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Absolute eosinophil count is a reliable prognostic marker in patients with liver cirrhosis: a cross-sectional study at rural central India

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Abstract

Background Various laboratory parameters like C-reactive protein (CRP), Cortisol, and Von Willebrand factor antigen have been evaluated independently in foreseeing outcomes of cirrhotic patients. As these parameters lack cost-effectiveness in a rural setup, there is a need for a cost effective and feasible prognostic marker for cirrhotic patients. The present study was aimed at evaluating the role of Absolute Eosinophil Count (AEC) as a prognostic marker in cirrhotic patients.

Methods This cross-sectional study was conducted at a rural tertiary care teaching hospital in central India from August 2019 to September 2021. AEC was measured from counter report as a part of automated complete blood counts. Child-Turcotte-Pugh (CTP) score and Model for end stage liver disease (MELD) score were calculated at the time of admission. AEC levels on admission were correlated with mortality and with CTP score and MELD score.

Results A total of 110 patients were enrolled with mean age of 46.37 ± 11.6 years. AEC was the significant predictor of mortality at cut off point of ≤ 120 with 80.30% (AUC 0.803; 95% CI: 0.716 to 0.873). AEC was the significant predictor of CTP score ≥ 11 at cut off point of ≤ 148 (AUC 0.726; 95% CI: 0.633 to 0.807). AEC was the significant predictor of MELD score ≥ 25 at cut off point of ≤ 136 (AUC 0.74; 95% CI: 0.647 to 0.819). Significant negative correlation was seen between AEC with Child–Pugh score and MELD score with correlation coefficient of -0.257 and -0.258.

Conclusion Low level of AEC on admission fairly predicted raised CTP score and MELD score on admission. Low AEC levels predicted increased mortality in cirrhotic patients making it a cheap and reliable prognostic marker in a rural setup.

Keywords Cirrhosis, Child–Pugh score, MELD score, Mortality, Absolute eosinophil count

Introduction

Cirrhosis of liver lies at the terminal stage of the spectrum of chronic liver disease [1, 2]. Morbidity and mortality revolving around cirrhosis of liver depend on various clinical factors like decompensation of the disease, an association of co-morbidities; biochemical parameters like liver function tests and morphological variables like the stage of the cirrhosis [3, 4]. Child-Turcotte-Pugh (CTP) score, Model for end-stage liver disease (MELD)

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and neutrophil–lymphocyte ratio (NLR) scores have been widely employed in clinical practice [5]. In case a patient with chronic liver disease (CLD) is admitted due to acute illness resulting in "systemic inflammatory response syndrome (SIRS)", both CTP and MELD scores may not be accurate in predicting the patient's short-term prognosis as well as survival [6]. When a patient with cirrhosis of liver with some element of acute stress event is admitted, the underlying stressor can have a complex impact on laboratory parameters like prothrombin time, serum creatinine, and serum bilirubin. Thus, their levels may not parallel mortality and morbidity [7]. Many biological factors like CRP, serum-free cortisol, copeptin, and vWF antigen are surrogates of "inflammatory stress" which are recognized recently as promising prognostic markers in patients with cirrhosis [8–10].

The absolute eosinophil count (AEC) levels enable to quickly identify individuals who are at a higher risk of death from sepsis [11]. Eosinophil counts are lower in cirrhotic patients with acute inflammatory processes, which may be because of the eosinophil sequestration as well as localization in the inflammatory region, and also suppression of eosinophil production and its release from the bone marrow [12, 13]. The role of AEC has been studied in various clinical scenarios. It has been reported as an accurate marker of survival and enables prompt recognition of high-risk individuals in cases of perforative peritonitis [14]. Its role has not been explored substantially in cases of cirrhosis of the liver. Hence, we aimed at evaluating its role as a prognostic tool and to correlate its levels with traditional scoring systems CTP score and MELD score.

Materials and methods

This cross-sectional study was carried out in the Department of Medicine at a tertiary care rural hospital in Central India from August 2019 to September 2021. All the patients aged more than 18 years with cirrhosis of liver irrespective of gender and etiology were screened for enrollment in the study. Patients who had history of asthma, hay fever, allergic skin diseases (such as pemphigus and dermatitis herpetiformis), autoimmune disorders (e.g., systemic lupus erythematosus, vasculitis), and drugs like steroids or other immunosuppressive therapy were excluded from the study. Patients having inflammatory conditions, parasitic infestations, and malignant tumors including hepatocellular carcinoma were also excluded from the study. The study was approved and received clearance from the institutional ethical committee in a letter numbered DMIMS (DU)/IEC/Aug-2019/8210. The study was conducted in accordance with Helsinki standards and in accordance with STROBE criteria of observational cross-sectional studies. Signed informed consent from all participants were obtained and kept in the record.

Patient evaluation

All the patients revealing history and physical examination suggestive of cirrhosis of liver were screened for enrolment in our study. Laboratory investigations including complete blood count with absolute eosinophil count, liver function tests, kidney function tests, prothrombin time were done on admission. AEC was measured as a part of automated complete blood count on counter report. Cirrhosis of liver was diagnosed on basis of history suggestive of high risk for development of chronic liver disease; clinical examination showing signs of liver cell failure; laboratory findings showing low serum albumin, increased prothrombin time and ultrasonography findings showing altered echotexture of liver, irregular margins and nodular surface [15]. Hepatitis serology like hepatitis B surface antigen and anti-hepatitis-C antibodies were done for the aetiology of hepatitis B and C. Ceruloplasmin and copper in 24-h urine sample was collected for Wilson disease. For autoimmune hepatitis, antinuclear antibodies, liver/kidney microsome antibodies, antibodies against soluble liver antigen and anti-mitochondrial antibodies were collected. Alfa feto protein was done to exclude hepatocellular carcinoma. CTP and MELD scores were calculated using the laboratory values within the initial 24 h of admission [11].

Sample size

Sample size formula was based on prevalence: $N = Z^2_{1-\alpha/2}$ X P (1-P)/d^2, where $Z_{1-\alpha/2}$ is standard normal variate, P = expected proportion/prevalence of cirrhosis of liver which was taken as 4.5% [16]. Since in the present study P value is considered significant below 0.05, hence 1.96 is used in the equation, d = absolute error or precision (0.04). Therefore, minimum of $\boldsymbol{N} = 93.80$ subjects were required. For better statistical representation, 110 subjects were taken and studied. Flow chart of the study has been highlighted in Fig. 1.

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data with normal distribution were presented as the means ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). Receiver operating characteristic curve was used to find out cut off point of AEC for predicting mortality. Sensitivity, specificity, positive predictive value and negative predictive value were calculated. Pearson correlation coefficient was used for correlation of AEC with Child–Pugh score and MELD score. Multivariate

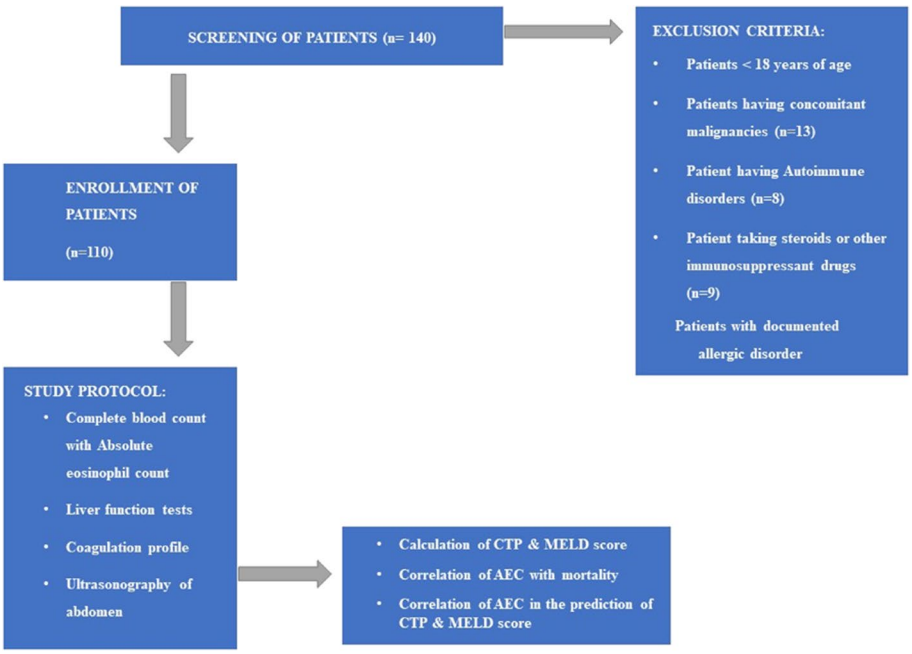

Fig. 1 Plan of study

logistic regression was used to find out significant risk factors of mortality and prolonged hospital stay. For statistical significance, p value of less than 0.05 was considered statistically significant. Software used for analysis was IBM Statistical Package for the Social Sciences (SPSS) Statistics 20 Windows (SPSS Inc., Chicago, USA).

Results

Out of the total 110 patients, 100 (90.91%) were male having mean age of 46.37 ± 11.6 years. Most common aetiology for cirrhosis was history of alcohol, seen in 100 (90.91%) patients followed by viral hepatitis (hepatitis B and C) found in 9 (8.18%). Mean value of AEC was 171.2 ± 76.7 in viral hepatitis. Mean value for CTP score and MELD score was 10.66 ± 1.87 and 24.95 ± 8.19 respectively. Majority of the patients 78 (70.91%) were in Child–Pugh class C. Out of 110 patients, 10 (9.09%) patients died while 100 patients got discharged. All other baseline parameters of the study have been depicted in Table 1.

AEC was the significant predictor of mortality at cut off point of ≤ 120 with 80.30% (AUC 0.803; 95% CI: 0.716 to 0.873) as shown in Fig. 2. 90.00% of patients who died had AEC ≤ 120 and 69.00% of patients who survived had AEC > 120 stating its sensitivity and specificity, respectively. If AEC ≤ 120, then there was 22.50% probability of mortality and if AEC > 120, then 98.60% chances of survival stating its positive predictive value and negative predictive value, respectively as shown in Table 2.

Significant negative correlation was seen between AEC with Child–Pugh score and MELD score with correlation coefficient of -0.257 and -0.258 respectively as shown in Fig. 3.

AEC was the significant predictor of CTP score ≥ 11 at cut off point of ≤ 148 (AUC 0.726; 95% CI: 0.633 to 0.807) as shown in Fig. 4. The patients who had CTP score ≥ 11, 75.86% of patients had AEC ≤ 148 and among patients who had CTP score < 11, 69.23% of patients had AEC > 148 stating its sensitivity and specificity, respectively. If AEC ≤ 148, then there was 73.30% probability of CTP score ≥ 11 and if AEC > 148, then 72.00% chances of CTP score < 11 stating its positive predictive value and negative predictive value, respectively.

AEC was the significant predictor of MELD score ≥ 25 at cut off point of ≤ 136 (AUC 0.74; 95% CI: 0.647 to 0.819) as shown in Fig. 5. The patients who had MELD score ≥ 25, 68.42% of patients had AEC ≤ 136 and among patients who had MELD score < 25, 79.25% of patients had AEC > 136 stating its sensitivity and specificity, respectively. If AEC ≤ 136, then there was 78.00% probability of MELD score ≥ 25 and if AEC > 136, then 70.00% chances of MELD score < 25 stating its positive predictive value and negative predictive value, respectively.

Table 1 Baseline characteristics of the study

Baseline characteristics	Numbers ($n=110$)
Age (years) Mean ± SD	46.37 ± 11.6
Male (percentage)	100 (90.91%)
Female	10 (9.09%)
History of Alcoholism	100 (90.91%)
Viral hepatitis B	3 (2.73%)
Viral hepatitis C	6 (5.45%)
Hemoglobin (gm/dL)	Median (25th-75th percentile), range 8.7 (7.325–9.975), 3.1–16.3
WBC count (per µL)	Median (25th-75th percentile), range 8800 (5525–15000), 900–39600
Platelet count (per µL)	Median (25th-75th percentile), range 99500 (68250–177,000), 10000–718000
Absolute Eosinophil count (per µL)	Median (25th-75th percentile), range 142.5 (103.25–211.5), 26–620 Mean 171.2 ± 76.7 (in hepatitis)
Serum creatinine(mg/dL)	Median (25th-75th percentile)—1.6 (1–2.175)
Serum sodium(mmol/L)	Median (25th-75th percentile)—132.5 (128–138)
Total bilirubin(mg/dL)	Median (25th-75th percentile)—4.5 (2.4–7.7)
Serum albumin(g/dL)	Median (25th-75th percentile)- 2.5 (2.2–2.8)
International normalized ratio	Median (25th-75th percentile)—1.7 (1.5–2)
SGPT(U/L)	Median (25th-75th percentile)—33 (22–58.75),
SGOT(U/L)	Median (25th-75th percentile)—76 (42.5–115.75)
Prothrombin time(seconds)	Median (25th-75th percentile)—21.15 (19.5–25.25)
Child–Pugh score	Mean ± SD -10.66 ± 1.87; Median (range)—11(9–12)
MELD score	Mean ± SD-24.95 ± 8.19; Median (range) -25(19–32)
Mortality	10 (9.09%)

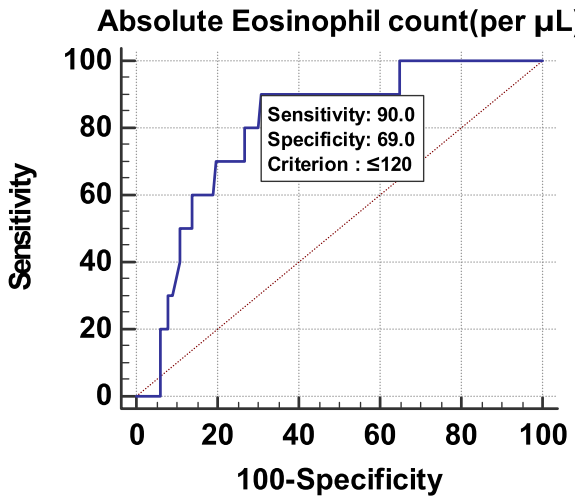

Fig. 2 Receiver operating characteristic curve of Absolute Eosinophil count (per µL) for predicting mortality

Table 2 Receiver operating characteristic curve of Absolute Eosinophil count (per µL) for predicting mortality

Parameters	Value
Area under the ROC curve (AUC)	0.803
Standard Error	0.0634
95% Confidence interval	0.716 to 0.873
P value	< 0.0001
Cut off	≤ 120
Sensitivity (95% CI)	90% (55.5—99.7%)
Specificity (95% CI)	69% (59.0—77.9%)
PPV (95% CI)	22.5% (10.8—38.5%)
NPV (95% CI)	98.6% (92.3—100.0%)
Diagnostic accuracy	70.91%

Discussion

In the present study, we found a definite role of AEC as a substantial tool for the prediction of mortality as well as its value as a prognostic marker. As far as long-term prognosis of cirrhotic patients is concerned, the MELD and CTP scores seem to be more useful but not in acutely ill patients. There was inverse relationship between AEC with CTP score and MELD score in this study. Hence, AEC may be considered as important tool along with CTP and MELD in predicting prognostic outcome in cirrhotic patients.

AEC was the significant predictor of mortality at cut off point of ≤ 120 per µL with 80.30% chances of correctly predicting mortality. AEC less than or equal to 120, had probability of 22.50% mortality and if more than 120, 98.60% had chances of survival. The p-value for AEC with mortality was found to be 0.006 which had resonance with our study. Wilson V et al. also in their study found that the AEC was the substantial tool for predicting in-hospital mortality with cut-off level of 198.5 with 71.6% chances of correctly predicting mortality in cohort of patients of cirrhosis. But in their studies all the patients were with sepsis and SIRS [6].

Anoop KV et al. in their study found a cut-off point for AEC of 110 in predicting mortality with 87.5% chances ($P<0.001$) which was in agreement with our study [7]. Kotecha et al. in their study found to have a cut-off point for AEC 104 with 78.5% chances of correctly predicting mortality [8].

In the present study, substantial negative correlation was seen between AEC with Child–Pugh score and

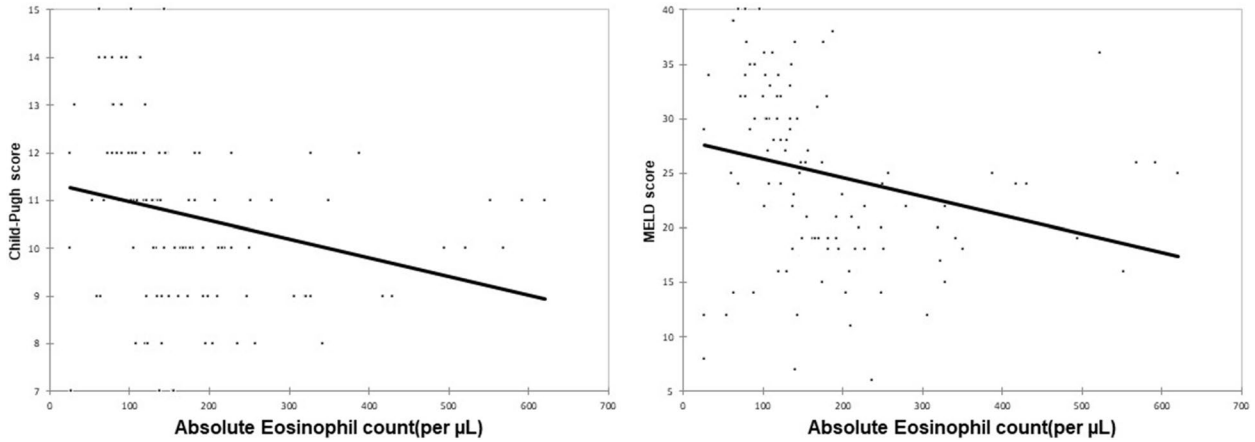

Fig. 3 Correlation of Absolute Eosinophil count (per µL) with CTP score & MELD score

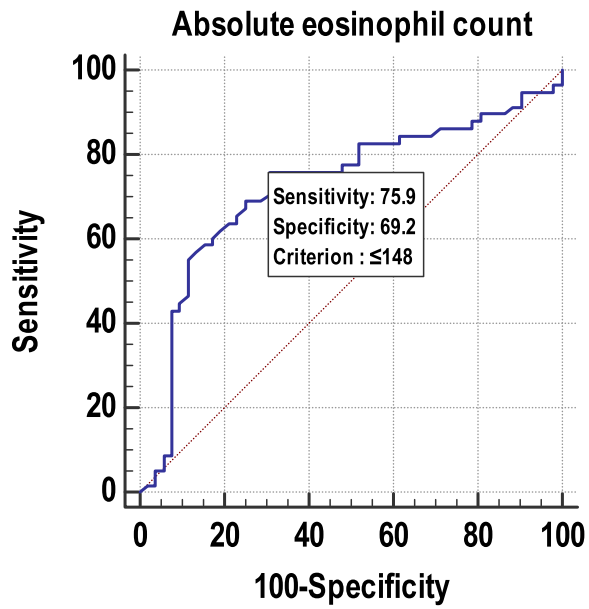

Fig. 4 Receiver operating characteristic curve of absolute eosinophil count for predicting CTP score > = 11

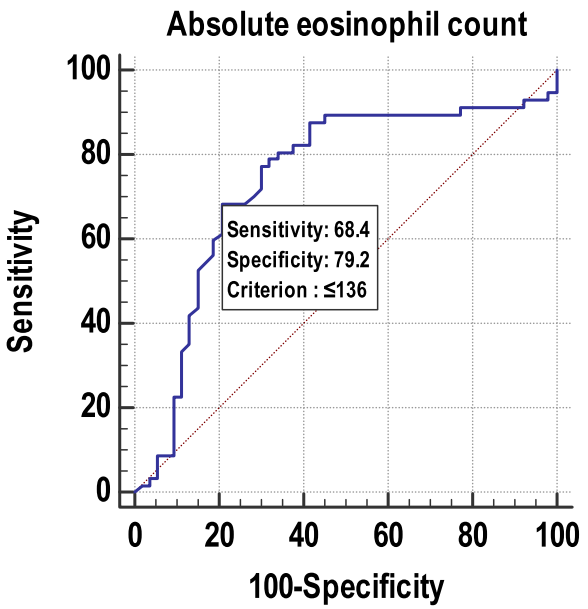

Fig. 5 Receiver operating characteristic curve of absolute eosinophil count for predicting MELD score > = 25

MELD score with correlation coefficient of -0.257 and -0.258 respectively. As far as long-term prognosis of cirrhotic patients is concerned, the MELD and CTP scores are more reliable. In this regard AEC may be better as compared to CTP and MELD in predicting short-term prognosis in terms of mortality in cirrhotic patients. In our study AEC less than 148 had 73.30% probability of high CTP score (≥11) and if more than 148 µL, then 72.00% chances of low CTP score (<11). AEC of less than or equal 136 µL, had 78.00% probability of MELD score of more than 25 and if more than136 µL, then 70.00% chances of MELD score < 25. In the study conducted by Kotecha et al. there was negative correlation of AEC with the CTP score and MELD score with Pearson's correlation coefficient – 0.268 and – 0.225 respectively [8].

Various studies supported the finding of eosinopenia as a poor prognostic marker with a hypothesis stating that eosinophil counts are decreased in cirrhotic patients with acute inflammatory processes, which may be because of the eosinophil sequestration as well as localization in the inflammatory region, and also suppression of eosinophil turnover and release from bone marrow [7, 8].

On literature search there was scarcity of study evaluating the significance of AEC in predicting prognostic outcome in patients with cirrhosis. This is probably the first study which was done in this regard.

Limitations

This study had certain limitation firstly being lack of exclusion of inflammatory, parasitic infestations like conditions which could affect the AEC. Also, being a cross-sectional single-centre study may be a limitation in its generalisation. Association of comorbidities and sepsis had not been stressed upon in the present study which can confound prognostic role of AEC. Eosinophils can falsify the prediction of mortality in the cases of Leucocytosis, as it can be positively or negatively associated with the development of Sepsis and SIRS. Measuring cytokine levels would have added some value.

Conclusion

The present study could establish substantial role of low AEC in the prediction of mortality. Low level of AEC on admission fairly correlated with the increased magnitude of morbidity and mortality in terms of raised CTP score and MELD score.

Author contributions

SK, PS, SA: clinical examination of recruited patients, reporting, writing, and revising the manuscript. SK, PS, CB, DT,MP: anthropometric measurements, shared in writing and revising the manuscript. SK,SA,AW, SB, SAg: introducing idea of this research and manuscript writing. All authors read and approved the fnal manuscript.

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Declarations

Competing interests

The authors declare no conflict of interest.

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