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Original Article

Predictive effect of systemic immune inflammatory index combined with neutrophil-to-lymphocyte ratio on prognosis of patients with acute-on-chronic liver failure

Xinchun He, Yihe Lin, Hanyu Qiu, Xiaofang Wang, Baining Zhu

Department of Infectious Disease, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha 410005, Hunan, P. R. China

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Abstract: Objective: To explore the predictive effect of systemic immune inflammatory index (SII) combined with neutrophil-to-lymphocyte ratio (NLR) on prognosis of acute-on-chronic liver failure (ACLF) patients. Methods: A retrospective analysis was conducted on the data of 160 patients diagnosed with hepatitis B virus (HBV)-ACLF in Hunan Provincial People's Hospital from June 2022 to June 2023. The patients were divided into a survival group and a death group based on their survival status within 90 days after admission. General data, laboratory indicators, and complications were recorded. The risk factors affecting prognosis of HBV-ACLF patients and the correlation between NLR, SII, and model for end-stage liver disease (MELD) score were analyzed, and the predictive effect of NLR and SII on prognosis was evaluated. Results: Compared to the survival group, the age, MELD score, and incidence of infection of the death group were higher, and the expression levels of total bilirubin, aspartate aminotransferase, serum creatinine, white blood count, neutrophil, NLR, SII, and international normalized ratio were increased, while the expression levels of alanine aminotransferase, platelets and lymphocytes were decreased (all $P<0.05$). NLR, SII and MELD score were all risk factors affecting the prognosis of HBV-ACLF patients (all $P<0.001$). There was a positive correlation between NLR, SII and MELD score ($P<0.001$). SII combined with NLR showed good performance in predicting the prognosis within 90 days after admission in ACLF patients. Conclusion: SII combined with NLR has a good prognostic effect on ACLF patients.

Keywords: Acute-on-chronic liver failure, systemic immune inflammatory index, neutrophil to lymphocyte ratio, prognosis, hepatitis B virus

Introduction

Liver failure results from various etiological factors, and leads to serious liver damage, and then to functional decompensation [1]. Acute-on-chronic liver failure (ACLF) denotes an acute decompensation in liver function superimposed on the underlying chronic liver disease. This disease causes multiple organ failure, and is characterized by rapid progression and high mortality [2]. According to the survey, the prevalence of ACLF is about 30%, among which 20% of people have symptoms of ACLF at the time of admission, and 10% have progressed from other diseases to ACLF after admission [3]. The main inducing factors of ACLF are infection, drugs and hepatotoxic substances, excessive alcohol consumption, and fatigue, among which hepatitis B virus (HBV) infection has become the main cause of ACLF. In China, HBV-ACLF accounts for 87%-91% of the total incidence population of ACLF [4]. At present, the main treatment methods for HBV-ACLF patients are basic medical treatment, liver support treatment, or liver transplantation [5]. In the absence of active treatment, HBV-ACLF progresses rapidly, which may lead to organ failure and death within 3 months [6]. Therefore, early diagnosis, prognosis evaluation, and intervention measures are very important for HBV-ACLF patients.

Neutrophil to lymphocyte ratio (NLR) can reflect the systemic inflammatory state of the body, and play a positive role in the condition evaluation and prognosis judgment of patients

with autoimmune diseases and tumors [7, 8]. Systemic immune inflammatory index (SII) is a comprehensive index based on platelets (PLT), NEU, and LYM, which can reflect the inflammatory state and immune state more comprehensively. It is a new biological inflammatory index to predict the clinical prognosis [9, 10].

Both NLR and SII have the advantages of convenient detection, good repeatability, and economy. However, the clinical relationship between the levels of NLR and SII in HBV-ACLF patients and the prognosis is still unclear. Hence, the objective of this study is to observe the prognostic value of NLR and SII in HBV-ACLF patients, aiming to offer valuable insights for improving patient survival.

Materials and methods

Clinical information

The data of 160 patients with ACLF admitted to Hunan Provincial People's Hospital from June 2022 to June 2023 were collected retrospectively. This study was approved by the Medical Ethics Committee of Hunan Provincial People's Hospital.

Inclusion criteria: Patients who were infected with HBV for more than 6 months; Patients who met the diagnostic criteria of HBV-ACLF [11]; Patients with an age >18 years old; Patients who received no antiviral treatment before onset; Patients with complete medical records.

Exclusion criteria: Patients complicated with other viral hepatitis; Patients complicated with malignant tumor; Patients complicated with hematologic diseases and autoimmune diseases; Patients complicated by serious chronic extrahepatic diseases; Patients who died of other non-liver diseases during the follow-up period; Pregnant or lactating women; Patients lost follow-up during the study.

Laboratory index detection

The general data of patients at admission were collected, including gender, age, concurrent disease (hypertension, diabetes), total bilirubin (TBIL), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Cr), white blood count (WBC), hemoglobin (HGBHGB), PLT, NEU, LYM, and international normalized ratio (INR). The NLR, SII, and score of model for end-stage liver disease (MELD) were calculated, with NLR=NEU/LY and SII=PLT × NEU/LYM. MELD score =3.8 × ln[TBIL (mg/dl)] + 11.2 × ln[INR] + 9.6 × ln[Cr (mg/dl)] + 6.4 × etiology (cholestasis and alcoholic cirrhosis are 0, and other causes are 1).

The complications of patients during hospitalization were collected, including infection, hepatic encephalopathy, hemorrhage, and ascites.

Prognosis assessment

The patients were followed up by outpatient service, telephone calls, and re-hospitalization. The prognosis of all patients was collected retrospectively, and the survival status of the patients within 90 days after admission was assessed. Patients were divided into a survival group and a death group.

Statistical methods

The data were processed by SPSS 22.0. Measured data were expressed as ($\overline{x}$±sd), and *t* test was used for comparison. Counted data were expressed by %, and χ^2 test was used for comparison. The risk factors were analyzed by binary Logistic regression. Pearson test was used to analyze the correlation between NLR, SII, and MELD score. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of NLR and SII for the prognosis of HBV-ACLF patients. $P<0.05$ indicated a significant difference.

Results

Comparison of general data between two groups

During the 90 day follow-up of 160 HBV-ACLF patients, 98 patients survived and 62 patients died. There was no difference between the two groups in gender, the proportion of complicating diseases, ALB or HGB (all $P>0.05$). Compared with the survival group, the age and MELD score of the death group were higher, and the expression levels of TBIL, AST, Cr, WBC, NEU, NLR, SII, and INR were increased, while

Table 1. Comparison of general data between two groups (n, %, $\bar{x}\pm sd$)

Index	Survival group (n=98)	Death group (n=62)	χ^2/t value	*P* value
Gender			0.010	0.919
Male	72 (73.47%)	46 (74.19%)		
Female	26 (26.53%)	16 (25.81%)		
Age (years)	47.98 ± 8.84	51.19 ± 8.58	2.263	0.025
Complicated by hypertension			0.524	0.469
With	19 (19.39%)	15 (24.19%)		
Without	79 (80.61%)	47 (75.81%)		
Complicated by diabetes			0.349	0.555
With	16 (16.33%)	8 (12.90%)		
Without	82 (83.67%)	54 (87.10%)		
TBIL (μmol/L)	279.72 ± 55.67	309.10 ± 54.23	3.285	0.001
ALB (g/L)	31.30 ± 4.21	30.34 ± 3.75	1.465	0.145
AST (U/L)	364.91 ± 37.32	389.29 ± 34.25	4.154	<0.001
ALT (U/L)	509.19 ± 30.57	463.18 ± 30.62	9.269	<0.001
Cr (μmol/L)	61.98 ± 8.71	65.18 ± 8.27	2.308	0.022
WBC ($\times 10^9$/L)	6.79 ± 1.85	7.66 ± 1.96	2.832	0.005
HGB (g/L)	134.87 ± 11.68	130.92 ± 14.21	1.914	0.057
PLT ($\times 10^9$/L)	99.19 ± 15.53	87.21 ± 12.54	5.109	<0.001
NEU ($\times 10^9$/L)	4.26 ± 1.23	5.97 ± 1.57	7.684	<0.001
LYM ($\times 10^9$/L)	1.48 ± 0.52	1.10 ± 0.30	5.226	<0.001
NLR	3.08 ± 0.90	5.57 ± 1.42	13.585	<0.001
SII	301.92 ± 92.65	496.43 ± 171.59	9.293	<0.001
INR	2.06 ± 0.45	2.47 ± 0.50	5.376	<0.001
MELD score (points)	20.97 ± 2.38	26.87 ± 2.72	14.447	<0.001

Notes: TBIL: total bilirubin; ALB: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: serum creatinine; WBC: white blood count; HGB: hemoglobin; PLT: platelets; NEU: neutrophils; LYM: lymphocytes; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune inflammation index; INR: international normalized ratio; MELD: model for end-stage liver disease.

Table 2. Comparison of complications between the two groups (n, %)

Complication	Survival group (n=98)	Death group (n=62)	χ^2 value	*P* value
Infection	35 (35.71%)	43 (69.35%)	17.201	<0.001
Hepatic encephalopathy	27 (27.55%)	20 (32.26%)	0.406	0.524
Hemorrhage	5 (5.10%)	8 (12.90%)	3.096	0.078
Ascites	30 (30.61%)	27 (43.55%)	2.771	0.096

the expression levels of ALT, PLT, and LYM were decreased (all P<0.05, **Table 1**).

Comparison of complications between the two groups

There was no difference in the incidence of hepatic encephalopathy (*P*=0.524), hemorrhage (*P*=0.078) or ascites (*P*=0.096) between the survival group and the death group. The incidence of infection in death group (69.35%) was significantly higher than that of the survival group (35.71%) (*P*<0.001, **Table 2**).

Analysis of risk factors affecting the prognosis of HBV-ACLF patients

The NLR, SII, and MELD score were all risk factors affecting the prognosis of HBV-ACLF patients (*P*<0.001, **Tables 3**, **4**).

Correlation between NLR, SII, and MELD score

Pearson analysis showed a positive corre lation between NLR, SII, and MELD score (*r*=0.626, *r*=0.708, *P*<0.001, **Figure 1**).

Table 3. Assignment of factors

Variable	Index	Assignment mode
Dependent variable	Prognosis	Survival =0; Death =1
Independent variable	Age	Measured value
	TBIL	Measured value
	AST	Measured value
	ALT	Measured value
	Cr	Measured value
	WBC	Measured value
	PLT	Measured value
	NEU	Measured value
	LYM	Measured value
	NLR	Measured value
	SII	Measured value
	INR	Measured value
	MELD score	Measured value

Notes: TBIL: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: serum creatinine; WBC: white blood count; HGB: hemoglobin; PLT: platelets; NEU: neutrophils; LYM: lymphocytes; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune inflammation index; INR: international normalized ratio; MELD: model for end-stage liver disease.

Table 4. Analysis of risk factors affecting prognosis of HBV-ACLF patients

Variable	*B*	*SE*	*Wald* value	*P* value	*OR* value	95% CI
Age	0.187	0.154	1.474	0.872	1.206	0.892-1.630
TBIL	0.140	0.085	2.713	0.468	1.150	0.974-1.358
AST	0.954	0.548	3.031	0.344	2.596	0.887-7.599
ALT	-0.553	0.326	2.877	0.915	0.575	0.303-1.089
Cr	0.376	0.242	2.414	0.530	1.456	0.906-2.340
WBC	1.308	0.825	2.513	0.503	3.698	0.734-18.634
PLT	-0.304	0.257	1.399	1.241	0.737	0.445-1.221
NEU	0.299	0.160	3.492	0.152	1.348	0.986-1.845
LYM	-0.460	0.311	2.187	0.969	0.631	0.343-1.161
NLR	0.742	0.219	11.479	<0.001	2.100	1.367-3.226
SII	0.317	0.105	9.115	<0.001	1.373	1.118-1.687
INR	1.021	0.374	7.453	0.059	2.776	1.334-5.778
MELD score	1.285	0.339	14.368	<0.001	3.615	1.859-7.025

Notes: TBIL: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: serum creatinine; WBC: white blood count; HGB: hemoglobin; PLT: platelets; NEU: neutrophils; LYM: lymphocytes; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune inflammation index; INR: international normalized ratio; MELD: model for end-stage liver disease.

Predictive effect of NLR and SII on prognosis of HBV-ACLF patients

The area under curve (AUC) for NLR in predicting the prognosis within 90 days after admission of HBV-ACLF patients was 0.929 (95% CI: 0.888-0.970). The AUC of SII in predicting the prognosis within 90 days after admission of HBV-ACLF patients was 0.837 (95% CI: 0.770-0.904). The AUC of SII combined with NLR in predicting the prognosis within 90 days after admission of HBV-ACLF patients was 0.959 (95% CI: 0.930-0.989) (**Table 5** and **Figure 2**).

Discussion

ACLF is characterized by the presence of abnormal coagulation, jaundice, and hepatic encephalopathy. These manifestations significantly impair the synthesis, secretion, and detoxification capabilities of the liver, leading to a rapid decline in liver function. ACLF often accompanied by the failure of extrahepatic organ function, which directly threatens the life safety of patients [12]. Therefore, how to effectively predict the prognosis of ACLF patients is a significant issue in clinical research. At present, although it has been recognized that the development and prognosis of ACLF are related to the systemic inflammatory response, it is still difficult to identify easily-available prognostic evaluation markers for ACLF patients [13].

In this study, no significant disparities were observed in the incidence of hepatic encephalopathy, hemorrhage, or ascites between the two groups, but the death group was more prone to infection. When ACLF patients are infected, pathogens such as bacteria or fungi release a large number of pathogen-related molecules, increase the secretion of inflammatory cytokines, and a large number of liver cells are necrotic, which eventually leads to the aggravation of the disease and

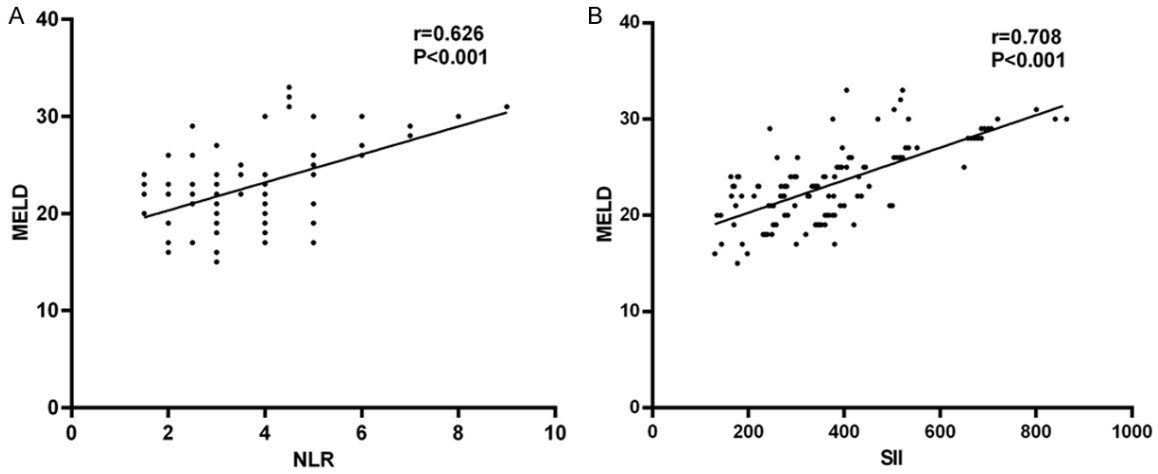

Figure 1. Correlation between NLR, SII, and MELD score. A. Correlation between NLR and MELD score; B. Correlation between SII and MELD score. Notes: NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune inflammation index; MELD: model for end-stage liver disease.

Table 5. Predictive value of NLR and SII for prognosis of HBV-ACLF patients

Variable	AUC	Asymptotic 95% CI		SE	Progressive Sig	Sensitivity (%)	Specificity (%)	Youden index
		Lower limit	Upper limit					
NLR	0.929	0.888	0.970	0.021	<0.001	75.8	94.9	0.707
SII	0.837	0.770	0.904	0.034	<0.001	75.8	82.7	0.585
NLR + SII	0.959	0.930	0.989	0.015	<0.001	88.7	95.9	0.846

Notes: NLR: neutrophil to lymphocyte ratio; SII: systemic immune inflammation index; MELD: model for end-stage liver disease; AUC: area under curve; HBV: hepatitis B virus; ACLF: acute-on-chronic liver failure.

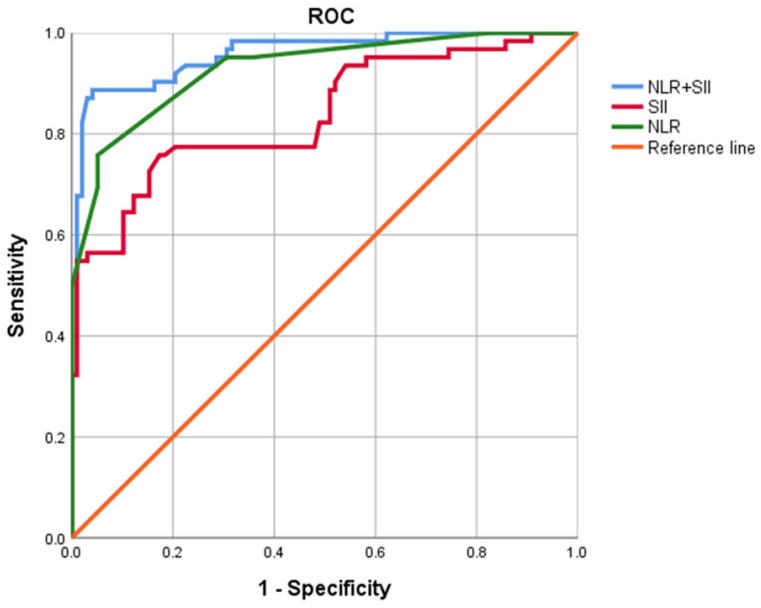

Figure 2. Predictive value of NLR and SII for prognosis of HBV-ACLF patients. Notes: NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune inflammation index; MELD: model for end-stage liver disease; HBV: hepatitis B virus; ACLF: acute-on-chronic liver failure.

poor prognosis [14]. Research has demonstrated that bacterial infection is a common risk factor for developing ACLF from chronic liver disease, with HBV-ACLF patients having a higher risk of infection [15]. It is reported that the probability of HBV-ACLF patients being complicated by infection before admission is as high as 55.7%, and patients with infection will have prolonged hospitalization time and increased risk of death [16]. When patients are infected, many inflammatory indicators change to varying degrees, contributing to the occurrence and progression of many diseases.

This study found that a high level of NLR was a risk factor

affecting the prognosis of HBV-ACLF patients, and the AUC of NLR level for predicting the prognosis of HBV-ACLF patients was 0.929. The results reveal that NLR can predict the short-term prognosis of HBV-ACLF patients, which is related to inflammation and the immune response. NEU has chemotaxis, phagocytosis, and sterilization effects, which can reflect the body's ability to cope with inflammation, and LYM can reflect the regulated immune system and the nutritional status of the body [17]. After HBV infection in the liver of ACLF patients, hepatocyte necrosis will result, and overexpression of T lymphocytes and B lymphocytes will be stimulated, leading to immune dysfunction and suppression of immune protection [18]. In the process of disease progression, many inflammatory mediators are released in the patients with HBV-ACLF, which mediate the chemotaxis of NEU to the liver, promote the body to secrete more chemokines and cytokines, and aggravate the systemic inflammatory response and liver injury, causing poor prognosis [19]. At the same time, stress will trigger a cascade inflammatory response. As the inflammatory response continues, the apoptosis of LYM cells increases. The systemic inflammatory reaction of ACLF patients is closely associated with a reduction in LYM synthesis [20]. Sun et al. followed up 494 patients with HBV-ACLF, revealing a striking high 90 days cumulative mortality rate up to 77.5% when NLR>4.78. NLR was found to be indicative of a bacterial infection in patients [21]. NEU and LYM both participate in the immune defense mechanism, and NLR is more stable than a single parameter for disease evaluation.

A high level of SII reflects excessive NEU, PLT, and relatively depleted LYM, revealing an imbalance of inflammatory regulation in the body. Compared with a single inflammatory factor, SII combines PLT, NEU, and LYM, which can affect the biologic behavior of cells, and more comprehensively reflects the immune status and the severity of inflammatory diseases [22, 23]. An increase of NEU level indicates activation of the inflammatory pathway, while a decrease of LYM level will damage the immune function of the body. It is worth noting that in this study, the expression level of PLT was decreased in the dead population. Secondary infection, endotoxemia, macrophage activation, coagulation dysfunction, and autoimmune lysis of platelets may be the main reasons for PLT reduction in ACLF patients who die. Kim et al. observed 57 patients and revealed that SII≥ 870 would increase the risk of death in 90 days [24]. Wang and others found that SII can reflect stronger inflammation and weaker immune response, and a high level of SII leads to poor survival in hepatocellular carcinoma patients, with a cut-off value of 461.5 [25]. The findings of this study align with the aforementioned conclusions, and the results show that SII showed good performance in predicting the survival of HBV-ACLF patients. The reason for this result is related to the functions of PLT, NEU, and LYM, and SII is related to inflammatory stress response and immune response intensity.

At present, a variety of prognosis evaluation models for patients with liver failure have been established, among which MELD scoring parameters are objective and repeatable, and it has become a commonly used prognostic scoring system for patients with ACLF [26]. However, in practical application, the calculation of a MELD score is complicated, the accuracy is not up to the ideal value, and the application still has limitations, so it needs to be evaluated jointly with other indicators. NLR and SII can be obtained directly through experimental testing, with low price, simple calculation, convenient operation, and no subjective factors involved. This study found that there was a positive correlation between NLR, SII, and MELD score, which suggests that NLR and SII were helpful to predict the prognosis of ACLF patients and could be used in combination with MELD score. In addition, the ROC of this study found that the AUC of SII combined with NLR for predicting the prognosis of HBV-ACLF patients was 0.959, and its prediction efficiency was significantly higher than that of any index alone. The combined application of the two indexes can improve the prediction accuracy of the model for the 90 day survival of ACLF patients.

To sum up, SII combined with NLR has a good prognostic value in ACLF patients, which can provide guidance for prognostic evaluation and clinical intervention. The limitations of this study include its retrospective nature, limited number of cases, and a short follow-up time, which may be one-sided in judging the progno-

sis of patients. A multi-center and extended follow-up prospective study should be conducted to confirm the conclusions.

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Disclosure of conflict of interest

None.

Address correspondence to: Xinchun He, Department of Infectious Disease, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha 410005, Hunan, P. R. China. E-mail: xinchunhe@hunnu.edu.cn

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