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ORIGINAL ARTICLE

Retrospective Study

High neutrophil-lymphocyte ratio indicates poor prognosis for acute-on-chronic liver failure after liver transplantation

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Abstract

AIM: To investigate the significance of pre-transplant neutrophil-lymphocyte ratio (NLR) in determining the prognosis of liver transplant (LT) recipients with acute-on-chronic liver failure (ACLF).

METHODS: Data were collected from the liver transplantation data bank. The NLR values and other conventional inflammatory markers were evaluated for their ability to predict the prognosis of 153 patients with ACLF after LT. The NLR cut-off value was based on a receiver operating characteristic curve analysis. A Kaplan-Meier curve analysis and univariate and multivariate Cox regression models were used to define the independent risk factors for poor outcomes.

RESULTS: The optimal NLR cut-off value was 4.6. Out of 153 patients, 83 (54.2%) had an NLR $\geqslant$ 4.6. The 1-, 3-, and 5-year overall survival rates were 94.3%, 92.5% and 92.5%, respectively, in the normal NLR group and 74.7%, 71.8% and 69.8%, respectively, in patients with high NLRs ($P < 0.001$). Furthermore, there was a significant difference in infectious complications after LT between the high and normal NLR groups. There were no significant differences for other complications. In the multivariate Cox regression model, a high NLR was defined as a significant predictor of poor outcomes for LT.

CONCLUSION: A high NLR is a convenient and available predictor for prognosis of LT patients and can potentially optimize the current criteria for LT in ACLF.

Key words: Liver transplantation; Acute-on-chronic liver failure; Neutrophil-lymphocyte ratio; Acute liver failure; Inflammation

Core tip: In China, because of a great many patients with hepatitis B, liver donation is far away from filling in

the need of liver transplantation. Therefore, improving the prognosis of liver transplant (LT) is a hot issue. However, the criteria of LT for acute-on-chronic liver failure (ACLF) are according to acute liver failure, and about 20% of liver recipients are still have poor survival outcomes. The pre-transplant high neutrophil-lymphocyte ratio is a reflection of suboptimal patient conditions and immune response disorder, which could precisely predict the prognosis of LT. This result potentially was applied to select appropriate candidates for LT and even improve the current criteria of LT for ACLF.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a serious condition with a varied etiology that depends on the geographic region and population; in addition, ACLF patients have an inordinately high mortality rate due to rapid disease progression and multiple organ dysfunction resulting from deterioration in liver function[1]. In China, the high prevalence of hepatitis B accounts for more than 80% of chronic liver diseases, which can progress to ACLF[2]. The primary precipitating events responsible for ACLF are quite distinct in the West and the East. Alcohol and drugs are largely responsible for acute insults in the West, whereas infectious incidents are most common in the East[3]. Some patients respond well to appropriate management and can be discharged from hospital quickly; however, a considerable proportion of patients develop complications of cirrhosis and multiple organ dysfunction. These symptoms are often recommended as a suitable indication for liver transplantation (LT). Moreover, several reports have revealed that LT is a convincing choice to improve the prognosis of ACLF patients[4,5]. However, the long-term mortality rate still reaches approximately 20% after LT for ACLF, and a generalizable set of selection criteria for LT remains lacking.

The predictive significance of several scoring systems that address the severity of chronic liver disease with respect to the prognosis of ACLF patients was evaluated[6]. The results revealed that the Model of End Stage Liver Disease (MELD)[7] or the Child-Pugh score[8] was similar to the Acute Physiology, Age and Chronic Health Evaluation (APACHE)[9] and the Sequential Organ Failure Assessment (SOFA)[10]. Thus, liver function is not the main factor affecting the outcomes of cirrhotic patients with ACLF. To our knowledge, the majority of ACLF patients who were currently receiving positive supportive treatments before LT, such as an artificial liver support system, were in relatively stable condition and did not show severe clinical manifestations of extrahepatic organ failure during LT. Predictably, the organ failure scores, such as the APACHE Ⅱ and SOFA, may be less helpful in predicting long-term survival following LT, which is consistent with a report by Binwei *et al*[11]. Therefore, an accurate biomarker to identify the benefits of LT for ACLF that facilitates organ allocation is needed.

Cytokines and inflammatory molecules play significant roles in the rapid development of ACLF[12]. Previous data have revealed that ACLF patients occasionally exhibited clinical manifestations of systemic inflammatory response syndrome (SIRS) and that the SIRS was associated with a pro-inflammatory milieu that exacerbated the previous circulatory disturbance caused by cirrhosis, which led to inadequate tissue perfusion and multiple organ failure[1,12,13]. In addition, SIRS is a significant independent determinant factor for outcomes of liver cirrhosis patients with acute renal failure[14]. SIRS was first defined in 1992; however, this characterization was a conglomeration of very crude and simple clinical and hematological measures using temperature, respiratory and heart rates, and absolute peripheral white cell counts[15]. Neutrophil amplification and lymphocytopenia are physiological responses to adverse stressful events, and a high neutrophil-lymphocyte ratio (NLR) implies the presence of subclinical inflammation. The NLR is normally relatively stable; an increased NLR has recently been suggested to indicate immune disorders and SIRS[16]. An elevated NLR inversely correlates with the overall and cancer-specific survival rates of various malignancies and the prognoses of non-tumorous diseases[17-21]. In addition, researchers explored the feasibility of expanding the LT pool for hepatic carcinoma (HCC) using the NLR[22,23]. Thus, the effect of pre-transplant NLR on ACLF patients after LT is warranted.

The aim of this study was to determine the utility of conventional inflammatory markers and the NLR in predicting the long-term survival outcomes of patients with ACLF following LT. We also determined the association between NLR and complications after LT.

MATERIALS AND METHODS

Ethics statement

The study was performed according to the ethics guidelines of the Declaration of Helsinki in 1975 and was approved by the ethics committee of Zhejiang University. Informed written consent was obtained from all patients.

Study objectives and data collection

The definition of ACLF used in this study conforms

Table 1 Patient characteristics (*P* values indicate differences between two groups)

Variable	High NLR (*n* = 83)	Normal NLR (*n* = 70)	*P* value
Age (yr), mean ± SD	43.9 ± 14.9	48.6 ± 15.3	0.059
Gender			0.585
Male	51	46	
Female	32	24	
WBC (/pL)	(6.87 ± 2.37)	(4.76 ± 2.56)	< 0.001
Neutrophil (/pL)	(5.87 ± 2.43)	(2.80 ± 1.77)	< 0.001
Lymphocyte (/pL)	(0.55 ± 0.28)	(1.21 ± 0.81)	< 0.001
Monocyte (/pL)	(0.53 ± 0.35)	(0.52 ± 0.34)	0.900
PLR	129.33 ± 101.44	60.94 ± 33.53	< 0.001
LMR	1.33 ± 0.97	3.69 ± 4.72	< 0.001
Albumin	32.71 ± 6.92	32.41 ± 6.24	0.779
Serum creatinine > 133	15	9	0.377
AFP > 25	35	15	0.006
Total bilirubin (μmol/L)	419.75 ± 223.78	301.01 ± 182.62	0.001
MELD score	31.01 ± 7.19	28.63 ± 7.26	0.046
INR	2.67 ± 1.33	2.57 ± 1.05	0.605
Diabetes	8	3	0.202
Hypertension	8	0	0.021
HE	36	21	0.088
Child-Pugh scores	11.29 ± 1.16	11.37 ± 1.39	0.690
Total ischemia time (min)	293.91 ± 241.78	255.82 ± 264.47	0.358

WBC: White blood cell; PLR: Platelet-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; AFP: Alpha feto protein; MELD: Model for end-stage liver disease; INR: International normalized ratio; HE: Hepatic encephalopathy.

to the recommendation provided by the Asian Pacific Association for the study of the liver (APASL). Specifically, ACLF was defined as "acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 wk by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease"[3]. Patients who were 18 years of age or older and met the aforementioned diagnostic criteria between January 2004 and December 2012 were enrolled in this study. The operative methods for LT depended on the origin of the donor liver and included both donation after cardiac death liver transplantation (DCDLT) and live donor liver transplantation (LDLT). The eligibility criteria of LT followed the standard King's College Hospital criteria. To exclude the impact of potential infections, patients with high pre-transplant white blood cell counts were withdrawn from the study. To reduce the heterogeneity of patients with ACLF, some patients were precluded from the study because their chronic liver diseases underlying ACLF were not caused by hepatitis B. Additional criteria were used to preclude subjects: (1) HCC confirmed by pathologic examination after LT; (2) loss to follow-up; (3) history of steroid administration that could influence the NLR before LT; and (4) presence of an ABO-incompatible LT with controversial survival outcomes. The primary precipitating events included recurrent hepatitis B, alcohol abuse, infection and upper gastrointestinal hemorrhage.

The demographics of patients, operative variables, preoperative treatments and clinical course were prospectively collected *via* the hospital information collection system of the LT database at the First Affiliated Hospital of Zhejiang University School of Medicine. Venous blood samples were routinely taken the day prior to LT, and the cut-off and predictive values of the NLR, white blood cells, neutrophils, lymphocytes, monocytes, lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) were defined using a receiver operating characteristic (ROC) curve analysis. All patients were divided into one of two groups based on either high or normal NLR. The demographics and clinical characteristics of the two groups are presented in Table 1.

Management after LT and subsequent surveillance

The patients were followed closely by the outpatient service or communication system from the date of hospital discharge to the date of death or the last follow-up visit. Graft function was monitored using biochemical tests, ultrasonography, emission computed tomography and liver puncture every 3 mo for 2 years post-transplant and every 6 months thereafter.

The immunosuppression protocol following LT consisted of tacrolimus, basiliximab and mycophenolate mofetil. Antibiotics for trigemini with piperacillin-tazobactam, fluconazole and ganciclovir were administered immediately after the surgery as an anti-infection strategy. To prevent the recurrence of hepatitis B, all liver recipients were treated with low-dose immunoglobulin and oral lamivudine.

Statistical analysis

Overall survival (OS) and graft survival (GS) were calculated from the date of surgery until death or graft dysfunction, respectively. The optimal cut-off values for high NLR, WBC, neutrophil, lymphocyte and monocyte counts, PLR and LMR were evaluated using an ROC curve analysis. Potential predictive factors were assessed using Kaplan-Meier curves and the log-rank test. Preoperative factors that reached significance ($P < 0.10$) for OS or GS in the univariate analysis were entered into a multivariate analysis model using the Cox proportional hazards model (backward selection likelihood function) to determine their independent effects. Fisher's exact test, independent sample *t*-test and Pearson's χ^2 test were performed to assess the differences in the clinicopathologic factors of ACLF patients with high and normal NLRs. The confidence interval (CI) was set at 95%, and the cut-off value for statistical significance was $P < 0.05$. All data analyses were conducted with SPSS ver. 19.0 for Windows (SPSS Company, Chicago, Illinois, United States).

RESULTS

Patient demographics and outcomes

Of the 153 adult patients who underwent LT for ACLF during the study period, 97 (63.4%) were men and 56 (36.6%) were women. The mean age of patients was 46.1 years (range: 24-72 years) at transplant.

Table 2 Univariate analysis of variables affecting overall survival after liver transplant

Variable (cut-off value/median/*n*)	*P* value	HR (95%CI)
Gender		
Male (*n* = 97)	0.370	1.429 (0.655-3.121)
Female (*n* = 56)	0.503	0.774 (0.366-1.638)
Age (46 yr)	< 0.001	4.860 (1.857-12.719)
NLR (4.6)	0.288	0.631 (0.270-1.475)
Albumin (35 g/L)	0.163	1.683 (0.809-3.500)
Total bilirubin (337 μmol/L)	0.010	3.251 (1.328-7.958)
MELD score (28)	0.824	0.912 (0.406-2.050)
Child-Pugh score (11)	0.360	1.371 (0.697-2.695)
INR (2.5)	< 0.001	3.823 (1.813-8.062)
Serum creatinine (133 μmol/L)	0.475	1.545 (0.468-5.100)
Pretransplant diabetes (11)	0.686	0.662 (0.090-4.873)
Hypertension before LT (8)	0.629	1.198 (0.576-2.491)
HE (57)	0.286	0.63 (0.27-1.472)
AFP (25 μg/L)		

NLR: Neutrophil lymphocyte ratio; PLR: Platelet-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; AFP: Alpha feto protein; MELD: Model for end-stage liver disease; INR: International normalized ratio; HE: Hepatic encephalopathy.

Seventy-nine (51.6%) patients received pre-transplant artificial liver support. The median international normalized ratio, total bilirubin, MELD score and Child Turcotte Pugh score were 2.5, 337 μmol/L, 28 and 11, respectively. Increased alpha fetoprotein and serum creatinine (Scr) were detected in 50 and 24 patients, respectively. A total of 57 (37.25%) subjects suffered hepatic encephalopathy at diagnosis. DCDLT and LDLT were performed in 129 and 24 patients, respectively. The median total ischemia time was 254 min.

Death was confirmed for 30 patients, and 6 patients underwent a second LT during follow-up. The main cause of death, which occurred in 20 patients, was sepsis/multi-organ dysfunction. Other causes of death included liver failure secondary to chronic rejection in 2 patients, gastrointestinal bleeding in 3 patients, recurrent hepatitis B in 2 patients, biliary complications in 2 patients and heart attack in 1 patient. The median follow-up time was 47.7 mo (range: 0.01-121 mo). The 1-, 3- and 5-year OS rates were 82.9%, 80.4% and 79.4%, respectively, and the GS rates were 81.7%, 76.8% and 75.8%, respectively.

Suitable cut-off value for NLR

The peripheral WBC, neutrophil, lymphocyte and monocyte counts, albumin, NLR, PLR and LMR are commonly considered as a reflection of immune function. Hence, these blood parameters were selected as candidates for predicting outcomes of ACLF patients after LT. The areas under the ROC curves for peripheral WBC, neutrophil, lymphocyte and monocyte counts, PLR, LMR and NLR were 0.542, 0.564, 0.397, 0.556, 0.425, 0.483 and 0.736, respectively. An NLR value of 4.6 presented a sensitivity of 76.7% and a specificity of 65.9%. This cut-off was used to divide patients into high and normal NLR groups (≥ 4.6 and < 4.6, respectively).

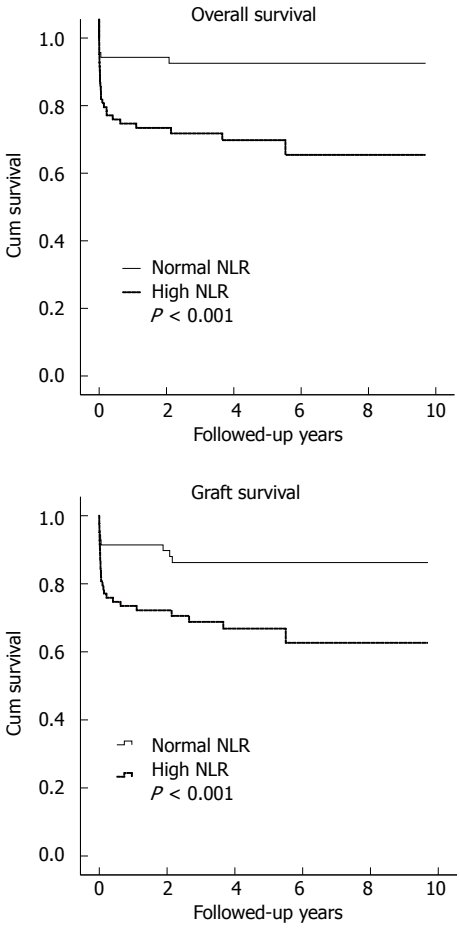

Figure 1 Kaplan-Meier results for overall survival and graft survival for patients classified according to their preoperative neutrophil-lymphocyte ratios. NLR: Neutrophil-lymphocyte ratio.

Predictive variables for OS, GS and complications

To determine whether the aforementioned blood parameters could serve as predictors for survival outcomes of ACLF patients following LT, we performed a univariate analysis. We found that an MELD score ≥ 28, NLR ≥ 4.6 and Scr > 133 were all preoperative risk factors of poor OS (Table 2). Of 153 patients, 83 (54.2%) had an NLR ≥ 4.6, and 24 (15.7%) had a high Scr. The respective 1-, 3-, and 5-year OS rates were 94.3%, 92.5% and 92.5% in the normal NLR group and 74.7%, 71.8% and 69.8% in the high NLR group ($P < 0.001$, Figure 1). In addition, the 1-, 3- and 5-year OS rates were significantly higher in the normal Scr group (86.8%, 84.9% and 84.9%, respectively) when compared with the high Scr group (62.5%, 62.5% and 55.6%, respectively); ($P < 0.001$, Figure 2). These three factors were selected for further multivariate analysis. The results showed that a MELD ≥ 28 did not reach statistical significance; however, a high NLR and increased Scr maintained their predictive value (Table 3). Patients who presented with a normal NLR and a normal Scr showed favorable survival

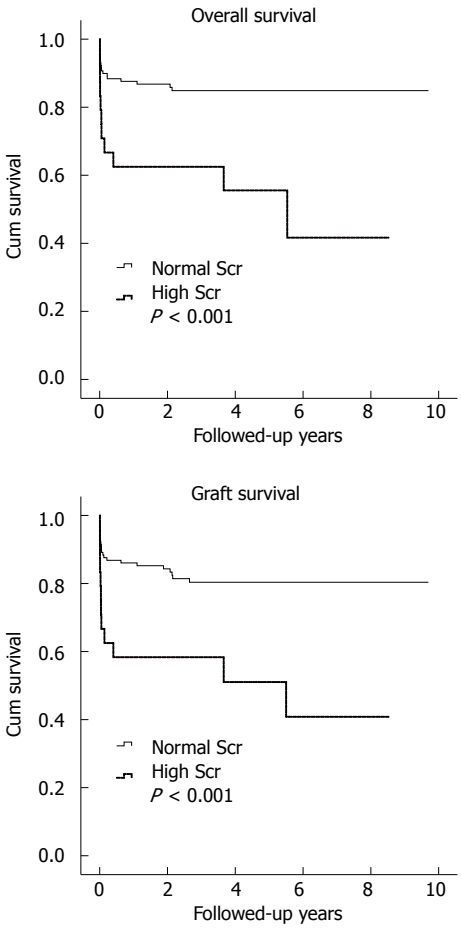

Figure 2 Kaplan-Meier results for overall survival and graft survival for patients classified according to their preoperative serum creatinine. Scr: Serum creatinine.

outcomes. The 1-, 3- and 5-year OS rates were up to 98.4%, 96.4% and 96.4%, respectively. Liver recipients with high NLRs and increased Scr presented with extremely adverse prognoses. The 1-, 3- and 5-year OS rates decreased to 60.0%, 60.0% and 50.0%, respectively (Figure 3).

The main complications after LT consisted of hyperglycemia, infectious diseases, hyperlipidemia, gastrointestinal hemorrhage, recurrent hepatitis B, biliary and neural complications, graft-*vs*-host disease and acute rejection. A total of 18 subjects showed acute rejection after LT as determined by pathologic findings according to the Banff criteria. Subsequent augmentative steroid administration was effective. The number of infectious complications in the high NLR group was greater when compared with the normal NLR group; however, there were no significant differences in other complications after LT (Figure 4).

DISCUSSION

In ACLF, both chronic and acute insults coincide. It is unclear how the survival outcome of the patient is influenced by the degree of acute and/or chronic insults in ACLF patients; however, a high mortality

Table 3 Multivariate analysis of factors affecting overall survival after liver transplant for acute-on-chronic liver failure

Variable	*P* value	HR (95%CI)
NLR ⩾ 4.6	0.003	4.305 (1.637-11.322)
Serum creatinine ⩾ 133	0.003	3.141 (1.486-6.639)
MELD ⩾ 28	0.242	1.793 (0.674-4.766)

NLR: Neutrophil-lymphocyte ratio; MELD: Model for end-stage liver disease.

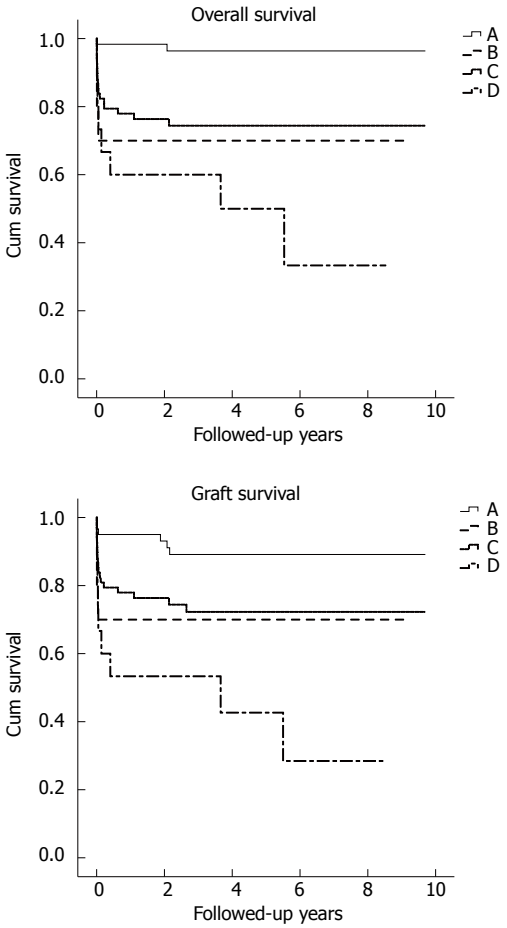

Figure 3 Kaplan-Meier results for overall survival and graft survival for patients with high serum creatinine and high neutrophil-lymphocyte ratios. The 1-, 3- and 5-year overall survival rates, respectively, were 98.4%, 96.4% and 96.4% in the A group (NLR < 4.6 and normal Scr), 66.7%, 66.7% and 66.7% in the B group (NLR < 4.6 and high Scr), 77.9%, 74.4% and 74.4% in the C group (NLR ⩾ 4.6 and normal Scr), 60.0%, 60.0% and 50.0% in the D group (NLR ⩾ 4.6 and high Scr). NLR: Neutrophil-lymphocyte ratio; Scr: Serum creatinine.

rate is clearly evident. According to the data of Jalan *et al*[1], the in-hospital mortality for ACLF ranged from 43% to 88%, and the intensive care unit (ICU) mortality ranged from 37% to 89%. Completion of LDLT or DDLT for ACLF showed encouraging post-transplant prognoses[5,11,24]. The King's College Hospital criteria are the most widely applied selection criteria for LT in acute liver failure with a high prognostic value, and it was also recommended for ACLF by APASL; however, the predictive value in ACLF requires

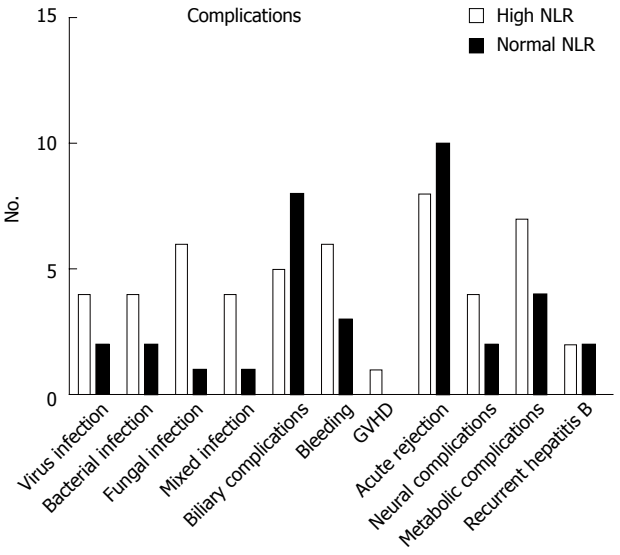

Figure 4 Incidence of postoperative complications in patients and the relationship between complications and neutrophil-lymphocyte ratio. NLR: Neutrophil-lymphocyte ratio; GVHD: Graft-*vs*-host disease.

further validation[25,26]. To facilitate graft allocation, it is important to establish clear selection criteria to define which candidates would most benefit from LT.

The imbalanced expression of both anti-inflammatory and pro-inflammatory cytokines contributes to the immunopathogenesis of ACLF[27-29]. Sen *et al*[28] described that multiple pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, and IL-8, were elevated in ACLF patients. Zou *et al*[29] revealed that interferon (INF)-γ, TNF-α and IL-10 were markedly up-regulated in ACLF when compared with chronic hepatitis B patients and normal controls. As a marker of immune disorders, patients with high NLRs presented worse clinical conditions before LT in our study. Furthermore, we found that patients with normal NLRs presented better survival outcomes when compared with patients that had elevated NLRs. However, other inflammatory markers did not show predictive effects. This study is the first to identify a relationship between increased NLR and poor outcomes of patients with ACLF after LT. The 5-year survival rate reached 92.5% in LT patients with normal NLRs, which validated the use of NLR as an indicator for selecting LT candidates. Although 4.6 was the optimal cut-off value in our study, the cut-off value of NLR has varied in previously reported articles; however, as expected, a greater value correlates with a worse prognosis. Therefore, the results and the optimal value of the NLR need to be further confirmed through prospective studies with larger sample sizes.

The precise mechanism underlying how the NLR affects OS remains unclear. We found that the main cause of death was sepsis/multiple organ failure. Of the 25 subjects with high NLRs who died, 18 (72%) showed sepsis/multiple organ failure. Furthermore, elevated NLRs were associated with infectious complications. A total of 18 patients (21.69%) presented with infectious complications postoperatively in the high NLR group; however, only 6 (8.57%) cases presented with this complication in the normal NLR group (P = 0.026). These results provide a possible explanation for high NLR resulting in a worse prognosis. Furthermore, previous studies revealed that SIRS and immunological dissonance were associated with multiple organ dysfunction syndrome and secondary infectious complications[30]. In our study, the majority of study subjects with high NLRs also possessed lower lymphocyte counts and higher neutrophil counts compared with normal NLR patients. Therefore, marked neutrophilia and lymphocytopenia were considered to be physiological responses of the immune system to various stressful events, and NLR can express the severity of affliction. Zahorec[16] suggested that NLR can be routinely applied to clinical ICU practice as an additional index for infection. Lymphocytes have an important role in the host immune system, and a lymphocytopenia-impaired immune response to pathogens showed a positive correlation with bacteremia[16,31,32]. However, patients with acute or chronic hepatitis commonly presented with intestinal endotoxemia[33,34]. Several reports have disclosed that endotoxins significantly decrease the phagocytic capacity of neutrophils and induce a functionally heterogeneous neutrophil compartment that increases the susceptibility to infection[35]. In addition, Yang *et al*[36] demonstrated that neutrophils unexpectedly inhibited protective immune responses in fatal bacterial infection-induced toxic shock. These data explain why high NLR patients with pro-inflammatory milieu are prone to infection.

A high NLR is currently regarded as an available indicator of SIRS because it closely correlates with the presence of system inflammation[16]. SIRS is a common insult that precipitates liver dysfunction in a patient with previously compensated liver diseases. Moreover, the mortality rates of patients with cirrhosis or acute liver failure are higher with the presentation of SIRS[37-39]. SIRS is an earlier stage of multiple organ dysfunction and represents serious immune response dysfunction; thus, the presence of SIRS promotes postoperative infection and negative survival outcomes. The factors affecting the NLR consisted of underlying liver diseases, infection and steroidal drugs. Patients with these factors were excluded from the study. Therefore, we did not assess the relationship between NLR and SIRS in this study due to the absence of complete white blood cell counts.

In addition to the elevated NLR, high Scr was also an independent adverse factor for prognosis in ACLF patients after LT. Of the 24 patients with high Scr levels, 13 (54.2%) died. Moreover, liver recipients with high NLRs and increased Scr presented the worst survival outcomes. The 1-, 3- and 5- year survival rates were 60.0%, 60.0% and 50.0%, respectively. Although there was poor sensitivity for Scr to determine the extent of renal dysfunction[40],

the results revealed that markers of pre-transplant extrahepatic organ dysfunction can affect LT prognosis. Thus, these markers combined with NLR would provide effective predictive value.

Notably, there were several inevitable limitations of this study. First, only 24 (15.7%) liver recipients showed high Scr levels. Further analyses and larger sample sizes are needed. In addition, lymphocyte and neutrophil subsets were not routinely measured before LT. Hence, basic contributing mechanisms require further assessment.

In summary, high NLR corresponded to the severity of pre-transplant chronic liver diseases and immune disorders, and it showed powerful predictive value compared with general inflammatory markers. ACLF patients with high NLRs presented poorer OS and GS after LT. Neutrophil paralysis and lymphocytepenia promote infections that may result in poorer outcomes in ACLF patients with high NLRs following LT.

COMMENTS

Background

Liver transplantation (LT) is an optimal choice for patients with acute on chronic liver failure (ACLF), with reported survival rates of around 80%. The criteria of LT for ACLF are according to acute liver failure, and about 20% of liver recipients still have poor survival outcomes. In China, because of a great many patients with hepatitis B, liver donation is far away from filling in the need of liver transplantation. Therefore, improving the prognosis of LT is a hot issue. Recently published data revealed that immune response played an important role in progression of ACLF. Thus, finding a precise marker of immune response that is correlated with outcomes of LT potentially improves the criteria of LT for ACLF.

Research frontiers

Neutrophil amplification and lymphocytopenia are physiological responses to adverse stressful events, and a high neutrophil-lymphocyte ratio (NLR) is a new precise marker of inflammation. An elevated NLR inversely correlates with the overall and cancer-specific survival rates of various malignancies and the prognoses of non-tumorous diseases. In addition, researchers explored the feasibility of expanding the LT pool for hepatic carcinoma using the NLR.

Innovations and breakthroughs

The area under the receiver operating characteristic curve for NLR was 0.736 and an NLR value of 4.6 presented a sensitivity of 76.7% and a specificity of 65.9%. Using a Kaplan-Meier curve analysis and univariate and multivariate Cox regression models, we defined that a high NLR was a significant predictor of poor outcomes for LT. The 1-, 3-, and 5-year overall survival rates were 94.3%, 92.5% and 92.5%, respectively, in the normal NLR group and 74.7%, 71.8% and 69.8%, respectively, in patients with high NLR ($P < 0.001$).

Applications

This study showed that liver recipients with high NLRs had a tendency for infection and presented poorer survival outcomes after LT. These results implied that up-regulated NLR could be used as an indicator of antibiotic prophylaxis and improve the criteria of LT for ACLF to scientifically allocate the donor livers or expand the LT pool.

Terminology

NLR means neutrophil-lymphocyte ratio, which is a new marker of immune response.

Peer-review

This is a nice study. Results would have clinical relevance if alternative treatments other than LT were offered to high NLR patients. Furthermore, the commonly assessed marker creatinine is equally predictive.

REFERENCES

1 **Jalan R**, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on chronic liver failure. *J Hepatol* 2012; **57**: 1336-1348 [PMID: 22750750 DOI: 10.1016/j.jhep.2012.06.026]

2 **Zhang Z**, Zou ZS, Fu JL, Cai L, Jin L, Liu YJ, Wang FS. Severe dendritic cell perturbation is actively involved in the pathogenesis of acute-on-chronic hepatitis B liver failure. *J Hepatol* 2008; **49**: 396-406 [PMID: 18644645 DOI: 10.1016/j.jhep.2008.05.017]

3 **Sarin SK**, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, de Silva HJ, Hamid SS, Jalan R, Komolmit P, Lau GK, Liu Q, Madan K, Mohamed R, Ning Q, Rahman S, Rastogi A, Riordan SM, Sakhuja P, Samuel D, Shah S, Sharma BC, Sharma P, Takikawa Y, Thapa BR, Wai CT, Yuen MF. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009; **3**: 269-282 [PMID: 19669378 DOI: 10.1007/s12072-008-9106-x]

4 **Stärkel P**, Horsmans Y, Geubel A, Ciccarelli O, Goubau P, Rahier J, Lerut J. Favorable outcome of orthotopic liver transplantation in a patient with subacute liver failure due to the emergence of a hepatitis B YMDD escape mutant virus. *J Hepatol* 2001; **35**: 679-681 [PMID: 11690717 DOI: 10.1016/S0168-8278(01)00178-7]

5 **Liu CL**, Fan ST, Lo CM, Wei WI, Yong BH, Lai CL, Wong J. Live-donor liver transplantation for acute-on-chronic hepatitis B liver failure. *Transplantation* 2003; **76**: 1174-1179 [PMID: 14578749 DOI: 10.1097/01.TP.0000087341.88471.E5]

6 **Cholongitas E**, Senzolo M, Patch D, Kwong K, Nikolopoulou V, Leandro G, Shaw S, Burroughs AK. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. *Aliment Pharmacol Ther* 2006; **23**: 883-893 [PMID: 16573791 DOI: 10.1111/j.1365-2036.2006.02842.x]

7 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

8 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

9 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249 DOI: 10.1097/00003246-198510000-00009]

10 **Vincent JL**, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239 DOI: 10.1007/BF01709751]

11 **Duan BW**, Lu SC, Wang ML, Liu JN, Chi P, Lai W, Wu JS, Guo QL, Lin DD, Liu Y, Zeng DB, Li CY, Meng QH, Ding HG, Chen XY, Liao HY, Ma LQ, Chen Y, Zhang J, Xiang HP, Duan ZP, Li N. Liver transplantation in acute-on-chronic liver failure patients with high model for end-stage liver disease (MELD) scores: a single center experience of 100 consecutive cases. *J Surg Res* 2013; **183**: 936-943 [PMID: 23558257 DOI: 10.1016/j.jss.2013.03.008]

12 **Jalan R**, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. *Blood Purif* 2002; **20**: 252-261 [PMID: 11867872 DOI: 10.1159/000047017]

13 **Mookerjee RP**, Sen S, Davies NA, Hodges SJ, Williams R, Jalan R. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut* 2003; **52**: 1182-1187 [PMID: 12865279 DOI: 10.1136/gut.52.8.1182]

14 **Thabut D**, Massard J, Gangloff A, Carbonell N, Francoz C, Nguyen-Khac E, Duhamel C, Lebrec D, Poynard T, Moreau R. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007; **46**: 1872-1882

[PMID: 17972337 DOI: 10.1002/hep.21920]
15 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864-874 [PMID: 1597042]
16 **Zahorec R**. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 2001; **102**: 5-14 [PMID: 11723675]
17 **Kayadibi H**, Sertoglu E, Uyanik M, Tapan S. Neutrophil-lymphocyte ratio is useful for the prognosis of patients with hepatocellular carcinoma. *World J Gastroenterol* 2014; **20**: 9631-9632 [PMID: 25071363 DOI: 10.3748/wjg.v20.i28.9631]
18 **Li X**, Chen ZH, Ma XK, Chen J, Wu DH, Lin Q, Dong M, Wei L, Wang TT, Ruan DY, Lin ZX, Xing YF, Deng Y, Wu XY, Wen JY. Neutrophil-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. *Tumour Biol* 2014; **35**: 11057-11063 [PMID: 25095975 DOI: 10.1007/s13277-014-2360-8]
19 **Varol E**, Bas HA, Aksoy F, Ari H, Ozaydin M. Relationship Between Neutrophil-Lymphocyte Ratio and Isolated Low High-Density Lipoprotein Cholesterol. *Angiology* 2013; **65**: 630-633 [PMID: 23921506 DOI: 10.1177/0003319713497992]
20 **Biyik M**, Ucar R, Solak Y, Gungor G, Polat I, Gaipov A, Cakir OO, Ataseven H, Demir A, Turk S, Polat H. Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2013; **25**: 435-441 [PMID: 23249602 DOI: 10.1097/MEG.0b013e32835c2af3]
21 **Gibson PH**, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, Jeffrey RR, Buchan KG, El-Shafei H, Hillis GS. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J* 2007; **154**: 995-1002 [PMID: 17967611 DOI: 10.1016/j.ahj.2007.06.043]
22 **Motomura T**, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, Fukuhara T, Uchiyama H, Ikegami T, Yoshizumi T, Soejima Y, Maehara Y. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. *J Hepatol* 2013; **58**: 58-64 [PMID: 22925812 DOI: 10.1016/j.jhep.2012.08.017]
23 **Limaye AR**, Clark V, Soldevila-Pico C, Morelli G, Suman A, Firpi R, Nelson DR, Cabrera R. Neutrophil-lymphocyte ratio predicts overall and recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Hepatol Res* 2013; **43**: 757-764 [PMID: 23193965 DOI: 10.1111/hepr.12019]
24 **Chan AC**, Fan ST, Lo CM, Liu CL, Chan SC, Ng KK, Yong BH, Chiu A, Lam BK. Liver transplantation for acute-on-chronic liver failure. *Hepatol Int* 2009; **3**: 571-581 [PMID: 19680733 DOI: 10.1007/s12072-009-9148-8]
25 **Polson J**, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology* 2005; **41**: 1179-1197 [PMID: 15841455 DOI: 10.1002/hep.20703]
26 **Cholongitas E**, Theocharidou E, Vasianopoulou P, Betrosian A, Shaw S, Patch D, O'Beirne J, Agarwal B, Burroughs AK. Comparison of the sequential organ failure assessment score with the King's College Hospital criteria and the model for end-stage liver disease score for the prognosis of acetaminophen-induced acute liver failure. *Liver Transpl* 2012; **18**: 405-412 [PMID: 22213443 DOI: 10.1002/lt.23370]
27 **Wasmuth HE**, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, Bach J, Geier A, Purucker EA, Gressner AM, Matern S, Lammert F. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J Hepatol* 2005; **42**: 195-201 [PMID: 15664244 DOI: 10.1016/j.jhep.2004.10.019]
28 **Sen S**, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R, Jalan R. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. *Liver Transpl* 2004; **10**: 1109-1119 [PMID: 15350001 DOI: 10.1002/lt.20236]
29 **Zou Z**, Li B, Xu D, Zhang Z, Zhao JM, Zhou G, Sun Y, Huang L, Fu J, Yang Y, Jin L, Zhang W, Zhao J, Sun Y, Xin S, Wang FS. Imbalanced intrahepatic cytokine expression of interferon-gamma, tumor necrosis factor-alpha, and interleukin-10 in patients with acute-on-chronic liver failure associated with hepatitis B virus infection. *J Clin Gastroenterol* 2009; **43**: 182-190 [PMID: 18633332 DOI: 10.1097/MCG.0b013e3181624464]
30 **Bone RC**. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS) *Ann Intern Med* 1996; **125**: 680-687 [PMID: 8849154 DOI: 10.7326/0003-4819-125-8-199610150-00009]
31 **Hawkins CA**, Collignon P, Adams DN, Bowden FJ, Cook MC. Profound lymphopenia and bacteraemia. *Intern Med J* 2006; **36**: 385-388 [PMID: 16732866 DOI: 10.1111/j.1445-5994.2006.01076.x]
32 **de Jager CP**, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. *Crit Care* 2010; **14**: R192 [PMID: 21034463 DOI: 10.1186/cc9309]
33 **Uchihara M**, Izumi N, Sato C, Marumo F. Clinical significance of elevated plasma endothelin concentration in patients with cirrhosis. *Hepatology* 1992; **16**: 95-99 [PMID: 1535610 DOI: 10.1002/hep.1840160117]
34 **Han DW**. Intestinal endotoxemia as a pathogenetic mechanism in liver failure. *World J Gastroenterol* 2002; **8**: 961-965 [PMID: 12439906]
35 **Pillay J**, Ramakers BP, Kamp VM, Loi AL, Lam SW, Hietbrink F, Leenen LP, Tool AT, Pickkers P, Koenderman L. Functional heterogeneity and differential priming of circulating neutrophils in human experimental endotoxemia. *J Leukoc Biol* 2010; **88**: 211-220 [PMID: 20400675 DOI: 10.1189/jlb.1209793]
36 **Yang Q**, Ghose P, Ismail N. Neutrophils mediate immunopathology and negatively regulate protective immune responses during fatal bacterial infection-induced toxic shock. *Infect Immun* 2013; **81**: 1751-1763 [PMID: 23478316 DOI: 10.1128/IAI.01409-12]
37 **Leithead JA**, Ferguson JW, Bates CM, Davidson JS, Lee A, Bathgate AJ, Hayes PC, Simpson KJ. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. *Gut* 2009; **58**: 443-449 [PMID: 19001057 DOI: 10.1136/gut.2008.154120]
38 **Rolando N**, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000; **32**: 734-739 [PMID: 11003617 DOI: 10.1053/jhep.2000.17687]
39 **Cazzaniga M**, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009; **51**: 475-482 [PMID: 19560225 DOI: 10.1016/j.jhep.2009.04.017]
40 **Tomlanovich S**, Golbetz H, Perlroth M, Stinson E, Myers BD. Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. *Am J Kidney Dis* 1986; **8**: 332-337 [PMID: 3538857 DOI: 10.1016/S0272-6386(86)80107-X]

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