

RESEARCH ARTICLE

Neutrophil count to albumin ratio as a prognostic indicator for HBV-associated decompensated cirrhosis

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ABSTRACT

Background: To explore the value of neutrophil count to albumin ratio (NAR) in predicting the outcomes of patients with HBV-associated decompensated cirrhosis (HBV-DeCi).

Methods: One hundred and fifty-four HBV-DeCi patients were enrolled. The 30-day mortality was determined. Multivariate analysis was applied to identify risk factors for poor outcomes. Receiver operating characteristic curve analyses was performed to evaluate prognostic accuracy.

Results: The 30-day mortality was 10.4%. NAR was significantly higher in non-survivors than in survivors and was an independent predictor for unfavorable prognosis.

Conclusions: The present results indicate that increased NAR is associated with poor survival in HBV-DeCi patients and has potential for clinical application.

KEYWORDS

decompensated cirrhosis, hepatitis B virus, mortality, neutrophil count to albumin ratio, prognostic factor

1 | INTRODUCTION

Hepatitis B virus (HBV) infection is the predominant cause of liver cirrhosis in China.¹ The gradual transition of cirrhosis from the compensated phase to the decompensated phase is characterized by the development of various complications, which are responsible for death.² Although several treatments are available, HBV-associated decompensated cirrhosis (HBV-DeCi) patients have a low survival rate.³ Therefore, identification of effective biomarkers related to prognosis will help to improve the clinical management and survival rate of HBV-DeCi patients.

Systemic inflammation is relatively common in patients with complicated cirrhosis and is linked to their mortality.^{4,5} Some serum-based scores have been explored for their diagnostic and prognostic roles in HBV-associated liver diseases. For example, C-reactive protein (CRP) to albumin ratio,⁶ Albumin-Bilirubin score,⁷ and international normalized ratio to albumin ratio⁸ were proven to be available for stratifying

disease severity and predicting prognosis in HBV-DeCi patients. Neutrophil count to albumin ratio (NAR), a novel inflammatory indicator, has recently been investigated and confirmed to be a predictor of clinical outcomes in patients with pancreatic cancer⁹ and COVID-19.¹⁰ Meanwhile, NAR can also reflect inflammatory status in patients with schizophrenia.¹¹ In the present study, we aimed to determine the role of NAR in predicting the prognosis of HBV-DeCi patients.

2 | METHODS

2.1 | Patients

Adult patients aged ≥ 18 years admitted to Shengzhou People's Hospital and diagnosed with HBV-DeCi were recruited between 01 February 2018 and 01 June 2020. The study was approved by the

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Ethics Committee of the hospital. DeCi was diagnosed on the basis of histological findings or clinical, laboratory, and imaging data, and presence of ascites, variceal bleeding, encephalopathy, or hepatorenal syndrome.¹² The exclusion criteria were: (i) confirmed merging with other hepatotropic infections; (ii) presence of human immunodeficiency virus infection; (iii) hepatocellular carcinoma; (iv) autoimmune hepatitis; (v) alcohol abuse; (vi) hematological diseases; and (vii) immunomodulatory therapy within the previous 6 months. Finally, 154 patients were enrolled. Survival was evaluated at 30 days by reviewing their medical records.

2.2 | Data collection

HBV-DeCi patients were enrolled in the study at admission. Demographic characteristics, clinical information, and blood-test parameters (such as routine blood tests, coagulation parameters, hepatic tests, and renal function tests) were collected on admission. NAR was calculated as neutrophil count ($\times 10^9/L$) divided by albumin (g/dL). Liver function was assessed by the Model for End-Stage Liver Disease (MELD) score as previously described.¹³

2.3 | Statistical analysis

Data were expressed as median (interquartile range) or count (n). Differences between the two groups were analyzed for statistical significance by the Mann-Whitney U test for quantitative data and the chi-square test for categorical data. Correlations between variables were examined by Spearman's analysis. To identify potential correlates of poor outcomes, univariate analyses were first performed in clinical variables. A multivariate regression was subsequently

performed to include variables with $p < 0.10$ in the univariate analysis. Finally, a stepwise selection with the same set of variables was conducted using $p < 0.05$ as a criterion for inclusion. The prognostic power of the identified predictors was evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC). All statistical analyses were performed using SPSS ver. 13.0 and MedCalc ver. 10.0 software. Statistical significance was accepted for values of $p < 0.05$.

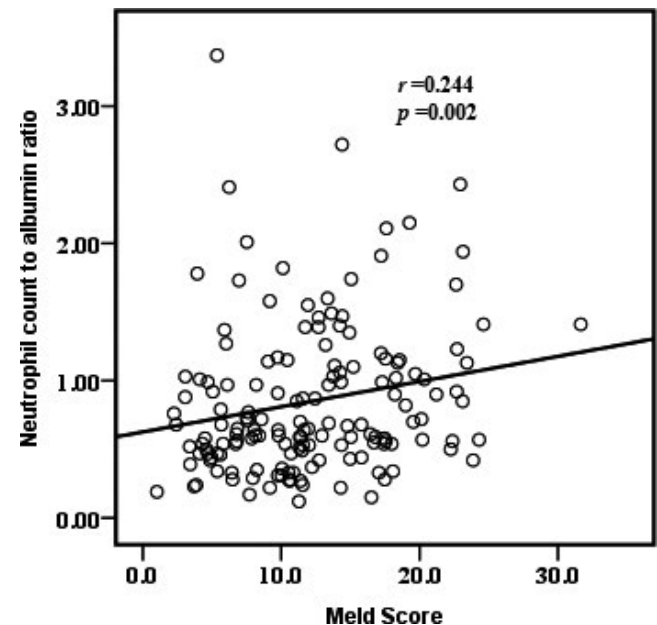


FIGURE 1 Scatterplot illustrating the correlation between Meld score and NAR

TABLE 1 Patient characteristics at baseline

	All patients (n = 154)	Surviving patients (n = 138)	Non-surviving patients (n = 16)	p
Gender (female/male)	32/122	28/110	4/12	0.910
Age (years)	53.0 (46.0–63.0)	53.0 (46.0–62.0)	57.5 (47.5–666.5)	0.386
Total protein (g/dL)	6.12 (5.46–6.69)	6.12 (5.70–6.69)	5.81 (5.17–6.67)	0.183
Albumin (g/dL)	3.11 (2.71–3.46)	3.12 (2.71–3.48)	3.01 (2.69–3.22)	0.277
Alanine aminotransferase (U/L)	29.5 (17.0–48.0)	29.0 (17.0–48.0)	43.0 (23.5–100.5)	0.197
Aspartate aminotransferase (U/L)	46.0 (28.0–73.0)	46.0 (28.0–71.5)	49.0 (30.5–164.5)	0.300
Serum creatinine ($\mu\text{mol/L}$)	74.0 (61.0–87.0)	73.5 (61.0–84.0)	110.5 (66.5–127.0)	0.007
Total bilirubin ($\mu\text{mol/L}$)	41.0 (19.0–96.0)	36.0 (19.0–86.0)	84.0 (70.5–267.5)	0.003
INR	1.34 (1.19–1.59)	1.32 (1.18–1.57)	1.57 (1.33–1.77)	0.023
Neutrophil ($\times 10^9/L$)	2.10 (1.40–3.21)	2.00 (1.40–2.90)	3.40 (2.30–4.95)	0.002
NAR	0.68 (0.49–1.11)	0.64 (0.47–1.02)	1.26 (0.81–1.69)	0.002
Hemoglobin (g/L)	104.0 (86.0–120.0)	105.5 (86.0–121.0)	99.5 (90.5–116.3)	0.492
MELD score	11.5 (7.5–16.7)	11.0 (6.8–15.0)	19.9 (15.8–22.6)	<0.001

Data are expressed as number or median (interquartile range).

Abbreviations: INR, international normalized ratio; MELD, Model for End-stage Liver Disease; NAR, neutrophil count to albumin ratio.

TABLE 2 Logistic regression analyses to identify risk factors associated with mortality in patients with HBV-DeCi

	Univariate			Multivariate		
	Odds ratio	95% CI	<i>p</i>	Odds ratio	95% CI	<i>p</i>
Albumin (g/dL)	0.622	0.242–1.600	0.325			
MELD score	1.290	1.146–1.452	<0.001	1.277	1.131–1.443	<0.001
Neutrophil ($\times 10^9/L$)	1.576	1.189–2.091	0.002			
NAR	3.347	1.504–7.446	0.003	3.237	1.221–8.567	0.018
Age	1.018	0.972–1.67	0.454			

Abbreviations: CI, Confidence interval; MELD, Model for End-stage Liver Disease; NAR, neutrophil count to albumin ratio.

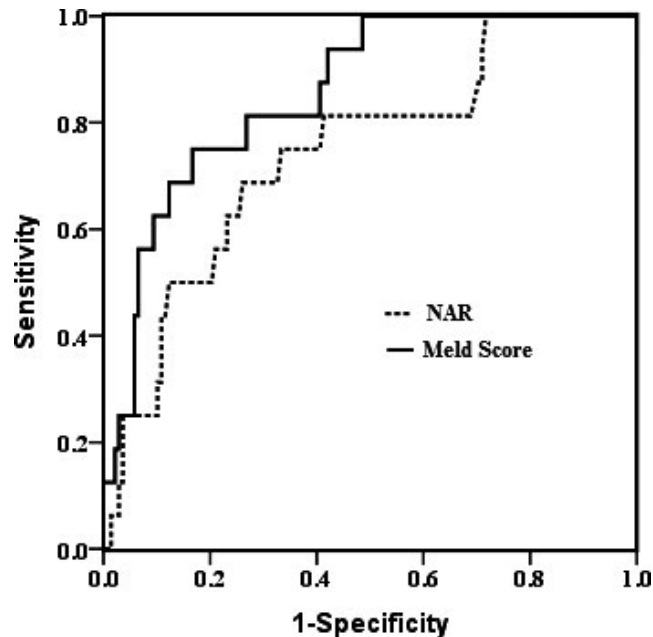


FIGURE 2 Receiver operating curves showing the relative prognostic performances of Meld score and NAR for prediction of mortality in patients with HBV-DeCi

3 | RESULTS

3.1 | Patients' characteristics

A total of 154 patients were enrolled. The main reasons for admission were ascites (74.6%, 115/154), variceal bleeding (16.2%, 25/154), hepatorenal syndrome (7.8%, 12/154), and encephalopathy (2.6%, 4/154). As shown in Figure 1, NAR and MELD score had a marked positive correlation ($r = 0.244$, $p = 0.002$).

A total of 16 (10.4%) patients died within 30 days after admission. The causes of death were liver failure in six patients, hepatic encephalopathy in three patients, variceal bleeding in four patients, and hepatorenal syndrome in three patients. Subsequently, the HBV-DeCi patients were divided into non-survivors and survivors according to their 30-day outcomes. As shown in Table 1, there were significant differences in creatinine, total bilirubin, international normalized ratio (INR), MELD score, neutrophil count, and NAR between

the survivors and non-survivors (all $p < 0.05$). However, age, gender, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, and hemoglobin were similar between the two groups.

3.2 | Factors associated with death

On univariate analysis, MELD score, neutrophil count, and NAR were associated with poor outcomes. On multivariate analysis, only NAR and MELD score remained significant independent predictors for death (Table 2). ROC curve analyses were carried out to estimate the value of NAR and MELD score for predicting mortality (Figure 2). The cutoff values for NAR and MELD score were 0.99 (sensitivity 68.8%, specificity 73.9%) and 17.2 (sensitivity 75.0%, specificity 83.3%), respectively. The AUC for NAR for predicting 30-day mortality (0.685 [0.67–0.77]) was similar to that for MELD score (0.74 [0.70–0.78]), with no significant difference ($Z = 1.763$, $p = 0.078$).

3.3 | Clinical and laboratory findings related to NAR

The participants were stratified into two groups based on the cut-off value for NAR (≤ 0.99 , $n = 104$ vs. > 0.99 , $n = 50$). Patients with NAR > 0.99 had lower serum albumin, higher MELD score, higher aspartate aminotransferase, higher total bilirubin, higher neutrophil count, and higher mortality than patients with NAR ≤ 0.99 (Table 3).

4 | DISCUSSION

The MELD score is widely adopted to evaluate the severity of liver dysfunction and predict the prognosis of patients with liver disease and employs serum creatinine, total bilirubin, and INR.¹³ In the present study, we found that non-survivors had higher NAR than survivors. Moreover, high NAR was an independent risk factor for unfavorable prognosis in HBV-DeCi patients, with a similar predictive power to MELD score. By comparison, NAR, which only requires testing of blood samples, is more easily calculated and has a lower cost than MELD score. Notably, previous studies identified associations of several objective indicators obtained in routine tests with

	Low group (NAR ≤ 0.99, n = 104)	High group (NAR > 0.99, n = 50)	p
Gender (female/male)	19/85	13/37	0.371
Age (years)	53.0 (46.0–62.5)	52.0 (46.0–63.0)	0.795
Total protein (g/dL)	6.16 (5.80–6.71)	5.89 (5.37–6.68)	0.101
Albumin (g/dL)	3.21 (2.86–3.56)	2.92 (2.52–3.14)	0.001
Alanine aminotransferase (U/L)	29.0 (15.0–47.5)	30.5 (20.0–62.0)	0.145
Aspartate aminotransferase (U/L)	41.5 (27.0–70.0)	48.5 (32.0–88.0)	0.047
Total bilirubin (μmol/L)	34.0 (16.5–82.5)	65.0 (26.0–136.0)	0.001
INR	1.32 (1.18–1.59)	1.37 (1.26–1.59)	0.280
Serum creatinine (μmol/L)	74.5 (60.0–84.0)	74.0 (64.0–104.0)	0.303
MELD score	10.7 (6.7–15.1)	14.2 (9.7–18.3)	0.003
Hemoglobin(g/L)	104.0 (82.5–118.0)	104.5 (93.0–125.0)	0.146
Neutrophil (×10 ⁹ /L)	1.70 (1.20–2.10)	3.75 (3.10–5.30)	<0.001
30-day mortality (yes/no)	5/99	11/39	0.003

TABLE 3 Clinical data according to NAR levels

Data are expressed as number or median (interquartile range).

Abbreviations: INR, international normalized ratio; MELD, Model for End-stage Liver Disease.

adverse outcomes in cirrhotic patients, including CRP to albumin ratio,⁶ Albumin-Bilirubin score,⁷ and INR to albumin ratio.⁸ The present study complements these previous studies and indicates that NAR may be useful for predicting prognosis in HBV-DeCi patients.

There are at least two possible explanations for why NAR can be a novel independent risk factor for death in HBV-DeCi patients. The first and most important is that inflammatory responses play essential roles in the development and progression of HBV-associated liver diseases in patients. Accumulated evidence suggests that inflammation is frequently present in advanced cirrhotic patients and linked to adverse outcomes.^{4,5} Activation of systemic inflammation is characterized by a profile of excessive proinflammatory cytokines. Neutrophils are stimulated and activated by these inflammatory cytokines to promote their phagocytosis and bactericidal effects and reflect ongoing inflammation.¹⁴ In turn, neutrophils promote inflammation by secreting a series of inflammatory cytokines (IL-1 or IL-8) and releasing granule-containing enzymes such as oxidants, proteases, and antimicrobial proteins that mediate liver inflammation, apoptosis, and necrosis of hepatocytes.¹⁵ It has been proposed that baseline neutrophils may be linked to tissue damage severity, reinfarct risk, and poor neurological outcomes.^{16–19} In a previous study, newly intensified hepatic inflammation in DeCi patients during liver injury flare-up was shown to trigger a large neutrophil response.¹⁵ The present study indicated that neutrophils were markedly elevated in non-survivors compared with survivors. Neutrophils drive the early inflammatory response following acute infection, and a high neutrophil count can act as an important index for systemic infection. Thus, neutrophils can be actively recruited during acute-phase reactions and act as a marker of disease severity and tissue inflammation.¹⁵ Furthermore, serum albumin is known to be a negative acute-phase reactant, with low blood levels in acute inflammation and an inverse association with magnitude of systemic inflammatory

response. Several studies demonstrated that decreased albumin was associated with poor outcomes in acutely ill patients.^{20–23} We noted that serum albumin was slightly lower in non-survivors compared with survivors. Besides inflammatory responses, another possible explanation for the poor outcomes is nutritional status. Albumin is an index that reflects nutritional status, and it is well known that low albumin is often associated with malnutrition. Albumin is produced by the liver, and low albumin was demonstrated to be a common complication in cirrhotic patients that could lead to ascites or edema, and account for increased mortality.^{24,25} Our results demonstrated that the elevated NAR mainly resulted from increased neutrophils and decreased albumin. Thus, we propose that the prognostic value of NAR is related to inflammatory responses and poor liver function. We also found a significant association between NAR and MELD score as well as an association between high NAR and high in-hospital mortality, suggesting that high NAR may be a predictive factor for liver injury severity and progression in HBV-DeCi patients. Thus, we believe that NAR could be beneficial for prediction of outcomes in HBV-DeCi patients.

The present study had some limitations. First, the study had a retrospective design and a small sample size. Second, we did not assess whether NAR was correlated with other scores or ratios, such as CRP to albumin ratio, Albumin-Bilirubin score, and INR to albumin ratio, in HBV-DeCi patients. Third, we did not evaluate some inflammatory markers, such as C-reactive protein and interleukin-6. The evaluation of these markers which help to elucidate the mechanism underlying the findings presented here. Finally, NAR was only measured at baseline and not serially.

In summary, the present study suggests that NAR can be a novel and potentially useful predictor for outcomes in HBV-DeCi patients. This new method may be useful for classification of patients to facilitate appropriate management toward improved prognosis.

Nevertheless, larger prospective studies are warranted to corroborate the present findings.

CONFLICT OF INTEREST

None of the authors have any commercial or other association that might pose a conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request.

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