Pretreatment Neutrophil–Lymphocyte Ratio
An Independent Predictor of Survival in Patients With Hepatocellular Carcinoma

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Abstract: The neutrophil-to-lymphocyte ratio (NLR) has been shown to be associated with prognosis in various types of cancer. We evaluated pretreatment NLR as a predictor of poor prognosis in patients with hepatocellular carcinoma (HCC), and we compared the prognostic value of NLR with other prognostic scores.

We retrospectively analyzed 825 patients diagnosed with HCC between October 2008 and May 2012. Baseline data, including the NLR and the Child–Pugh class or Model for End-Stage Liver Disease (MELD) staging, were scored before treatment. The relationships between overall survival (OS) and the study variables were assessed using univariate and multivariate analyses and receiver operating characteristic (ROC) curves. The prognostic value of NLR was assessed using a Kaplan–Meier survival analysis and compared with that of the Barcelona Clinic Liver Cancer (BCLC) and Tumor, Node, Metastasis (TNM) staging.

The NLR, γ-glutamyltranspeptidase, α-fetoprotein ≥400 ng/mL, tumor number ≥3, tumor size ≥5 cm, lymph node metastasis, portal vein involvement, and Child–Pugh class were significantly associated with OS. The NLR demonstrated the strongest prognostic value (area under ROC curve = 0.811). An NLR ≥2.7 was a significant predictor of poor OS (P < 0.0001), and the survival period of patients with an NLR ≥2.7 decreased with more advanced BCLC and TNM stage.

Pretreatment NLR is a useful prognostic biomarker in HCC patients. The prognostic value of NLR ≥2.7 is superior to that of MELD stage or Child–Pugh class, and correlates with that of BCLC and TNM staging scores.

(INTRODUCTION)

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and has the third highest mortality rate among cancers. The incidence of HCC is the highest in countries where the hepatitis B virus (HBV) is endemic. In the Asia-Pacific region, where the incidence of viral hepatitis is relatively high, HCC is a major public health problem, with the incidence of HCC in China alone accounting for 55% of HCC cases worldwide in 2002. In the USA, HCC-related mortality in patients chronically infected with the hepatitis C virus (HCV) has become the fastest-rising cause of cancer-related death. Despite the many recent advances in the treatment of HCC, the 5-year survival rate of HCC patients remains low, compared with other types of cancer.

Various methods have been proposed for staging and predicting the prognosis of HCC patients, including the Barcelona Clinic Liver Cancer (BCLC) staging system, the Tumor, Node, Metastasis (TNM) classification system, the Japanese Integrated Staging score, the Cancer of the Liver Italian Program, the Child–Pugh classification system, and the Model for End-Stage Liver Disease (MELD). However, no worldwide consensus has been reached regarding which is the best system for predicting HCC outcomes. In addition, the application of these methods can be cumbersome, and they have been used primarily in clinical trials. The identification of more straightforward prognosticators for HCC, such as serum biomarkers, for the reliable prediction of metastatic recurrence would better facilitate the development of more efficacious therapeutic strategies for HCC.

Mounting evidence suggests that components of the systemic inflammatory response are predictors of outcome in various types of cancer, including HCC. Previous studies have shown that a high neutrophil count (NC) is associated with angiogenesis, and that DNA damage and tumor metastasis suppress lymphocyte activity through the upregulation of cytokines that counteract the antitumor immune response.

Previous studies suggested that pretreatment neutrophil-to-lymphocyte ratios (NLRs) are predictors of tumor recurrence and survival in HCC patients undergoing specific treatments. Conversely, it has also been noted that, though NLR was predictive for overall survival (OS) in a univariate
analysis, it was not predictive in a multivariate analysis and was inferior to other inflammation-based prognostic scores. In addition, a Western center study did not support the prognostic value of NLR to guide therapy for HCC, whereas MELD and Child–Pugh score were more predictive. We conducted our current study to determine whether the pretreatment NLR is associated with the clinical outcome of patients with HCC and to compare the prognostic value of the pretreatment NLR with other prognostic methods of predicting survival in Chinese HCC patients. Our findings show that the pretreatment NLR is a useful prognostic biomarker in HCC patients, and that the prognostic value of NLR correlates with that of the BCLC and TNM staging scores.

PATIENTS AND METHODS

Study Population

We retrospectively reviewed the data of 906 patients who were newly diagnosed with HCC between October 2008 and May 2012 at Beijing Ditan Hospital (Beijing, China), which is affiliated with the Capital Medical University. The study was approved by the ethics committee of Beijing Ditan Hospital (Beijing, China). Patient records and information was anonymized and deidentified prior to analysis. The diagnosis of HCC was based on the detection of a histopathologically confirmed HCC lesion using at least 2 different imaging techniques or the detection of 2 such lesions using 1 imaging technique combined with a serum concentration of α-fetoprotein (AFP) ≥400 ng/mL. The imaging techniques used included transabdominal ultrasonography, abdominal computed tomography, magnetic resonance imaging, and hepatic angiography. Patients who were <18 years of age, had an active bacterial infection or upper respiratory viral infection, or had received any medications that could affect the NLR, such as granulocyte-colony stimulating factor (G-CSF), interferon, or high-dose steroids, were excluded from our study. Patients for whom data regarding tumor size, tumor number, or the above-mentioned clinical, laboratory, and imaging criteria were unavailable were also excluded. Finally a total of 825 HCC patients were included in our study.

All of the HCC patients were evaluated for potential curative therapies, which included surgical resection and liver transplantation. Patients who were not suitable candidates for curative treatments were treated with locoregional approaches, which included ablation and transarterial embolization. Radiofrequency ablation, microwave ablation, or percutaneous alcohol injection were performed in patients with 2 to 3 tumors that were each <3 cm in size. Transcatheter arterial chemoembolization and/or lipiodol-transcatheter arterial infusion were performed in patients with >4 tumors, a tumor >3 cm in size, or a Child–Pugh class of A or B. Molecular targeted therapy or systemic chemotherapy, which included sorafenib and FOLFOX (Folinic acid - Fluorouracil - Oxaliplatin) regimens, was performed in HCC patients who had distant metastasis and were not suitable candidates for surgery. The best supportive care (BSC) was provided for patients with distant metastasis or a Child–Pugh class of C. Patients with chronic hepatitis B or C received antiviral therapy, and patients with cirrhosis or liver dysfunction received medical treatment to reduce transaminase activity.

Study Variables

The various demographic, medical history, serum biochemical, and clinical characteristics were analyzed at baseline. The patient characteristics analyzed included age, sex, history of alcohol use, history of smoking, and family history of HCC. The following serum biochemical variables were analyzed: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), serum albumin (ALB), alkaline phosphatase (ALP), γ-glutamyltranspeptidase (GGT), serum creatinine, prothrombin time (PT), prothrombin activity (PTA), international normalized PT ratio, AFP, white blood cell (WBC) count, absolute NC, absolute lymphocyte count (LC), and absolute platelet count (PLT).

Statistical Analysis

All of the statistical procedures were performed using the SPSS version 19.0 software (IBM, Armonk, NY). The categorical data are reported as the number or percentage of observations. Normally distributed continuous variables are reported as the mean ± standard deviation. Univariate and multivariate analyses of the relationships between OS and the study variables was performed using Cox proportional hazard models. Variables that were shown to be associated with OS in the univariate analysis were evaluated in the multivariate Cox proportional hazard model. The likelihood ratios forward stepwise method was used for the multivariate Cox proportional analysis. A receiver operating characteristic (ROC) curve was constructed for each study variable shown to be significantly associated with OS in the multivariate analysis, and the area under the curve (AUC) was calculated to evaluate the discriminatory capacity of each. The cut off value for the maximum sensitivity and specificity of the NLR was calculated, and the patients were divided into 2 groups based on the NLR cut off value. A Kaplan–Meier survival analysis was performed to compare the OS of the patients in different groups, and the significance of the intergroup difference was evaluated using the log-rank test. A Pearson correlation analysis was performed to determine the relationship between NLR and the BCLC and TNM staging scores. All of the probability values calculated were 2-sided, and the results of comparisons with P < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics and Outcomes

A total of 825 HCC patients were included in our study. The baseline characteristics of the study population are shown in Table 1. The patients ranged in age from 25 to 75 years, and the mean age was 54.5 ± 9.8 years. The HCC cohort consisted of 690 men (83.6%) and 135 women (16.4%), among whom 116 (14.1%) of the patients had a family history of HCC. Hepatitis B, hepatitis C, and alcoholic liver disease was diagnosed in 739, 56, and 117 patients, respectively.
TABLE 1. Univariate and Multivariate Analyses of OS in Patients With HCC (N = 825)

| Variable                          | Value \(1\)   | Univariate HR (95% CI)          | Multivariate HR (95% CI)  |
|----------------------------------|---------------|--------------------------------|---------------------------|
| Age, y                           | 54.5 ± 9.8    | 0.985 (0.976–0.995)*            |                           |
| Men/women                        | 690/135       | 0.649 (0.485–0.868)*            |                           |
| Family history of HCC            | 116           | 1.137 (0.858–1.507)             |                           |
| History of smoking               | 321           | 1.207 (0.993–1.468)             |                           |
| History of alcohol use           | 325           | 1.324 (1.210–1.448)*            |                           |
| Number of tumors ≥ 3             | 292           | 2.892 (2.380–3.516)*            |                           |
| Tumor size ≥ 5 cm                | 268           | 3.928 (3.224–4.785)*            |                           |
| Lymph node metastasis            | 77            | 3.905 (3.024–5.041)*            |                           |
| Portal vein involvement          | 207           | 9.072 (7.325–11.236)*           |                           |
| ALT, IU/L                        | 57.2 ± 73.8   | 1.001 (1.000–1.002)             |                           |
| AST, IU/L                        | 70.5 ± 86.3   | 1.003 (1.002–1.003)*            |                           |
| TBil, μmol/L                     | 27.2 ± 26.2   | 1.009 (1.007–1.011)             |                           |
| ALB, g/L                         | 36.4 ± 6.5    | 0.963 (0.949–0.977)*            |                           |
| ALP, IU/L                        | 122.7 ± 81.0  | 1.005 (1.004–1.006)*            |                           |
| GGT, IU/L                        | 104.2 ± 113.6 | 1.004 (1.003–1.004)*            |                           |
| Cr, μmol/L                       | 69.6 ± 29.7   | 1.005 (1.002–1.007)*            |                           |
| PTA, %                           | 76.1 ± 18.7   | 0.983 (0.978–0.988)*            |                           |
| WBC, 10^9/L                      | 4.6 ± 1.9     | 1.182 (1.126–1.241)*            |                           |
| ANC, 10^9/L                      | 2.8 ± 1.5     | 1.395 (1.319–1.475)*            |                           |
| PLT, 10^9/L                      | 112.0 ± 67.8  | 1.003 (1.001–1.004)*            |                           |
| NLR                              | 2.8 ± 1.9     | 1.343 (1.298–1.390)*            |                           |
| PLR                              | 99.9 ± 58.2   | 1.008 (1.007–1.010)*            |                           |
| AFP ≥400 ng/mL                   | 204           | 3.015 (2.467–3.686)*            |                           |
| MELD score                       | 5.9 ± 5.0     | 1.057 (1.042–1.072)*            |                           |
| Child–Pugh class                 |               |                                 |                           |
| A                                | 513           | Reference                       |                           |
| B                                | 253           | 2.037 (1.652–2.511)*            | 1.598 (1.275–2.024)*      |
| C                                | 59            | 4.959 (3.638–6.760)*            | 4.943 (4.484–7.012)*      |

\* Data are presented as the number of observations or the mean ± standard deviation.

\(P < 0.05\).

At the time of diagnosis, 513 (62.2%), 253 (30.7%), and 59 (7.1%) of the patients were classified as Child–Pugh class A, B, or C, respectively. A total of 268 (32.5%) of the patients had a tumor ≥ 5 cm in size, and 292 (35.9%) of the patients had ≥ 3 tumors. Seventy-seven (9.3%) of the patients had lymph node metastasis, and 208 (25.2%) of the patients had portal vein involvement. The mean levels of ALT and TBil were 57.2 IU/L and 27.2 μmol/L, respectively, and the mean NLR was 2.8.

Surgical resection was performed in 90 (10.9%) of the patients, and locoregional approaches were administered in 698 (89.3%) of the patients. The remaining 59 patients (4.7%) received BSC. At the end of the 2-year follow-up period, 414 (50.2%) of the patients had survived, whereas 411 (49.8%) of the patients had died. The median OS period was 24 months. The 6-, 12-, and 24-month OS rates were 82.9%, 66.2%, and 50.2%, respectively.

Prognostic Value of Pretreatment NLR in HCC

To identify predictors of HCC survival, the prognostic value of 26 variables were evaluated. The univariate analysis showed that age, sex, history of alcohol use, tumor number ≥ 3, tumor size ≥ 5 cm, lymph node metastasis, portal vein involvement, AST, TBil, ALB, ALP, GGT, Cr, PTA, WBC, ANC, ALC, PLT, NLR, PLR, AFP ≥ 400 ng/mL, MELD score, and Child–Pugh class were associated with OS in HCC patients \((P < 0.05, \text{Table 1})\). In the multivariate Cox regression analysis, only NLR, tumor number ≥ 3, tumor size ≥ 5 cm, lymph node metastasis, portal vein involvement, Child–Pugh class, GGT, and AFP ≥ 400 ng/mL were significantly associated with OS \((P < 0.05, \text{Table 1})\).

To compare the predictive value of NLR, GGT, AFP ≥ 400 ng/mL, tumor number ≥ 3, tumor size ≥ 5 cm, lymph node metastasis, portal vein involvement, and Child–Pugh class for the prognosis of HCC, we compared the ROC curves of these parameters. As shown in Figure 1, the ROC curve for NLR (0.811) had the highest AUC, compared with that for tumor number ≥ 3 (0.666), tumor size ≥ 5 cm (0.702), lymph node metastasis (0.592), portal vein involvement (0.748), Child–Pugh class (0.640), GGT (0.745), and AFP ≥ 400 ng/mL (0.634) at 24 months posttreatment. The AUC value for NLR was also higher than that of the other study variables at 6 months (0.789).
and posttreatment NLR <2.7 (n = 66, cohort 3), and pretreatment and posttreatment NLR ≥2.7 (n = 189, cohort 4). As shown in Figure 2C, patients with lower posttreatment NLR had an improved OS when compared with patients with higher posttreatment NLR (cohort 1 vs 2, \( P < 0.0001 \); cohort 1 vs 4, \( P < 0.0001 \); cohort 3 vs 2, \( P = 0.004 \); cohort 3 vs 4, \( P < 0.0001 \)). Persistence of NLR levels (cohort 1, 4) retained prognostic significance, whereas a new elevation of NLR (cohort 2) was associated with a dismal prognosis.

**Correlation of Pretreatment NLR Cut Off Value With BCLC and TNM Staging of HCC**

The relationship between the pretreatment NLR and the BCLC and TNM stages for the prognosis of HCC was evaluated. Positive linear correlations were observed between the NLR and the BCLC (\( r = 0.462, P < 0.001 \)) and TNM (\( r = 0.363, P < 0.001 \)) stages. The NLR increased with increasing BCLC stage (Figure 3A), with NLR values of 2.08 ± 1.18 in stage 0/A; 2.70 ± 1.71 in stage B; 3.80 ± 1.93 in stage C; and 4.34 ± 2.41 in stage D (stage 0/A vs B, \( P < 0.0001 \); stage B vs C, \( P < 0.0001 \); stage C vs D, \( P = 0.1251 \)). Likewise, the NLR increased with increasing TNM stage (Figure 3B), with NLR values of 1.70 ± 0.69 in stage I; 2.23 ± 1.38 in stage II; 3.82 ± 2.12 in stage III; and 3.75 ± 1.66 in stage IV (stage I vs II, \( P = 0.0972 \); stage II vs III, \( P < 0.0001 \); stage III vs IV, \( P = 0.5735 \)).

We also performed Kaplan–Meier survival analyses to evaluate the relationships between the NLR cut off value and the BCLC and TNM stages for the prognosis of HCC. The OS of patients with an NLR ≥2.7 was significantly poorer than that of patients with an NLR <2.7 for all BCLC stages (\( P < 0.0001 \) to \( P = 0.0066 \)), and the OS period of patients with an NLR ≥2.7 decreased with more advanced BCLC stage throughout the 2-year follow-up (Figure 4A–D). The OS of patients with an NLR ≥2.7 was significantly poorer than that of patients with an NLR <2.7 for TNM stages II, III, and IV (\( P < 0.0001 \) to \( P = 0.0365 \), Figure 4F–H), whereas the OS of the small number of TNM stage I patients (n = 2) with an NLR ≥2.7 was not significantly different than that of the TNM stage I patients with an NLR <2.7 (\( P = 0.7518 \), Figure 4E). The OS period of patients with an NLR ≥2.7 also decreased with more advanced TNM stage throughout the 2-year follow-up.

**DISCUSSION**

During the last decade, multiple studies have shown that the pretreatment NLR is a predictor of clinical outcome in various malignancies, including HCC.\(^7,11,13\) In our current study, the pretreatment NLR was an independent prognostic factor for reduced OS in HCC patients, and the prognostic value of NLR ≥2.7 is superior to that of other common serum biochemical variables, tumor characteristics, MELD stage or Child–Pugh class. The findings were reproducible at a second independent time point with another NLR determination. By subgroup analyses, we also found that elevated NLR correlated with BCLC and TNM stage (\( r = 0.462, P < 0.001 \); \( r = 0.363, P < 0.001 \), respectively), with patients with a higher NLR tending to have greater liver involvement and metastasis. These findings suggest that high NLR is predictive of an aggressive HCC phenotype that contributes to poor OS.

Although measured easily, the clinical relevance of NLR is complex because it represents a combination of factors related to both inflammation and host immunity. Chronic HBV or HCV infection are associated with HCC, and both types of viral
infection cause persistent inflammation. The systemic and local inflammatory responses to viral infection may provide a microenvironment that is favorable for tumor growth and metastasis. A high NLR has been shown to be associated with more numerous tumor-associated macrophages and an increased level of interleukin (IL)-17, which may promote systemic neutrophilia through the secretion of IL-6, IL-8, and CC chemokine ligand 2. In addition, the expression of G-CSF and macrophage colony-stimulating factor at high levels in tumor and peritumoral tissues, respectively, is associated with an elevated NC. Neutrophils are a primary source of circulating vascular endothelial growth factor, which plays a key role in angiogenesis and neutrophils can contribute to metastasis by promoting the motility of tumor cells and the adhesion of metastatic tumor cells in liver sinusoids.

Lymphocytopenia can indicate the suppression of innate cellular immunity, which may attenuate lymphocyte-mediated antitumor immunity. Neutrophils have been shown to suppress the cytotoxic activity of lymphocytes, natural killer cells, and activated T cells through the production of arginine, nitric oxide, and reactive oxygen species. Therefore, patients with elevated NLR may have mild lymphocytopenia and neutrophilic leukocytosis, which creates a microenvironment that favors metastasis and suppresses cellular immunity. Thus, NLR may

**FIGURE 2.** (A) Kaplan–Meier survival curves for HCC patients with an NLR ≥2.7 and those with an NLR <2.7 for the 2-year follow-up period. (B) Confirmation of the prognostic significance of NLR using the cut off <2.7 and ≥2.7 at a second independent timepoint using a second NLR determination. (C) Impact of NLR dynamic between the first and second NLR determination on OS. HCC = hepatocellular carcinoma, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival.

**FIGURE 3.** Box plots of the NLR and the BCLC and TNM stages of the patients with HCC. BCLC = Barcelona-Clinic Liver Cancer, HCC = hepatocellular carcinoma, NLR = neutrophil-to-lymphocyte ratio, TNM = Tumor, Node, Metastasis.
reflect the balance between tumorigenic inflammatory processes and antitumor cellular immunity.

In our current study, the prognostic value of the pretreatment NLR was superior to that of GGT, AFP, tumor number, tumor size, lymph node metastasis, portal vein involvement, and Child–Pugh class. We determined that an NLR of 2.7 was the best cut off value for distinguishing between patients with a poor prognosis and those with a better prognosis. This finding is similar to that of Mano et al., who also found that elevated NLR was an independent predictor of survival in HCC patients. However, such findings are inconsistent with those of certain previous studies.

FIGURE 4. BCLC- and TNM-stage-specific Kaplan–Meier survival curves for HCC patients with an NLR ≥ 2.7 and those with an NLR < 2.7. BCLC = Barcelona-Clinic Liver Cancer, HCC = hepatocellular carcinoma, NLR = neutrophil-to-lymphocyte ratio, TNM = Tumor, Node, Metastasis.
our study may have influenced our results, thus contributing to differences between our findings and those of previous investigations. However, our stringent exclusion of patients with fever or a concurrent bacterial or nonhepatitis viral infection was likely sufficient to minimize the influence of confounding comorbidities with inflammatory components.

In conclusion, our results demonstrated that a pretreatment NLR \( \geq 2.7 \) is a strong predictor of poor survival in patients with HCC, and the prognostic value of an NLR \( \geq 2.7 \) correlates with BCLC and TNM stage scores. Therefore, a pretreatment NLR \( \geq 2.7 \) is a useful prognostic biomarker for predicting clinical outcomes in HCC patients. Future prospective, randomized studies with larger samples are warranted to confirm our results. Future investigations of possible links between immunological factors that influence the NLR and processes that promote tumor metastasis are also warranted to clarify the clinical relevance of NLR levels in cancer patients.

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