Background: The neutrophil-lymphocyte ratio (NLR) has been shown to be a valuable predictor of survival in various clinical conditions. The aim of this study was to determine whether pre-transplant NLR provides independent risk factors for short-term mortality and post-transplant complications in acute-on-chronic liver failure (ACLF) patients after liver transplantation (LT).

Methods: A total of 153 consecutive patients with ACLF undergoing LT were enrolled in the study. NLR was calculated as the number of neutrophils divided by the number of lymphocytes. The optimal cut-off value of NLR was determined using receiver operating characteristic (ROC) curve analysis. The correlation and interaction between NLR and other traditional inflammatory markers were evaluated. Kaplan-Meier survival curves were used to compare overall survival rates. The Independent risk factors for short-term mortality for ALCF after LT were analyzed using a multivariate Cox regression model.

Results: The optimal cut-off value of NLR was 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). In patients with high NLRs, the infectious complications were significantly higher than in the normal NLR group. In the multivariate Cox regression model, NLR was defined as an independent predictor of poor outcomes for LT.

Conclusion: The pre-transplant NLR can provide independent risk factors for short-term mortality and post-transplant infectious complications for ALCF patients after LT. The optimal cut-off value of NLR was 4.6. A high NLR may be a convenient and available tool for predicting poor outcomes after LT in ALCF patients. In the multivariate Cox regression model, NLR was defined as a significant predictor of poor outcomes for LT.
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 conglomerate 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-tumor 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
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 (DCDLT) and live donor liver transplantation (LDLT). The eligibility criteria of LT 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 yrs 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 χ² 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 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 (/µL)                       | 6.87 ± 2.37       | 4.76 ± 2.56         | <0.001  |
| Neutrophil (/µL)                | 5.87 ± 2.43       | 2.80 ± 1.77         | <0.001  |
| Lymphocyte (/µL)                | 0.55 ± 0.28       | 1.21 ± 0.81         | <0.001  |
| Monocyte (/µL)                  | 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   |
| APF > 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 ± 241.28   | 255.82 ± 264.47     | 0.358   |

WBC: White blood cell; PLR: Platelet-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; AFP: Alpha fetoprotein; MELD: Model for end-stage liver disease; INR: International normalized ratio; HE: Hepatic encephalopathy.
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 (0.404-2.050) |
| 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 (0.090-4.973) |
| 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 81.7%, 76.8% and 75.8%, respectively, and the 1-, 3- and 5-year GS rates were 82.9%, 80.4% and 79.4%, 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).

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.
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 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

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**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.
A total of 18 patients (21.69%) with high NLRs were associated with infectious complications. Of the 24 patients with high Scr, 13 (54.2%) 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$^{[40]}$, 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$^{[30]}$ 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.
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 lymphocytopenia 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 hepatits 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 adverse stressful events, and a high neutrophil-lymphocyte ratio (NLR) is a new precise marker of inflammation.

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 78.7% 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.

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