared to other markers of sepsis like CRP and procalcitonin. CRP is considered to be an inconclusive marker of sepsis in chronic liver disease. The statistical analysis of our study suggested that CRP is an inappropriate marker in predicting mortality in chronic liver disease patients.

In our study population, absolute eosinophil count at the time of admission was analyzed for predicting in-hospital mortality. The AUROC was plotted, and the area under the curve was 0.881. The cutoff of AEC by Youden's index was found to be 110 cells/cumm in predicting mortality (sensitivity 91.3% and specificity 89%, positive predictive value 87.5%, negative predictive value 93%). The AUROC was better than other variables like total leukocyte count, CTP, MELD, and albumin. Univariate analysis showed that the odds ratio in predicting in-hospital mortality was highest for absolute eosinophil count (92.75) compared to MELD (24.05), total leukocyte count (20.475), CTP(10), and SIRS (9.08). The study by Abidi et al. showed the significance of eosinophil count for diagnosing sepsis and AEC performed better than CRP in this regard [5]. There are similar studies showing the eosinophil count as a predictor of mortality in various other populations like critically ill non-cardiac vascular surgery patients [6] and COPD patients [7] and in predicting unexpected readmission and mortality in ICU

Table 5 Univariate analysis of various factors in predicting mortality

	Dead (*N* = 46)		Alive (*N* = 59)		Total		*P*	OR	95% CI for OR	
	N	%	*N*	%	*N*	%			L	U
Presence of SIRS	41	89.1	28	47.5	69	65.7	< 0.001	9.08	3.15	26.20
MELD > 24	41	89.1	15	25.4	56	53.3	< 0.001	24.05	8.02	72.11
CTP2 > 12	38	82.6	19	32.2	57	54.3	< 0.001	10.00	3.92	25.54
AEC < 110	42	91.3	6	10.2	48	45.7	< 0.001	92.75	24.57	350.12
TC > 9100	42	91.3	20	33.9	62	59.0	< 0.001	20.475	6.43	65.22

discharge patients [8]. There is a similar study which has shown that patients with eosinopenia and SIRS had high mortality in a cohort of cirrhosis patients [9]. This study is significant in the sense that this study has evaluated the significance of eosinophil count in predicting mortality in sepsis patients with cirrhosis, which is very few in the literature.

Conclusion

Our conclusion is that absolute eosinophil count is a simple marker of predicting in-hospital mortality among cirrhosis patients and is a better predictor of mortality than CRP. According to our study, the cutoff of absolute eosinophil count in predicting in-hospital mortality among cirrhosis patients with sepsis was < 110/cumm. Early prediction of bad prognosis is important, so that in-hospital mortality of sepsis in cirrhosis patients can be predicted and better hospital care can be offered, which can improve the overall outcome. Further studies are required to validate absolute eosinophil count in predicting in-hospital mortality among cirrhosis patients.

Abbreviations

AEC: Absolute eosinophil count; ICU: Intensive care unit; MELD: Model for end-stage liver disease; CTP: Child-Pugh Turcot; ESR: *Erythrocyte sedimentation rate*; ALT: Alanine aminotransferase; SIRS: Systemic inflammatory response syndrome; AUROC: Area under the receiver operating characteristics; EET: Eosinophil extracellular traps; ROC: *Receiver operating characteristics*; CRP: *C-reactive protein*; NAFLD: Non-alcoholic fatty liver disease; SBE: Spontaneous bacterial empyema; SBP: Spontaneous bacterial peritonitis; AIH: Autoimmune hepatitis; LRTI: Lower respiratory tract infection; UTI: Urinary tract infection; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

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None.

Authors' contributions

AKV contributed to the conception of the study, design of the work, analysis, and interpretation of the data. KD contributed to the acquisition of the data, drafted the work, and substantively revised the work. JV drafted the work. All authors have read and approved the final manuscript.

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Availability of data and materials

1. https://pubmed.ncbi.nlm.nih.gov/24903083/
2. https://journals.sagepub.com/doi/10.1177/0310057X1304100130

Declarations

Ethics approval and consent to participate

Consent to participate in study is not applicable since it was a retrospective study.
The study was submitted to and approved by the institutional ethics committee with ID no. A2/SBMR/02/2019/MCT held on 09/04/2019.

Consent for publication

Obtaining informed consent to publish the information from the study participants is not applicable since it was a retrospective study.

Competing interests

The authors declare that they have no competing interests.

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References

1. Yousefi S, Simon D, Simon H-U (2012) Eosinophil extracellular DNA traps: molecular mechanisms and potential roles in disease. Curr Opin Immunology 24:736–739
2. David A (1977) BASS reproduction of the eosinopenia of acute infection by passive transfer of a material obtained from inflammatory exudate infection and immunity, pp 410–416
3. Care C (2014) Prognostic and diagnostic value of eosinopenia, C-reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis, Jose Garnacho-Montero et al. Crit Care 18(3):R116. https://doi.org/10.1186/cc13908
4. Bone RC, Balk RA, Cerra FB et al (1992) American College of Chest Physicians/Society of Critical Care Medicine consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20(6):864–874
5. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units by Khalid Abidi,[1] Ibtissam Khoudri,[1] Jihane Belayachi,[1] Naoufel Madani,[1] Aicha Zekraoui,[1] Amine Ali Zeggwagh, Crit Care. 2008
6. Nutrition, metabolism and cardiovascular diseases, eosinopenia and post-hospital outcomes in critically ill non-cardiac vascular surgery patients, Gerdine C.I.von Meijenfeldt[ab] SowmyaChary[c] M.J.van der Laan[a] C.J.A.M.Zeebregts[a] Kenneth B.Christopher.2019
7. Ali A, Ibrahim J et al (2019) Role of eosinopenia in predicting mortality and morbidity in patients with chronic obstructive pulmonary disease (COPD). European Respiratory Journal
8. Eosinopenia as a predictor of unexpected re-admission and mortality after intensive care unit discharge C. B. Yip, K. M. Ho anesthesia intensive care 2013
9. Wilson V, Kantan Velayudhan K, Rao H et al (2021) Low absolute eosinophil count predicts in-hospital mortality in cirrhosis with systemic inflammatory response syndrome. Cureus 13(1):e12643. https://doi.org/10.7759/cureus.12643

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