The value of neutrophil to lymphocyte ratio and gamma-glutamyl transpeptidase to platelet ratio in patients with hepatocellular carcinoma

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Abstract
Our study aimed to evaluate the value of neutrophil to lymphocyte ratio (NLR) and gamma-glutamyl transpeptidase to platelet ratio (GPR) in patients with hepatocellular carcinoma (HCC).

A total of 565 patients with pathological diagnosis of HCC were retrospectively analyzed and 414 patients diagnosed with cirrhosis were treated as a control group. All clinical materials were collected from the First Affiliated Hospital of Guangxi Medical University. The preintervention NLR, GPR, and α-fetoprotein (AFP) were significantly higher in HCC patients than in the controls (P_{NLR}<.000, P_{GPR}<.000, P_{AFP}<.000). The NLR and GPR were correlated with the Barcelona clinic liver cancer (BCLC) stages, Child-Pugh grades, and tumor size, but not with Edmondson–Steiner grades. Combined use of NLR or GPR with AFP produced larger area under the curve (AUC) (AUC_{NLR+AFP}=0.916; AUC_{GPR+AFP}=0.953) than NLR (P<.000), GPR (P<.000), or AFP (P<.000) used alone.

The preintervention hematologic parameters (NLR and GPR) studied herein were associated with the BCLC stages of HCC. Combined use of NLR or GPR with AFP may improve early detection and diagnosis of HCC.

Abbreviations: AFP = α-fetoprotein, BCLC = Barcelona clinic liver cancer, GGT = gamma-glutamyl transpeptidase, GPR = gamma-glutamyl transpeptidase to platelet ratio, HCC = hepatocellular carcinoma, LYM = lymphocyte count, NEU = neutrophil count, NLR = neutrophil to lymphocyte ratio, PLT = platelet.

Keywords: Barcelona clinic liver cancer (BCLC) stages, Edmondson–Steiner grades, gamma-glutamyl transpeptidase to platelet ratio, hepatocellular carcinoma, neutrophil to lymphocyte ratio

1. Introduction
Hepatocellular carcinoma (HCC) is the third most common malignancy responsible for mortality after gastric and esophageal cancers.[1] HCC is difficult to detect at an early stage and is characterized by a long incubation period, rapid development, high malignancy, and high mortality.[2] The incidence rate of HCC is particularly high in developing countries due to environmental variables, dietary habits, and inadequate medical care.[3]

Tumor progression is closely related to inflammatory factors.[4] The process of hepatitis, cirrhosis, and HCC staging is linked to a network of inflammatory signaling pathways and changes in the tumor microenvironment.[5,6] Previous studies have demonstrated the clinical importance of inflammation-based hematological markers, like the C-reactive protein,[7] and the aspartate aminotransferase to platelet count ratio index.[8] Recently, hematologic markers of inflammation, such as the neutrophil to lymphocyte ratio (NLR) and gamma-glutamyl transpeptidase to platelet ratio (GPR), have attracted increasing attention due to their clinical application in various diseases (e.g., cervical squamous cell carcinoma, colorectal cancer, liver fibrosis, and cirrhosis).[9–11] However, their clinical importance in HCC staging remains unexplored.

Inflammatory factors have been closely associated with the stages of tumor.[12] Previous studies have evaluated the predictive value of NLR and GPR in HCC.[13,14] Limited numbers of studies have examined the relationship between hematologic markers and tumor clinicopathological features.[9,15] An analysis of hematologic parameters and clinicopathological features would provide information for early diagnosis of diseases. Our study aimed to explore the preintervention values of the NLR and GPR in HCC.

2. Materials and methods
2.1. Study population and design
A total of 565 patients with pathologically diagnosed HCC were enrolled in this study. All preintervention hematologic parameters, pathological grades, and clinical features of HCC patients who attended the First Affiliated Hospital of Guangxi Medical
Table 1
Comparison of hematologic characteristics between HCC group and control group.

| Characteristics | HCC group N = 865 | Control group N = 441 | P value |
|-----------------|-------------------|----------------------|--------|
| Gender (Male/Female) | 482/3 | 365/76 | .296 |
| Age, y | 47.00 (40.00, 56.00) | 46.00 (38.00, 54.00) | .050 |
| PLT (×10^9/L) | 179.00 (138.40, 226.15) | 245.90 (214.00, 277.95) | <.000 |
| NEU (×10^9/L) | 3.54 (2.70, 4.61) | 3.62 (2.98, 4.33) | .448 |
| LYM (×10^9/L) | 1.73 (1.35, 2.18) | 2.29 (1.93, 2.74) | <.000 |
| AFP, µg/L | 57.00 (35.00, 108.00) | 31.00 (22.00, 45.00) | <.000 |
| NLR | 2.02 (1.46, 2.83) | 1.56 (1.26, 1.91) | <.000 |
| GPR | 0.32 (0.19, 0.64) | 0.13 (0.09, 0.19) | <.000 |

AFP = α-fetoprotein, GGT = gamma-glutamyl transpeptidase, GPR = gamma-glutamyl transpeptidase to platelet ratio, HCC = hepatocellular carcinoma, LYM = lymphocyte count, NEU = neutrophil count, NLR = neutrophil to lymphocyte ratio, PLT = platelet count.

Table 2
Relationship between hematological characteristics and clinicopathological features.

| Variables | Number of patients | NLR | GPR | AFP |
|-----------|--------------------|-----|-----|-----|
| BCLC stage | | ≥2.02 | <2.02 | ≥0.21 | <0.21 | ≥8.72 | <8.72 |
| A | 287 | 120 | 167 | <.001 | 187 | 100 | <.001 | 201 | 86 | .003 |
| B | 164 | 89 | 75 | 123 | 41 | 124 | 40 |
| C | 114 | 76 | 38 | 98 | 16 | 97 | 17 |
| Edmondson–Steiner grade | | | | | | | |
| I–II | 313 | 146 | 167 | .254 | 221 | 92 | .594 | 221 | 92 | .063 |
| III | 159 | 83 | 76 | 116 | 43 | 125 | 34 |
| Unknown | 93 | 57 | 36 | 71 | 22 | 75 | 18 |
| Child-Pugh grade | | | | | | | |
| A | 509 | 248 | 261 | .014 | 357 | 152 | <.001 | 381 | 128 | .789 |
| B/C | 56 | 37 | 19 | 51 | 5 | 41 | 15 |
| Tumor size | | | | | | | |
| ≤5 cm | 294 | 110 | 184 | <.001 | 198 | 96 | .007 | 200 | 94 | <.001 |
| >5 cm | 271 | 175 | 96 | 210 | 61 | 222 | 49 |

AFP = α-fetoprotein, BCLC stage = Barcelona clinic liver cancer stage, GPR = gamma-glutamyl transpeptidase to platelet ratio, NLR = neutrophil to lymphocyte ratio.
(P < .001), GPR (P < .001), and AFP levels (P = .003) were correlated with BCLC stages. However, the Edmondson–Steiner grades were not correlated with any of the hematologic parameters (NLR and GPR) or AFP level (all P > .05). NLR > 2.02 (P = .014) and GPR > 0.21 (P < .001) were positively correlated with Child-Pugh grades. However, the level of AFP was not significantly related to the Child-Pugh grades. Tumor size was correlated with all the hematologic parameters (NLR, P < .001; GPR, P = .007; and AFP level, P < .001).

3.3. Comparisons of different hematologic parameters according to the HCC staging

The significance of the HCC staging with preintervention NLR, GPR, and AFP values was determined by the Mann–Whitney U test using the median with interquartile range to indicate the level of each hematologic ratio at different BCLC stages (Fig. 1) or Edmondson–Steiner grades (Fig. 2). Sustained rises in the NLR (all P < .05) and GPR (all P < .05) levels were significantly correlated with the BCLC stages, while AFP (P = .066) was not statistically significant in comparing BCLC stage B and BCLC stage C. Thus, NLR and GPR may be comparable to or even exceed AFP in differentiating between BCLC stage B and BCLC stage C. NLR and GPR cannot distinguish Edmondson–Steiner grades, while AFP (all P < .05) made a significant difference in distinguishing gradually increasing Edmondson–Steiner grades.

3.4. Diagnostic efficacy of NLR, GPR, and AFP alone or in combination in differentiating patients with HCC from controls

ROC analysis method was used for evaluating the diagnostic ability of preintervention NLR, GPR, and AFP values alone or in combination to differentiate HCC patients from controls. The results are presented in the Table 3 and Fig. 3. AFP had high

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**Table 3**

|                | Sensitivity (%) | Specificity (%) | LR+   | LR−   | AUROC (95% CI) |
|----------------|----------------|-----------------|-------|-------|----------------|
| NLR            | 49.91          | 79.59           | 2.45  | 0.63  | 0.663 (0.633–0.692) |
| GPR            | 70.44          | 82.99           | 4.14  | 0.36  | 0.853 (0.830–0.875) |
| AFP            | 74.69          | 98.41           | 47.05 | 0.26  | 0.916 (0.897–0.932) |
| NLR + AFP      | 74.69          | 99.55           | 164.69| 0.25  | 0.916 (0.916–0.932) |
| GPR + AFP      | 86.73          | 96.60           | 25.50 | 0.14  | 0.953 (0.938–0.966) |

AFP = a-fetoprotein, AUROC = area under the receiver operating characteristic curve, GPR = gamma-glutamyl transpeptidase to platelet ratio, LR+ = positive likelihood ratio, LR− = negative likelihood ratio, NLR = neutrophil to lymphocyte ratio.
sensitivity and specificity (74.69% and 98.41%, respectively) in differentiating HCC group from control group. Combined use of NLR and AFP produced larger AUC (0.916, 0.897–0.932) than NLR (P < .000) or AFP (P < .000) used alone. The sensitivity of differentiating HCC group from control group increased when GPR was used in combination with AFP. Moreover, the combination of GPR and AFP performed production larger AUC (0.953, 0.938–0.966) compared with GPR (P < .000) or AFP (P < .000) used alone.

4. Discussion

Inflammation plays an important role in the development of HCC. In the current study, we mainly assessed the diagnostic value of inflammatory markers (NLR and GPR) in HCC. The results suggested that NLR and GPR in the HCC group were significantly higher than those in the control group, which was consistent with previously reported findings. The Edmondson–Steiner grades, Child-Pugh grades, and tumor size were closely related to HCC. Songlin et al revealed the association between AFP and clinicopathological features of HCC, including Child-Pugh grades and tumor size, which was consistent with our findings. In other studies, the relationship between hematologic parameters (NLR and GPR) and clinical characteristics (Child-Pugh grades and tumor size) has been demonstrated. The NLR has traditionally been regarded as a marker of inflammation (systemic and subclinical). Previous studies have reported a significant difference in the NLR of patients with severe preeclampsia and systemic lupus erythematosus versus that of controls. Studies have also demonstrated that the NLR was significantly associated with the pathological grading of laryngeal carcinomas. Thus, the relationship between NLR and the clinicopathological features of HCC appears to be different from other cancers or diseases.

However, none of the studies reveal the relationship between NLR, GPR, and Edmondson–Steiner grades in HCC. Our current findings indicated that NLR and GPR have no correlation with Edmondson–Steiner grades.

The mechanism by which the hematologic ratios in this study can be used to monitor the stages of HCC is unclear. Du et al followed 230 patients with cirrhosis and found that preoperative NLR elevation was associated with an increased risk of progression to HCC in patients with cirrhosis. Jin et al evaluated the prognostic value of NLR in 556 patients with HCC in BCLC stage A, and found that increased NLR was a poor prognostic indicator. Park et al evaluated the predictive value of GPR in patients with HCC and divided the included patients into low-risk and high-risk groups according to the GPR cut-off value. The results indicated that the relative risk of HCC development in the high-risk GPR group was significantly higher than in the low-risk GPR group. In the present study, an increase in the NLR and GPR was associated with the BCLC stages of HCC, which was consistent with previous studies.

AFP is a well-known marker for the diagnosis of HCC. The results of this study are consistent with those of Bertino et al who suggested that AFP had important predictive value in HCC and that the AUC was very large. Interestingly, in this study, the value of NLR and GPR was comparable to or higher than the commonly used marker AFP in differentiating between BCLC stage B and BCLC stage C. In clinical laboratory applications, accurate detection of AFP requires expensive and special equipment, and its detection speed and application are limited. In contrast, hematologic parameters have a number of advantages, including simple operation, low cost, rapid detection, and wide application. Hematologic ratios, such as the NLR and GPR, may become an alternative or auxiliary diagnostic indicator to AFP in the clinical values of HCC, especially in developing countries with limited resources where HCC is most prevalent.

AFP is a glycoprotein, which is closely related to the occurrence and development of various tumors (e.g., testicular cancer and dedifferentiated endometrioid adenocarcinoma). In our study, the comparison of HCC group and control group revealed that AFP used alone gave the best diagnostic efficacy compared with NLR or GPR used alone, which was consistent with the results reported by previous studies. In addition, our study found that the combined use of NLR or GPR with AFP was larger in AUC than that of NLR, GPR, and AFP used alone. Hence, we speculate that the combined use of NLR or PLR with AFP may improve the early diagnosis of HCC.

There were some limitations to our study. Firstly, this was a retrospective analysis. As such, it was prone to a variety of biases (e.g., selection bias and recall bias). Secondly, we were not able to directly analyze the relationship between factors and diseases. Finally, the sample size was limited and was not sufficient to explain the value of the NLR and GPR in predicting HCC progression. These problems could be resolved by increasing the sample size, setting strict inclusion criteria, and conducting rigorous prospective studies. However, our study is the first to assess the relationship between hematological parameters (NLR and GPR) and HCC staging (BCLC stages and Edmondson–Steiner grades), and establish that NLR and GPR had no correlation with Edmondson–Steiner grades. Our study is also the first to explore the diagnostic value of combined use of NLR, GPR, and AFP in HCC.

In summary, the hematologic ratios (NLR and GPR) studied herein might be associated with the BCLC staging of HCC.
Combined use of NLR or GPR with AFP may improve early detection and diagnosis of HCC in order to enable early treatment of the disease.

Author contributions
Xue Qin and Shan Li drafted the overall design of this paper as the co-corresponding authors. Zuojian Hu and Huaping Chen wrote the article as the co-first authors. Siyuan Chen and Zhili Huang collected the laboratory data. Shanzi Qin and Jianing Zhong analyzed the data.

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