Higher levels of neutrophil percentage-to-albumin ratio predict increased mortality risk in patients with liver cirrhosis: a retrospective cohort study

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Background Recent studies indicated that the neutrophil percentage-to-albumin ratio (NPAR) was a predictor of mortality in several diseases. There has been no evidence to prove the predictive function of NPAR in patients with liver cirrhosis. Therefore, this study aimed to investigate the association between NPAR and clinical outcomes in cirrhotic patients.
Methods We retrospectively recruited hospitalized decompensated cirrhotic patients from the tertiary grade-A hospital. Patients with malignancy or severe cardiac, respiratory and kidney diseases were excluded. Demographical data, liver functions, complications and outcomes of cirrhosis were recorded. NPAR was calculated through the ratio of neutrophil percentage (%)/serum albumin concentration (g/dL) at admission to the hospital. Cox proportional hazards models were performed to evaluate the prognostic values of NPAR, and subgroup analyses were utilized to ensure stable results.
Results A total of 376 patients with decompensated liver cirrhosis at baseline were enrolled. The liver dysfunction, cirrhosis-related complications and mortality rate increased along with the tertiles of NPAR. In multivariate analysis, higher NPARs were independently associated with increased risk of mortality in patients with liver cirrhosis after adjustments for confounding factors (tertile 3 versus tertile 1: adjusted HR = 1.92; 95% CI, 1.04–3.56; *P* trend = 0.008) and each unit increase of NPAR implicated a 4% increase risk of mortality. Subgroup analysis demonstrated no significant interactions in most subgroups.
Conclusion Increased NPAR was independently correlated with a higher risk of mortality in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 35: 198–203

Introduction

Liver cirrhosis, one of the leading causes of mortality, is distributed worldwide [1]. Cirrhosis is a consequence of various chronic liver injuries including viral hepatitis, alcoholic liver diseases, non-alcoholic steatohepatitis, and so on. It is reported that liver cirrhosis was considered as the 15th leading cause of death in the USA and causes about one million deaths each year worldwide [2], which brings a huge burden to the family and society.

However, the pathological mechanisms of the formation and progression of liver cirrhosis were complex. Inflammation showed a close relationship with the liver and played a malignant role in the process of liver cirrhosis [3]. As one of the classic inflammation factors, neutrophils release a wide range of cytokines, reactive oxygen species [4], which lead to liver injury. Albumin served as the main component of maintaining plasma osmotic pressure, as well as exhibited anti-inflammatory actions [5]. As a potential biomarker, NPAR is calculated as the ratio of neutrophil percentage (%)/serum albumin concentration (g/dL) ratio [6]. Recently, several studies have reported that NPAR may serve as the prognostic indicator in patients with palliative pancreatic cancer [7], acute kidney injury [8], myocardial infarction [9], and so on. Nevertheless, to the best of our knowledge, the prognostic value of NPAR in liver cirrhosis remains unknown. Therefore, based on the above, we hypothesize that NPAR may affect the prognosis of liver cirrhosis and performed a retrospective study to validate the assumption. We present the following article in accordance with the STROBE reporting checklist.

Materials and methods

Study design

The present research was a retrospective cohort study. Hospitalized adult patients with liver cirrhosis were consecutively included from August 2017 to October 2021. The study protocol was approved by Beijing Youan Hospital Ethics Committee (NO: 2022-036). The research was performed according to the guidelines of the Helsinki Declaration (6th revision, 2008).

European Journal of Gastroenterology & Hepatology 2023, 35:198–203

Keywords: inflammation, liver cirrhosis, mortality, neutrophil percentage-to-albumin ratio, prospective study

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Received 12 August 2022 **Accepted** 21 September 2022

Patient selection and enrollment criteria

Study subjects were eligible for enrollment based on the following criteria: (1) age ≥18 years old and (2) diagnosed with decompensated cirrhosis. Cirrhosis was diagnosed according to laboratory tests, ultrasound or radiology imaging results whereas patients with the development of ascites, bleeding and hepatic encephalopathy were diagnosed as decompensated. The major exclusion criteria were:(1) HIV-coinfections; (2) a serious disease of the heart, lung or kidney which might impact the survival of the patients and (3) patient with incomplete follow-up data for the extraction of clinical variables.

The standard care and data collection

The standard care included etiological treatment, supportive care, treatment of complications of cirrhosis and anti-infection treatment when necessary. Complications of cirrhosis were treated according to guidelines. Demographical data, laboratory parameters and cirrhosis-related complications were recorded. The severity of cirrhosis was evaluated by the Child-Pugh score and model of end-stage liver disease (MELD) score. The MELD score was calculated as $9.57 \times \ln$ (serum creatinine) $+ 3.78 \times \ln$ (bilirubin) $+ 11.2 \times \ln$ [international standard ratio (INR)] $+ 6.43 \times$ (0 for alcohol-related liver disease or cholestatic liver disease; one for all other causes) [10]. Hepatic encephalopathy was staged as minimal, Grade I, Grade II, Grade III and Grade IV according to West Haven criteria [11]. Ascites were staged to mild, moderate and large ascites according to clinical practice guidelines [12]. The NPAR was calculated at baseline at admission to the hospital according to the formula: (neutrophil percentage%) × 100/albumin(g/dL).

Statistical analysis

Continuous variables were described as mean ± SD and analyzed with Student's *t*-test if the distribution was normal with Kolmogorov-Smirnov tests; otherwise, variables were presented by medians (interquartile ranges, IQRs) and nonparametric Mann-Whitney U test was utilized. Categorical data were expressed as numbers and percentages and were analyzed using the chi-square test. Patients were stratified according to NPAR tertiles. We employed multivariable Cox proportional hazard regression to investigate the independent relationship between NPAR and mortality of cirrhosis patients after accounting for significant confounders, and the hazard ratio (HR) and β were obtained. To prove the stability of the results, three regression models were developed with continuous variable and NPAR tertiles and confounders which changed the estimates of NPAR on mortality by more than 10% were adjusted. Moreover, survival comparison was analyzed with a log-rank test and displayed with Kaplan–Meier survival curves. Subgroup analysis was conducted to determine whether the association of NPAR and overall mortality differed across various subgroups classified by sex, age, etiology, white blood count (WBC), hemoglobin, platelet, bilirubin, creatinine, ascites, hepatic encephalopathy and esophageal gastric variceal bleeding. Statistical analyses were performed using EmpowerStats software 2.0 (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, Massachusetts, USA) and R (http:// www.R-project.org) software. Graphs were performed with GraphPad Prism Software Version 5 (GraphPad Software, La Jolla, California, USA, 2012). $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients with different neutrophil percentage-to-albumin ratio level

Based on the exclusion criteria, 61 patients with malignancy, 13 patients coinfected with HIV, 28 patients with serious disease in other organs, 101 patients with compensated liver cirrhosis and 15 patients lost to follow-up were excluded. Finally, a total of 376 patients with decompensated liver cirrhosis were enrolled in this study. The main etiologies of cirrhosis included hepatitis B, hepatitis C, alcoholic liver diseases and autoimmune hepatitis. Among them, 254 (67.55%) cases were male and the median follow-up time was 12.86 (7.39–16.13) months and 111 cases (29.52%) died or underwent liver transplantation. The patients were divided into low tertile, middle tertile and high tertile NPAR groups according to their baseline NPAR. Characteristics of patients in the whole and each group are listed in Table 1. As is shown, patients in the high NPAR group (NPAR ≥21.52) were elder and had higher levels of WBC, neutrophils percentage, bilirubin, creatinine, INR, Child-Pugh scores and MELD scores and lower levels of albumin. Besides, they were more likely to complicate with severer ascites, but not with esophageal gastric varices bleeding and hepatic encephalopathy. In the cohort, there were more male patients than female in the high NPAR group, similar to alcoholic-related cirrhosis patients when compared to cirrhosis with other etiologies.

Prediction of mortality by baseline neutrophil percentage-to-albumin ratio

To explore the prognostic significance of NPAR, we used NPAR as the independent variable, mortality as the dependent variable, whereas sex, age, INR, fibrinogen, bilirubin, albumin, platelet and creatinine as the covariates which were adjusted in multivariate Cox regression analysis. NPAR was described both as the continuous values and tertiles. In the crude model, none of the parameters was adjusted. In the model I, gender, age and etiology were adjusted, whereas in the model II, sex, age, INR, fibrinogen, bilirubin, albumin, platelet and creatinine were adjusted. Model II demonstrated that each unit increase of NPAR implicated a 4% increase in risk of mortality (HR = 1.04; 95% CI, 1.00–1.08; $P = 0.049$). When being compared with the low NPAR group, patients in the high NPAR group showed an increase of 92% mortality risk (HR = 1.92; 95% CI, 1.04–3.56; P trend = 0.008) (Table 2).

Subgroup analysis

There were no significant interactions in most subgroups (Fig. 1). But increased mortality risk was observed in patients with higher platelet count and bilirubin (P for interaction = 0.039 and 0.047).

Table 1. Baseline characteristics of patients with decompensated liver cirrhosis in neutrophil percentage-to-albumin ratio tertile group

		Tertiles of NPAR			
	Whole group	Low group (≤17.31)	Medium group (17.34–21.46)	High group (≥21.52)	*P* value
N	376	97	134	145	
Male (N, %)	254 (67.55%)	61 (62.89%)	82 (61.19%)	111 (76.55%)	0.012
Age (years)	56.86 ± 11.41	54.08 ± 12.74	57.31 ± 11.54	58.30 ± 10.01	0.016
Etiology (N/%)					0.086
HBV	125 (33.24%)	32 (32.99%)	50 (37.31%)	43 (29.66%)	
HCV	59 (15.69%)	18 (18.56%)	23 (17.16%)	18 (12.41%)	
Auto-immune	28 (7.45%)	10 (10.31%)	11 (8.21%)	7 (4.83%)	
Alcoholic	114 (30.32%)	25 (25.77%)	30 (22.39%)	59 (40.69%)	
Others/unknown	50 (13.30%)	12 (12.37%)	20 (14.93%)	18 (12.41%)	
Laboratory parameters					
WBC ($\times 10^9$/L)	4.03 ± 2.67	3.33 ± 1.89	3.48 ± 2.00	5.00 ± 3.30	<0.001
Neutrophils (%)	63.35 ± 12.35	51.77 ± 10.59	60.83 ± 7.15	73.36 ± 8.89	<0.001
Hemoglobin(g/L)	92.82 ± 26.58	97.76 ± 27.35	91.56 ± 26.43	90.67 ± 25.94	0.100
Platelet ($\times 10^9$/L)	75.79 ± 48.98	78.23 ± 45.76	75.35 ± 52.89	74.56 ± 47.60	0.843
ALT (U/L)	18.00 (12.00–29.00)	20.00 (12.00–31.00)	17.00 (12.00–26.00)	21.00 (12.00–29.00)	0.753
AST (U/L)	33.00 (24.00–50.25)	32.00 (26.00–46.00)	31.50 (23.25–44.00)	37.00 (24.00–63.00)	0.537
Bilirubin (μmol/L)	34.85 (22.17–75.90)	27.90 (20.30–57.50)	31.55 (22.00–52.03)	46.00 (27.60–111.20)	<0.001
Albumin (g/dL)	31.42 ± 5.02	35.56 ± 4.99	31.64 ± 3.41	28.45 ± 4.22	<0.001
Creatinine (mmol/L)	63.25 (52.00–80.00)	60.00 (52.00–75.00)	62.00 (49.00–76.60)	67.00 (55.10–89.00)	0.008
INR	1.40 (1.26–1.70)	1.34 (1.23–1.50)	1.38 (1.26–1.62)	1.54 (1.30–2.07)	<0.001
Complications, *N*/(%)					
Ascites					0.001
None	44 (11.70%)	11 (11.34%)	16 (11.94%)	17 (11.72%)	
Mild	184 (48.94%)	64 (65.98%)	65 (48.51%)	55 (37.93%)	
Moderate	118 (31.38%)	18 (18.56%)	40 (29.85%)	60 (41.38%)	
Large	30 (7.98%)	4 (4.12%)	13 (9.70%)	13 (8.97%)	
Hepatic encephalopathy					0.239
None	293 (77.93%)	83 (85.57%)	104 (77.61%)	106 (73.10%)	
Stage 1	68 (18.09%)	12 (12.37%)	27 (20.15%)	29 (20.00%)	
Stage 2–4	15 (3.99%)	2 (2.06%)	3 (2.24%)	10 (6.90%)	
Esophageal gastric varices bleeding					0.157
No	256 (68.09%)	64 (65.98%)	85 (63.43%)	107 (73.79%)	
Yes	120 (31.91%)	33 (34.02%)	49 (36.57%)	38 (26.21%)	
Liver function					
Child–Pugh score	9.06 ± 2.31	7.89 ± 2.12	8.75 ± 1.96	10.14 ± 2.26	<0.001
MELD score	8.50 (4.85–12.90)	6.06 (3.80–9.78)	7.99 (3.78–11.51)	9.85 (7.01–15.62)	<0.001
Living status					00.002
Alive	265 (70.48%)	78 (80.41%)	99 (73.88%)	88 (60.69%)	
Non–alive (%, N of death/LT)	111 (29.52%, 98/33)	19 (19.59%,15/4)	35 (26.12%, 31/4)	57 (39.31%, 52/5)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase, HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international standard ratio; MELD, model of end–stage liver disease; LT, liver transplantation; WBC, white blood cell. .

Table 2 Multivariate Cox regression for neutrophil percentage-to-albumin ratio and mortality

	Non–adjusted		Model I		Model II	
Exposure	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
NPAR continuous	1.09 (1.05–1.13)	<0.001	1.09 (1.05–1.14)	<0.001	1.04 (1.00–1.08)	0.049
NPAR tertiles						
Low	1.0		1.0		1.0	
Medium	1.84 (1.02–3.29)	0.041	1.86 (1.01–3.43)	0.046	1.40 (0.76–2.58)	0.284
High	3.64 (2.09–6.32)	<0.001	3.84 (2.12–6.95)	<0.001	1.92 (1.04–3.56)	0.037
P trend	0.004		0.007		0.008	

CI, confidence interval; HR, hazard ratio; NPAR, neutrophil percentage-to-albumin ratio.

Kaplan–Meier curve of neutrophil percentage-to-albumin ratio tertiles

The mortality rates (including death and liver transplantation) in the low, medium and high NPAR groups were 19.59%, 26.12% and 39.31%, respectively ($P < 0.001$, Table 1). The death reasons included esophageal gastric varices bleeding ($n = 42/98$; 42.86%), liver failure ($n = 19/98$; 19.39%), spontaneous bacterial peritonitis ($n = 18/98$; 18.37%), hepatic encephalopathy ($n = 5/98$; 5.10%), hepatorenal syndrome ($n = 5/98$; 5.10%) and other causes ($n = 9/98$; 9.18%). Kaplan–Meier curves for the low, medium and high NPAR groups showed that patients in the high NPAR group showed significantly higher risk than patients in the low (log-rank test: $P < 0.001$) and medium ($P = 0.004$) NPAR groups (Fig. 2).

The prognostic value of neutrophil percentage-to-albumin ratio compared to model of end-stage liver disease score

The receiver operating curve curves were generated to evaluate the predictive ability, and the area under curve (AUC) of mortality for NPAR was 0.64 (95% CI, 0.60–0.68; $P = 0.031$), which was superior to neutrophils (%)

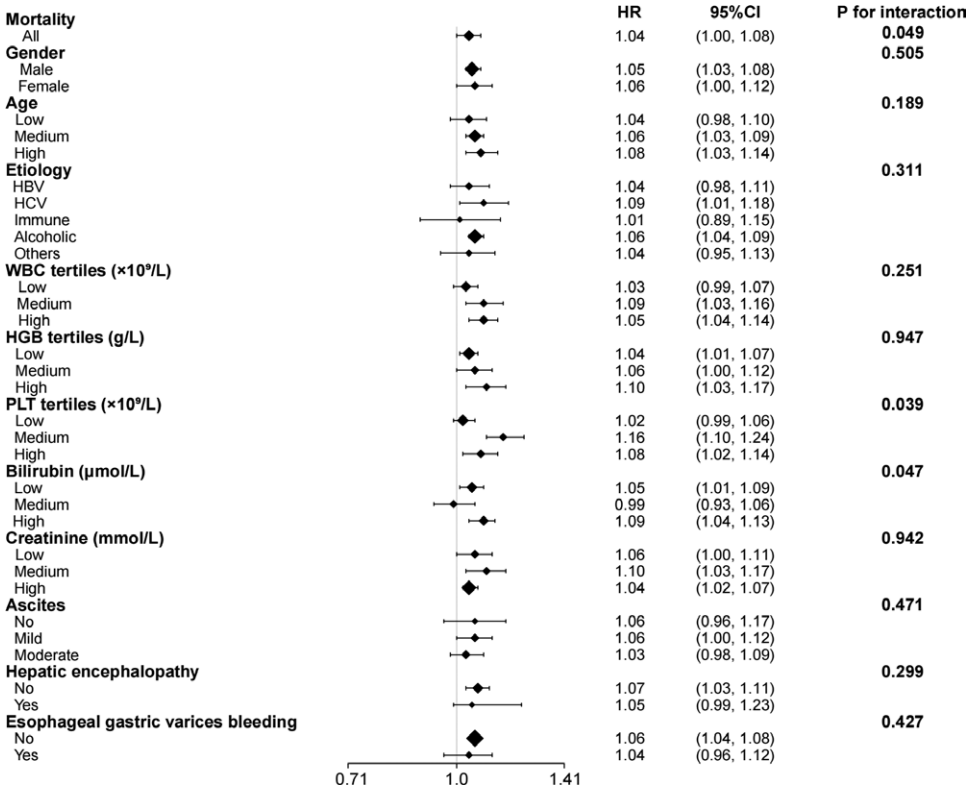

Fig. 1. Subgroup analysis of the association between NPAR and mortality. NPAR, neutrophil percentage-to-albumin ratio.

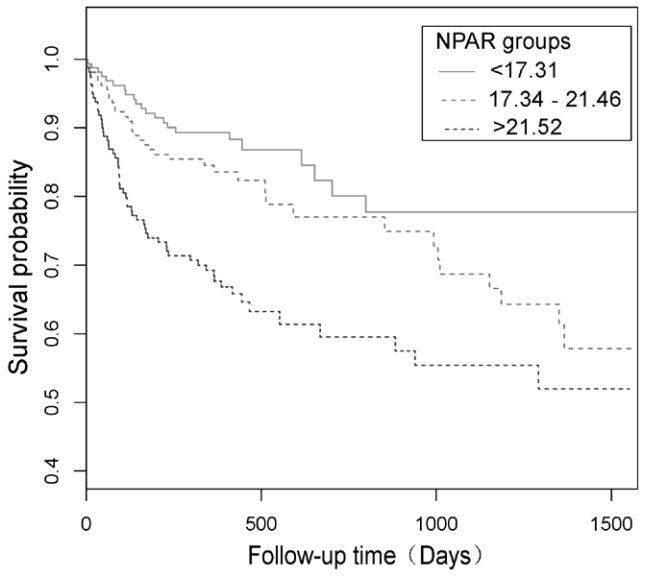

Fig. 2. Kaplan–Meier (K-M) survival curves for mortality in liver cirrhosis.

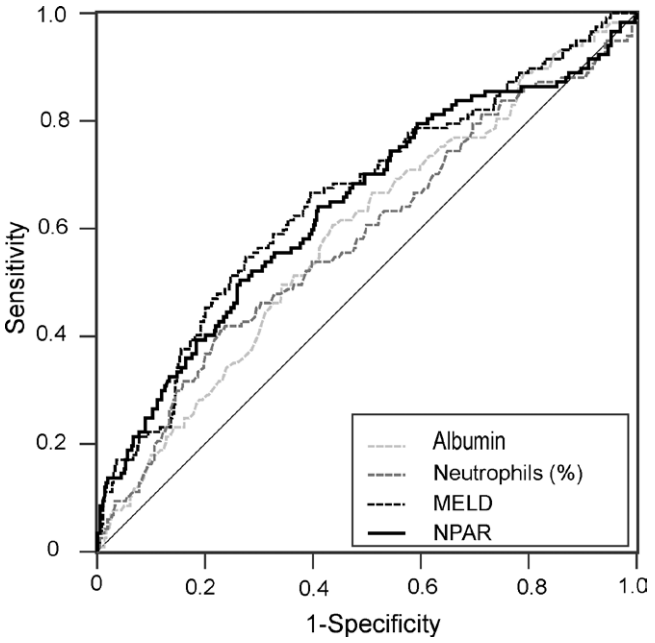

Fig. 3. Receiver operating characteristic curve of NPAR value, neutrophils (%), albumin and MELD. MELD, model of end-stage liver disease; NPAR, neutrophil percentage-to-albumin ratio.

(AUC, 0.58; 95% CI, 0.54–0.63; $P = 0.032$) and albumin (AUC, 0.59; 95% CI, 0.54–0.65; $P = 0.030$) alone ($P = 0.003$ and 0.041, separately). The cut-off of NPAR was 19.5, with the sensitivity and specificity of 63.72 and 59.08%, separately. Besides, the AUC of NPAR was similar to the AUC of MELD (AUC, 0.66; 95% CI, 0.61–0.70; $P = 0.030$) ($P = 0.646$), which are shown in Fig. 3.

Discussion

To our knowledge, this is the first study on the prognostic value of NPAR and mortality in patients with liver cirrhosis. Multivariate regression showed the independent effect of NPAR on mortality even after adjusting for possible confounding variables. Also, subgroup analyses showed no significant interactions in most strata.

The pathophysiological mechanisms of liver cirrhosis were complex and multifactorial. Studies have shown that inflammation was one of the independent risk factors of liver cirrhosis [13,14]. Neutrophils played an essential role

in mediating inflammatory responses. Previous studies indicated infection increases mortality risk in decompensated liver cirrhosis patients [15]. As the protein synthesized specifically by the liver, serum albumin concentration was also influenced by inflammation [16]. Hypoalbuminemia was reported to be a strong indicator for poor prognosis in many diseases as a result of malnutrition and inflammation [17,18]. As is well-known that albumin was synthesized by the liver, and serum albumin significantly decreased in parallel with the severity of liver diseases.

As the ratio of two easily accessible parameters, NPAR possess advantages in convenience and feasible approach. The relationship between high NPAR levels and poor prognosis has been confirmed in several diseases. Previous studies proved that higher NPARs were associated with an increased risk of short-time and long-time mortality in critically ill patients with septic shock [19], coronary artery diseases [20] and cardiogenic shock [21] after adjustments for possible confounding factors. And NPAR >15.7 showed an increase of 90% in the risk of contrast-associated acute kidney injury [22].

In this study, we first proved that patients with higher NPAR showed severer liver dysfunctions, cirrhosis-related complications and higher mortality risk. Previous studies have proved that inflammatory processes are one of the main mechanisms in the progression of alcoholic-related cirrhosis patients [23]. This may explain the higher proportion of alcoholic cirrhosis in the high NPAR group. And in the multivariate Cox regression, NPAR was independent of other clinical indexes, including bilirubin, INR, etc. Although both neutrophil percentage and albumin are associated with the poor prognosis in liver cirrhosis, NPAR showed better predictive power than either neutrophils or albumin alone ($P = 0.003$ and 0.041, separately). This may be explained that inflammation resulted in a reverse response to neutrophil and albumin, and the ratio of neutrophil/albumin may further enhance the effect of inflammation. Therefore, NPAR proved to be more sensitive and reliable compared with neutrophil and albumin alone. And NPAR showed a similar prognostic value compared with relatively complex MELD, indicating the validity and reliability of NPAR. Besides, in subgroup analysis, the effect of NPAR on mortality tends to be strengthened in patients with higher platelet count and bilirubin. Increasing evidence suggests that platelets play critical roles in regulating inflammation [24]. In nonalcoholic steatohepatitis (NASH) patients, circulating platelets present a proinflammatory phenotype and antiplatelet therapy in NASH mice helps prevented NASH [25]. The participation of platelets in systemic inflammation may explain the enhanced effect of NPAR on mortality in higher platelet count.

This study was a single-center retrospective study which may lead to inevitable bias. Despite attempts to control for several potential confounding factors, residual confounding factors may remain. Second, we were unable to evaluate other inflammatory markers, such as C-reactive protein and procalcitonin, which may help to understand the possible mechanism. Therefore, a multicenter, prospective case-control study may be needed to verify the conclusion of this study.

In conclusion, this study indicated that higher NPAR was independently correlated with increased risk of mortality in patients with liver cirrhosis after adjusting for potential confounding factors. Thus, NPAR may alert clinicians and provide more guidance for clinical work.

Acknowledgements

The data are available from the corresponding author upon reasonable request.
Y.L. and J.Z. mainly contributed to the study conception, design and interpretation of data for the work and revision of the manuscripts. X.D. and X.W. mainly contributed to the database establishment, analysis and first proof. L.M., X.L. and H.G. are mainly responsible for the data collection. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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