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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) ($AUC_{NLR+AFP} = 0.916$; $AUC_{NLR+AFP} = 0.953$) 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]

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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 = 565	Control group N = 441	P value
Gender (Male/Female)	482/83	365/76	.296
Age, y	47.00 (40.00, 56.00)	46.00 (38.00, 54.00)	.050
PLT (×10⁹/L)	179.00 (138.40, 228.15)	245.90 (214.00, 277.95)	<.000
NEU (×10⁹/L)	3.54 (2.70, 4.61)	3.62 (2.98, 4.33)	.448
LYM (×10⁹/L)	1.73 (1.35, 2.18)	2.29 (1.93, 2.74)	<.000
GGT, U/L	57.00 (35.00, 108.00)	31.00 (22.00, 45.00)	<.000
AFP, μg/L	186.60 (8.43, 2325.00)	3.07 (2.06, 4.71)	<.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.

University between 2012 and 2017 were collected from the hospital's electronic medical records. Patients in HCC group need to meet the following 5 criteria to be included: Barcelona clinic liver cancer (BCLC) stages A, B, or C; Edmondson–Steiner grades I, II, or III; Child-Pugh grades A, B, or C; pathologically diagnosed as HCC; surgical resection treatment. Patients will be excluded if they meet one of the following: past history of HCC; blood system diseases; immune-related diseases; organic disease outside liver; presence of other types of cancers. The control group comprised 441 age- and sex-matched individuals diagnosed with cirrhosis. This study was approved by the Ethics Committee of First Affiliated Hospital of Guangxi Medical University. Informed consent was obtained from all the participants.

2.2. Data collection

All laboratory data were collected about a week before the patient underwent the first treatment. Data on the participant's age and sex were obtained. The values of platelet (PLT), neutrophil (NEU), and lymphocyte (LYM) counts; and the levels of α-fetoprotein (AFP) and gamma-glutamyl transpeptidase (GGT) were recorded. NLR and GPR were calculated using the following formulas:

NLR = neutrophil count/lymphocyte count
GPR = gamma-glutamyl transpeptidase level/platelet count

2.3. Statistical analysis

SPSS software version 17.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 5 software (http://www.graphpad.com/scientific-software/prism/) were used for data analysis. The distribution of variables was based on Kolmogorov–Smirnov test. Summary data were represented as the median, with interquartile ranges. A receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity and specificity of preintervention NLR and GPR. Appropriate cut-off values for the above hematological parameters were obtained through ROC analysis. The Mann–Whitney U test was conducted to compare the laboratory parameters of the HCC patients and controls, and a chi-square test or Kruskal–Wallis test was performed to compare categorical variables. P value <.05 (two-tailed) was considered to be statistically significant.

3. Results

3.1. Comparison of hematologic features of the HCC patients with controls

As shown in Table 1, the median serum AFP and GGT levels in HCC patients were significantly higher than those in controls (all $P < .001$). HCC patients had significantly lower platelet and lymphocyte counts compared with controls. Moreover, the median NLR and GPR values were higher in the HCC group as than in the control group (all $P < .001$), however, there was no significant difference in neutrophil counts between HCC patients and the controls ($P = .447$).

3.2. Correlation between hematologic parameters and clinicopathological features of HCC patients

As shown in Table 2, the columns of the table were stratified by the cut-off values for the HCC patients, and the rows of the table were stratified according to different clinicopathological features. The correlation of clinicopathological features with NLR, GPR, and AFP values was analyzed using the chi-square test. The NLR

Table 2

Relationship between hematological characteristics and clinicopathological features.

Variables	Number of patients	NLR ≥2.02	NLR <2.02	P value	GPR ≥0.21	GPR <0.21	P value	AFP ≥8.72	AFP <8.72	P value
BCLC stage										
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.
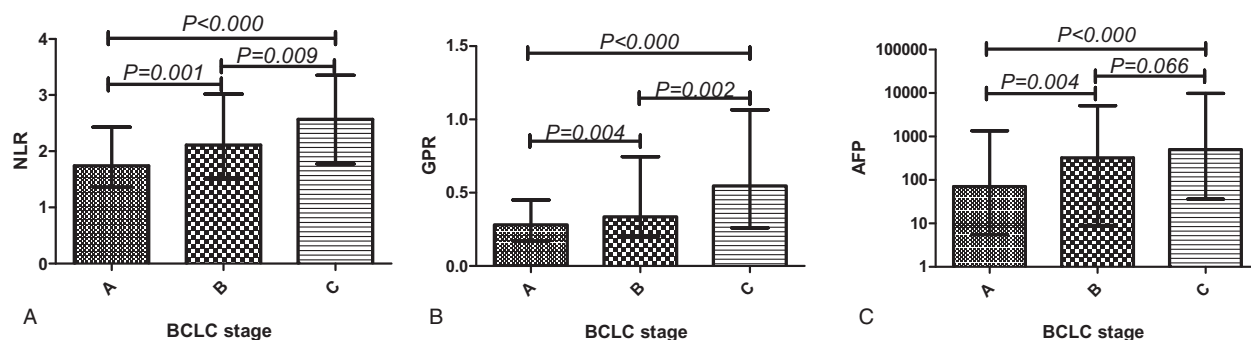
Figure 1. Comparisons of different hematologic parameters in HCC patients with different BCLC stages. BCLC=Barcelona clinic liver cancer, HCC=hepatocellular carcinoma.
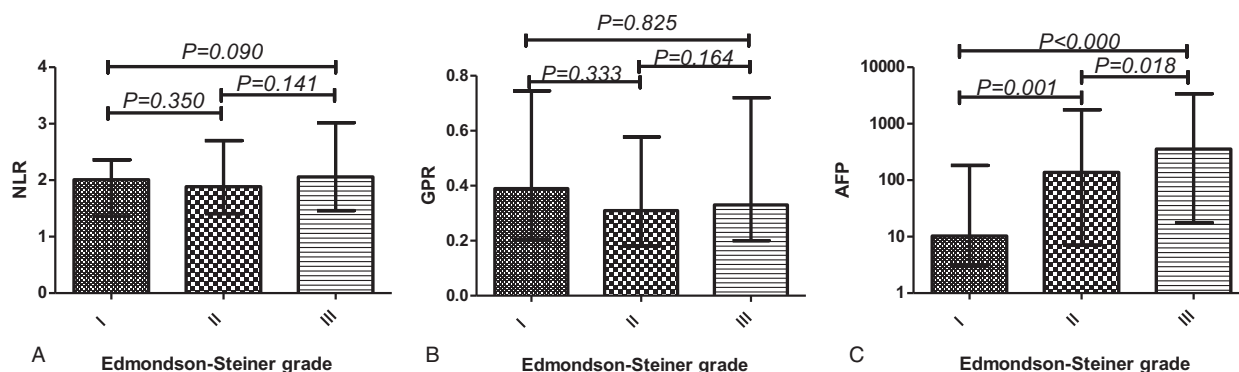

Figure 2. Comparisons of different hematologic parameters in HCC patients with different Edmondson–Steiner grades. HCC=hepatocellular carcinoma.

($P < .001$), 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

Table 3

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

	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	0.895 (0.874–0.913)
NLR + AFP	74.69	99.55	164.69	0.25	0.916 (0.897–0.932)
GPR + AFP	86.73	96.60	25.50	0.14	0.953 (0.938–0.966)

AFP = α-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.
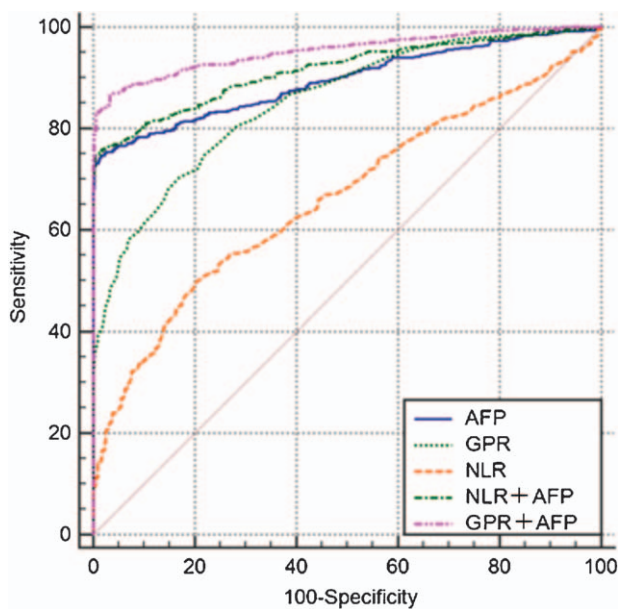
Figure 3. ROC curves of NLR, GPR, and AFP alone or in combination in differentiating patients with HCC from controls. AFP = α-fetoprotein, GPR = gamma-glutamyl transpeptidase to platelet ratio, HCC = hepatocellular carcinoma, NLR = neutrophil to lymphocyte ratio, ROC = receiver operating characteristic.

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 produced performance 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.[16] 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.[14,17]

Edmondson–Steiner grades, Child-Pugh grades, and tumor size were closely related to HCC.[18–20] Songlin et al[21] 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.[22,23] The NLR has traditionally been regarded as a marker of inflammation (systemic and subclinical).[9,24] Previous studies have reported a significant difference in the NLR of patients with severe preeclampsia and systemic lupus erythematosus versus that of controls.[25,26] Studies have also demonstrated that the NLR was significantly associated with the pathological grading of laryngeal carcinomas.[27] 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[28] 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[29] 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[14] 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.[30]

AFP is a well-known marker for the diagnosis of HCC.[31,32] The results of this study are consistent with those of Bertino et al,[33] 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).[34,35] 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.[36] 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.

Data curation: Siyuan Chen, Shanzi Qin.
Formal analysis: Jianing Zhong.
Investigation: Shan Li.
Software: Zhili Huang.
Writing – original draft: Zuojian Hu.
Writing – review & editing: Xue Qin, Huaping Chen.

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