Low Eosinophil Count : A Predictor of Inhospital Mortality in a Cohort of Cirrhosis Patients With Sepsis

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Abstract

Background and Aims:

Eosinopenia has recently been associated with sepsis. Thus, eosinopenia can be used as a marker of the severity of sepsis and high mortality, which helps in early identification of high risk patients, so better management can be offered to such patients. Aim of the study was to assess whether Absolute Esoinophil Count (AEC) at the time of ICU admission can be used as a predictor of inhospital mortality in cirrhotics.

Materials and Methods:

This study was a retrospective cohort study. The study population included cirrhosis patients admitted in ICU and High Dependency Unit with sepsis and their absolute eosinophil counts were assessed on the day of hospital admission.

Results:

A total of 105 patients were enrolled in the study. Among the various parameters analyzed, MELD score, CTP score, Albumin levels, Total count, CRP, ESR, ALT, Bilirubin, Creatinine, Urea, SIRS and Absolute Eosinophil Count(AEC) were statistically significant in predicting the mortality. AUROC of AEC for predicting mortality was 0.881. 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%) in predicting inhospital mortality. MELD AUROC was 0.78 with cut off of > 24 (sensitivity 89%, specificity 74.6%, positive predictive value 73% and negative predictive value 89%) to predict mortality.

Conclusion:

In critically ill cirrhosis patients, absolute eosinophil count less than 110 cells/cumm can predict inhospital mortality.

Background :

Eosinophil is a granulocyte with acidophilic granules and play an important role in inflammation and infection. Eosinophil is activated mainly by IL-5[1]. At the time of acute sepsis there will be increased level of cytokine and chemotatic factors[1]. It can result in margination and sequestration of eosinophil into the tissues and can result in a decrease in circulatory eosinophils[1]. In tissues, this eosinophils form Eosinophil Extracellular Traps(EET), which are eosinophil mitochondrial DNA secreted by eosinphils [1]. These DNA are sticky and esoinophil bind to these traps, get activated and get degranulated, which can result in killing of pathogenic organisms. Eosinophils does not have the capability to phagocyte pathogen; in short they are incapable of intracellular killing of pathogen. The characteristic eosinopenia that accompanies many acute infections was first mentioned by Ehrlich in 1880 and well described by

Zappert in 1893[2]. What we are postulating is that low 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 and result in proportional eosinopenia in the circulation. In short, low eosinophil count in sepsis can predict in-hospital mortality. As cirrhotic patients are more prone to infection and can have a detrimental course following infection, early identification of high risk patients is important in predicting poor prognosis and better management so that in-hospital mortality can be reduced. Numerous biomarkers have been evaluated to predict 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 Circulating cell-free DNA (cf-DNA), which is believed to be released from the apoptotic cells.[4]

Materials And Methods :

Aims and objectives :

The aim of the study was to assess whether Absolute Esoinophil Count (AEC) at the time of ICU admission can be used as a predictor of inhospital mortality in cirrhosis patients.

Study setting and design :

This study was a retrospective study which was conducted in the Department of Medical Gastroenterology, Medical college Trivandrum. Every consecutive patient of cirrhosis admitted to ICU/High dependency unit was taken up for the study. The following patients were excluded from the study :

1. patients who died within 24 hrs of hospital admission
2. patients who had malignancy
3. patients who had a chance 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 no absolute esoinophil count done at the time of admission.

An algorithm is shown below showing how the patients were selected and excluded from the study. (Algorithm 1 is given as Supplemental Digital Content).

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 were obtained by Romanowsky method using Leishman stain and 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.

Statistical analysis:

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

Results:

A total of 105 patients were enrolled for the study. Patients with sepsis having absolute esoinophil count at the time admission were taken up for the study. Out of the study population, 81 were males (77.1%) and 24 were females (22.9%). 15 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 (35) cases, HBV (12) cases, HCV (10) cases and others (8) cases as shown in Table no 1.

Among the study population, the most common source of sepsis was SBP(38 cases) followed by LRTI (28 cases), Cellulitis (11 cases), UTI (9 cases), SBE (6 cases), Unknown source (5 cases), Septic arthritis (3 cases), LRTI + SBP (3 cases) and Liver abscess (2 cases) as shown in Table no: 2 . Among the various etiologies highest percentage 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 Chi Square test, SIRS was statistically significant in predicting mortality in cirrhosis patients with sepsis as shown in Table no: 3.

Among the various variables analyzed, MELD score, CTP score, Albumin levels, Total count, ALT, Bilirubin, Creatitnine, Blood Urea, SIRS and Absolute Eosinophil Count (AEC) were statistically significant in predicting the mortality as shown in Table no: 4.

Absolute esoinophil count at the time of admission was analyzed for predicting in-hospital mortality. AUROC was plotted (Figure 1) and area under curve was 0.881 and Cutoff of AEC by Youden's index was 110 cells/cumm in predicating mortality (sensitivity 91.3% and specificity 89%, positive predictive value 87.5% and negative predictive value 93%). AUROC curve of AEC was 0.881 compared to 0.722 for CTP (Figure 2) with Cut off > 12, 0.784 for MELD (Figure 3) with cut off > 24, 0.73 for Albumin with cut off < 2.6 and 0.82 for total count (Figure 4) with cut off > 9100.

Odds ratio of predicting mortality was highest for Absolute eosinophil count (92.75) followed by MELD (24.57) followed by Total count (20.475), CTP (10) and Presence of SIRS (9.08) as shown in Table 5.

Discussion:

Cirrhosis patients are prone to infection and subsequent sepsis and they are more prone to develop severe sepsis. Early detection of bad prognosis can result in better hospital care and more intensive treatment. Margination and sequestration of eosinophil under the influence of chemotactic agents is 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 and as more eosinophils get sequestrated, there will be increased eosinophilic protein in tissue and we postulate that it can result in decreased EET formation and can result in widespread organ damage and mortality. Thus, low eosinophil can be an indirect predictor of severe sepsis and mortality. Eosinophil 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. Statistical analysis of our study suggests CRP is an inappropriate marker in predicting mortality in Chronic Liver disease patients. In our study population absolute esoinophil count at the time of admission was analysed for predicting in-hospital mortality. AUROC was plotted and the area under the curve was 0.881 and the cutoff of AEC by Youden's index was 110 cells/cumm in predicting mortality (sensitivity 91.3% and specificity 89%, positive predictive value 87.5%, negative predictive value 93%). AUROC was more than other variables like total leukocyte count, CTP, MELD and Albumin. Univariate analysis showed 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 Khalid Abidi et al showed the significance of eosinopenia for diagnosing sepsis and AEC performed better than CRP in this regard[3]. There are similar studies showing eosinopenia as a predictor of mortality in various other populations like critically ill non cardiac vascular surgery patients[5], COPD patients[6] and in predicting unexpected readmission and mortality in ICU discharge patients[7]. This study is novel in the sense that this is the first study evaluating the significance of eosinopenia in predicting mortality in sepsis patients with cirrhosis. To the best of our knowledge this is the first study which was done in this regard.

Conclusion:

Our conclusions are 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 was < 110/cumm. Early prediction of bad prognosis is important so that in-hospital mortality of sepsis in cirrhosis patients can be predicated 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.

Declarations:

Ethics approval and consent to participate :

Consent to participate in study : not applicable .

Ethical approval :

Not applicable

Consent for publication :

Obtaining informed consent to publish the information from the study participants : not applicable.

Availability of data and material :

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

Competing interests :

The authors declare that they have no competing interests.

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None

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Tables:

Table no: 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

Table no: 2

Sources of sepsis among 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 no: 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 no: 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	16758.04	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

Table no: 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

Figures

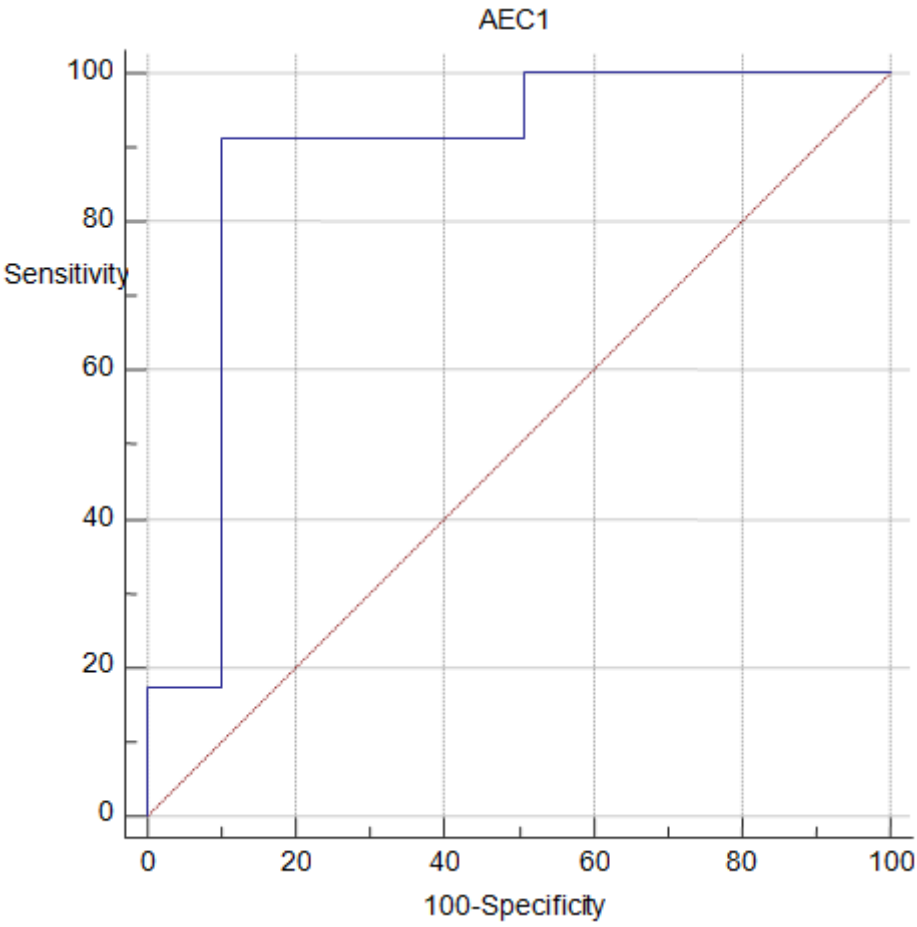

Figure 1

AUROC for AEC in predicting mortality

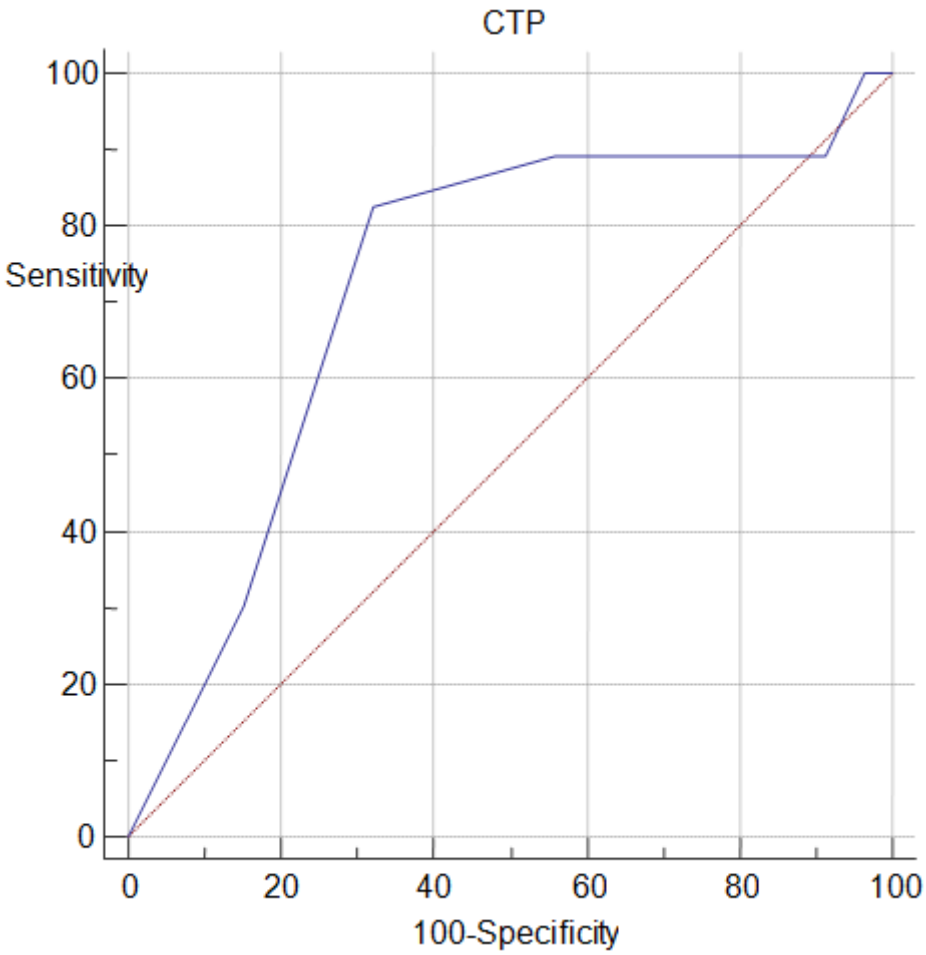

Figure 2

AUROC for CTP in predicting mortality

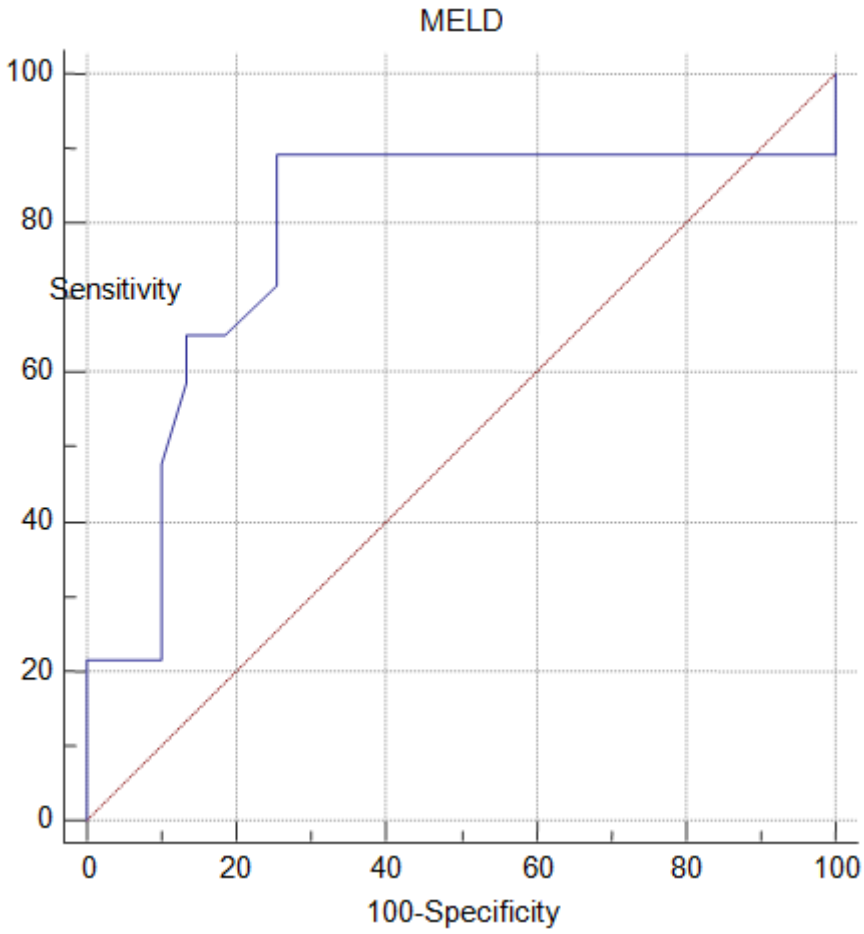

Figure 3

AUROC for MELD in predicting mortality

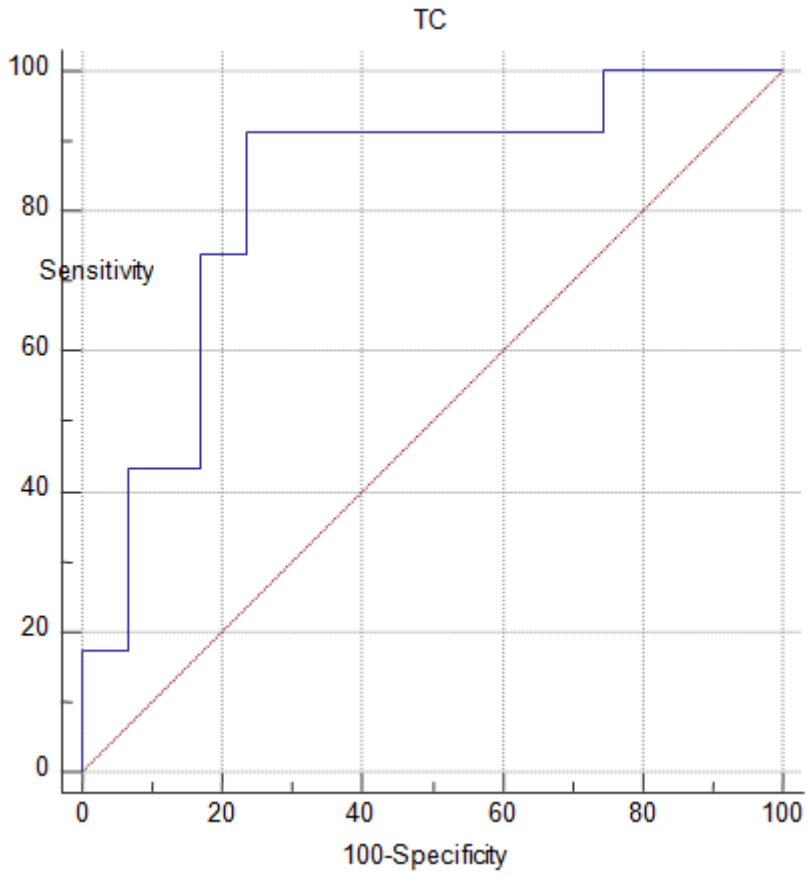

Figure 4

AUROC for Total count in predicting mortality

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Algorithm1.png