Predictive value of gamma-glutamyl transpeptidase to lymphocyte count ratio in hepatocellular carcinoma patients with microvascular invasion

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Abstract

Purpose: Microvascular invasion (MVI) is an independent risk factor for poor prognosis of hepatocellular Carcinoma (HCC), However, there is still a lack of preoperative markers to predict MVI of HCC. This study intends to explore the potential application value of gamma-glutamyl transpeptidase to lymphocyte count ratio (GLR) in predicting MVI of HCC, and provide guidance of clinical diagnosis and treatment.

Patients and methods: From March 2010 to December 2015, 230 HCC patients underwent surgical treatment in Affiliated Hospitals of Guilin Medical University were selected. Clinicopathological parameters between MVI group (n = 115) and non-MVI group (n = 115) were comparative analyzed. Gamma-glutamyl transpeptidase (GGT) to lymphocyte count ratio (GLR) was used as the key risk factor of HCC with MVI and its optimal cut-off value was estimated by using the receiver operating characteristic (ROC) curve. Kaplan-meier method was used to analyze the survival of HCC patients, and univariate and multivariate Cox regression analysis were used to establish independent predictors affecting postoperative HCC patients.

Results: The level of GLR in the MVI group and non-MVI group was 84.83 ± 61.84 and 38.42 ± 33.52 ($p < 0.001$) respectively. According to the ROC curve analysis, the optimal cut-off value of GLR was 56, and the area under ROC curve (AUC) was 0.781 (95%CI, 0.719 - 0.833) for risk prediction in HCC patients with MVI. Multivariate analysis results showed that the tumor size > 5 cm, HCC combined with MVI and GLR > 56 are independent risk factors for poor prognosis of HCC patients. In addition, compared with non-MVI group, patients with MVI had shorter progression-free survival (PFS) rates and overall survival (OS).

Conclusion: GLR could be a predictive biomarker of HCC after operation and a potential predictor of HCC patients combined with MVI.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. According to the global cancer statistics in 2018, the number of new cases of liver cancer was up to 841,080 and there were 781,631 death cases [1]. Liver cancer is a major public health problem facing the world [2], especially in China. Studies have shown that MVI is an important risk factor of poor postoperative prognosis of HCC. MVI leads to early postoperative recurrence and metastasis, which is an independent predictor of long-term postoperative survival [3]. The number of MVI, the depth of infiltration, and the distance of invasion all affect the prognosis of postoperative HCC patients [4, 5]. In recent years, there are many models for the diagnosis, treatment and prognosis of HCC [6, 7]. Therefore, the use of models to assess whether patients have preoperative HCC metastasis or combined with MVI, have great clinical significance of selecting appropriate individualized treatment methods, improving the prognosis and survival of HCC patients.

Studies have shown that tumors are malignant transformation stimulated by long-term inflammatory factors, with inflammation as the driving factor and cancer as the result. Inflammatory cytokines are

important participants in regulating tumor microenvironment, they can promote proliferation and survival of tumor cells and enhance angiogenesis, invasion and metastasis. Although chronic inflammation or inflammation-related factors are the premise or basis of tumorigenesis. But what are the key inflammatory factors? There is no final conclusion yet. If we only stay at this level of understanding, there is still no specific guiding significance for the prevention of corresponding tumors. Therefore, it is necessary to explore and excavate the related inflammatory factors affecting the occurrence and progression of tumors in order to assist clinical diagnosis and treatment, and achieve the fundamental purpose of treatment or prevention of tumors. Recent studies have found that, as inflammatory factors, GLR index play important role in tumor progression, and their prognostic potential are superior to other inflammatory scoring systems [8]. It is speculated that GLR may be a key factor in the occurrence of HCC combined with MVI, and affect the survival and prognosis of HCC patients.

This study aims to explore the potential value of GLR in predicting the risk of HCC with MVI and its significance in predicting the prognosis of HCC, so as to provide a new basis for the development of clinical treatment plans.

Material And Methods

Patients

In this article, 230 patients with hepatocellular carcinoma (115 for MVI and 115 for non-MVI) underwent surgical treatment in Affiliated Hospital of Guilin Medical University were selected. All patients were diagnosed by clinical, ultrasonography (US), magnetic resonance imaging (MRI), thoracic and abdominal CT, angiography and hematology. The resected samples of all patients were confirmed by pathological examination In this paper, according to the study of Sumie et al [9], we definded the group that MVI was not found as non-MVI group, the group that 1-5 MVI were found as M1 group, the group that more than 5 MVI were found as M2 group. Among MVI patients, 70 cases with group M1, and 45 cases of M2 group. Table 1 lists the clinicopathological parameters of the patient, such as demographic characteristics (age, gender, life history), history of hepatitis virus infection, hematological examination (blood routine, liver function, protein level, bilirubin, alpha-fetoprotein (AFP), GLR, etc.), and the characteristics of the tumor (the degree of cirrhosis, size and number). This study conformed to the Declaration of Helsinki and was approved by the research ethics committee of the Affiliated Hospital of Guilin Medical University. Written informed consent was obtained from all patients.

Surveillance after hepatic resection

Regarding the criteria for inclusion and exclusion of patients, as well as the contents and requirements of periodical follow-up, please refer to our previous and relevant reports [10, 11]. Progression-free survival (PFS) was defined as the period from the date of surgery to the date of recurrence, metastasis, death, or last follow-up, while the overall survival (OS) was defined as the period from the date of surgery to the date of death or last follow-up.

The ascertainment of cutoff value of GLR

In response to the risk of HCC combined with MVI, we analyzed the receiver operating characteristic (ROC) curve to determine the optimal cutoff value of preoperative GLR, and the obtained cutoff value should have relatively high sensitivity and specificity. Other clinical pathological date were dichotomized: gender (male *vs*. female), age (> 50 age *vs*. ≤ 50 age)，drinking (present *vs*. absent), HBsAg (positive *vs*. negative), tumor number (multiple *vs*. single), tumor size(> 5 cm *vs*. ≤ 5 cm), liver cirrhosis (present *vs*. absent), MVI type (MVI *vs*. non-MVI) and AFP level (> 20 ng/ml *vs*. ≤ 20 ng/ml).

Statistical analysis

Analyses for all statistics were performed using SPSS 21.0 and MedCalc 11.3.0. For the counting data conformed to normal distribution, the independent sample t test was used between the groups; for the data did not conform to the normal distribution, and non-parametric test (Mann-Whitney U method) was used among groups for data that did not conform to normal distribution; Pearson chi-square test was used to compare qualitative variables; ROC curve and Youden index were used to select the optimal cutoff value of GLR; and Kaplan-Meier method was used to obtain the survival curve. Log-rank test was used to study the differences among different groups. Then, the $p < 0.05$ variables were analyzed by multivariate analysis; Cox proportion hazards regression model was performed to determine the independent prognostic factors, $p < 0.05$ was considered to have significant difference.

Results

Clinicopathological parameters of HCC patients

By comparative analyzing of clinicopathological parameters of MVI group (n = 115) and non-MVI group (n = 115), it was found that the level of GLR in MVI group and non-MVI group was 84.83 ± 61.84 and 38.42 ± 33.52, respectively ($p < 0.001$). Except for GLR level, MVI group was higher than non-MVI group in tumor size, neutrophil cell count (NEUT), white blood cel (WBC), Globulin, direct bilirubin (DBIL), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and GGT (all $p < 0.05$), while lymphocyte count (LYMPH) and albumin were lower than those in the non-MVI group ($p < 0.05$) (Table 1). In addition, we found that there was a positive correlation between GLR level and AST level (r = 0.347, $p < 0.001$) (Fig. 1B). These results suggest that inflammatory factors, such as NEUT, WBC, Globulin and AST, increase the risk of MVI in patients with HCC, and GLR acts as an inflammatory factor.

Optimal cut-off value of GLR

The ROC curve was drawn and analyzed according to the existence of MVI in patients with HCC, the optimum cut-off value of GLR is 56, the area under the ROC curve (AUC) is 0.781, with the 95% confidence interval (95% CI) is 0.719 - 0.833. The sensitivity and specificity were 63.6% and 81.7% when the cut-off value of GLR was 56 (Fig. 1A). The results suggest that GLR may be a potential predictor for HCC complicated with MVI. In addition, in the following studies, we found that when the cut-off value of GLR

was 56,GLR had certain application value in predicting postoperative survival of patients who had HCC and who had HCC combined with MVI subgroup.

Univariate analysis and multivariate cox regression analysis

In Univariate Cox regression analysis, GLR > 56 was found to be a risk factor for postoperative PFS (HR = 2.36, 95% CI, 1.53 ≤ 3.08, $p < 0.001$) and OS (HR = 2.47, 95% CI, 1.80 ≤ 3.40, $p < 0.001$). In addition to GLR > 56, the adverse factors of postoperative OS and PFS included multiple tumor nodules, tumor size > 5 cm, MVI and AFP > 20 ng/ml. The statistically significant factors in univariate analysis were further analyzed by Cox proportional risk regression model to perform multivariate analysis. It was found that GLR > 56 was an independent risk factor for postoperative HCC PFS (HR = 1.56, 95 % CI, 1.18 ≤ 2.36, $p = 0.017$) and OS (HR = 1.63, 95% CI, 1.28 ≤ 2.31, $p = 0.006$). In addition, tumor size > 5 cm and combined MVI can be used as independent risk factors for poor PFS and OS in HCC patients (Table 2).

The value of MVI and GLR in postoperative survival and prognosis of patients with HCC

Kaplan-Meier analysis showed that the mean PFS and OS of non-MVI group (n = 115) were 51.1 months and 59.3 months, and those of MVI group (n = 115) were 26.9 months and 34.5 months, respectively. PFS of non-MVI group for 1 year, 3 years and 5 years was also significantly higher than those of MVI group (73.6% *vs*. 59.4%, 58.7% *vs*. 25.9% and 49.3% *vs*. 13.1%, respectively, all $p < 0.001$) (Fig. 2A). Similarly, the OS of the patients in non-MVI group at 1 year, 3 years and 5 years was significantly higher than those of MVI group (88.1% *vs*. 66.8%, 73.0% *vs*. 37.1% and 61.4% *vs*. 17.9%, $p < 0.001$) (Fig. 2B). In addition, we further discussed the postoperative survival and prognosis of M1 (n = 70) and M2 (n = 45) subgroups in the MVI group. Compared with M2 group patients, M1 group patients had longer PFS ($p = 0.019$) (Fig. 2C) and OS ($p = 0.010$) (Fig. 2D).

Of these 230 HCC patients involved in this study, compared with GLR ≤ 56 group (n = 138), GLR > 56 group (n = 92) had shorter mean PFS (46.9 months vs 28.1 months, $p < 0.001$) and OS (55.8 months vs 33.4 months, $p < 0.001$) (Fig. 3A, B). More interesting is that in M1 group patients (n = 70), patients with GLR > 56 (n = 38) had shorter mean PFS (36.7 months vs 21.5 months, $p = 0.012$) and mean OS (43.8 months vs 31.2 months, $p = 0.031$) (Fig. 3C, D). This indicates that GLR can also play a prognostic role in M1 group of HCC patients.

These results suggest that MVI(MVI subgroup) and GLR level are closely related to postoperative survival and prognosis of patients with HCC after operation.

Discussion

The role of inflammatory factors in tumors has attracted much attention of researchers. Inflammation plays a decisive role in different stages of cancer development, including initiation, promotion, malignant transformation, invasion and metastasis. In the early stage of tumorigenesis, inflammatory cells can become powerful tumor promoters, creating a favorable environment for tumor growth and promoting

blood vessels growth [12-14]. The pathogenesis of HCC with MVI is complex. In this study, we found that some inflammatory factors such as NEUT, WBC, Globulin and AST, seemed to promote the occurrence of HCC with MVI and accelerate the malignant process of HCC. This is consistent with the research results that anti-inflammatory therapy can effectively prevent the early stage of tumor occurrence and malignant transformation.12 In our study, GLR showed a positive correlation with AST, it suggested that GLR can act as an inflammatory factor.

In recent years, it has become a research hotspot to construct a model for diagnosis and prognosis prediction of hepatocellular carcinoma based on liquid biopsy [15-17]. The GLR prediction model constructed in this study was determined by the ratio of GGT to lymphocyte count. Intrahepatic GGT mainly exists in hepatocyte membrane and microsome, is a key enzyme in glutathione metabolism [18], it plays an important role in hepatocarcinogenesis, vascular invasion and metastasis [19-21]. In addition, the overall survival rate of liver cancer patients with increased GGT is not good after the treatment of liver tumor resection, radiofrequency ablation, and transcatheter arterial chemoembolization [22, 23]. Lymphocyte plays a key role in cytotoxic cell apoptosis, inhibiting the production of inflammatory cytokines, and inhibiting the proliferation and migration of tumors in the body's anti-tumor immune response [24-26]. In this study, prediction of postoperative Survival of patients with HCC and HCC complicated with MVI subgroup by GLR, which can provide a good individualized prediction ability for HCC patients combined with MVI after operation. Univariate analysis of follow-up data showed that multiple tumor nodules, tumor size > 5 cm, MVI, AFP > 20 ng/ml and GLR > 56 were correlated with shorter PFS and OS. Multivariate Cox regression analysis revealed that tumor size > 5cm, MVI and GLR > 56 were independent predictors of poor prognosis for HCC after operation. This is consistent with previous research findings that tumor size is an independent predictor of OS for HCC patients [27]. Other previous studies also shown that MVI characterized by vascular infiltration and invasive phenotypes, and is associated with poor prognosis of liver cancer [28]. The results of univariate and multivariate Cox regression analysis of the subjects in this study were consistent with those of the above studies, which further indicates that HCC with tumor size > 5 cm and combined with MVI has a higher degree of malignancy.

This study further found that patients in non-MVI group have better OS and PFS than those in MVI group, while OS and PFS of HCC patients with M1 group are better than those with M2 group. These results suggest that it is feasible and necessary for MVI patients to take active surgical treatment. Although the univariate analysis used in this study showed that multiple tumor nodules, AFP > 20 ng/ml, were predictors of poor PFS and OS, and none of these factors were identified as independent predictors in the multivariate analysis. However, this does not mean that there is no association between these factors and HCC prognosis and metastasis, they can also be used as potential prognostic factors for HCC patients after resection. For example, multiple or single tumor nodules determine the prognosis of liver cancer patients treated differently [27]; while the high level of AFP may affect the biological behavior of liver cancer, such as invasion, postoperative metastasis and recurrence, and prognosis, etc., Compared with AFP > 20 ng/ml patients, AFP < 20 ng/ml patients had relatively better survival rate and prognosis [29].

In clinical practice, simple, reliable, low-cost, non-invasive and prognostic serological indexes are of great significance in predicting of HCC patients combined with MVI. The relationship between elevated GLR, in addition to affecting MVI in HCC, and adverse prognosis is complex and needs to be further elucidated.

Conclusion

In conclusion, we fully believe that GLR can be one of the prognostic factors and an effective tool for predictive index of MVI in patients with HCC. However, this study is a retrospective study, there is a certain limitation, such as variable missing and selection bias, and limited by retrospective and small sample size. Therefore, we still need a large-scale prospective study to discover the potential role of GLR in HCC, which will be of great value to the formulation of individual precision intervention therapy for liver cancer and improvement of its prognosis.

Abbreviations

MVI: Microvascular invasion; HCC: hepatocellular Carcinoma; GLR: gamma-glutamyl transpeptidase to lymphocyte count ratio; GGT: Gamma-glutamyl transpeptidase; ROC: receiver operating characteristic; AUC: area under ROC curve; PFS: progression-free survival; OS: overall survival; AFP: alpha-fetoprotein; NEUT: neutrophil cell count; WBC: white blood cel; DBIL: direct bilirubin; TBIL: total bilirubin; AST: aspartate aminotransferase; ALP: alkaline phosphatase; LYMPH: lymphocyte count; HR: hazard ratio; CI: confidence interval; HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase;

Declarations

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Authors' Contributions

WL designed the research; HZ, YZ, YL, WQ, YZ, YL, XQ and HX collected data; WL and HZ performed the data analysis and model development; YZ and YL composed the first draft of the manuscript. HZ, WL and ZH critically edited and reviewed the final draft of the manuscript. All the authors contributed to the conception of the study and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on a reasonable request.

Ethics approval and consent to participate

The study ethic approval was granted from the local ethical committee of Affiliated Hospital of Guilin Medical University, and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, including the patient who died during the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing of interests.

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Tables

Table 1. Clinical and biochemical data of examined patients.

Parameter	Non MVI	MVI	*p* value
	Mean±SD* (n = 115)	Mean±SD* (n = 115)	
Gender: female / male (n)	21 / 94	9 / 106	**0.019**
Age (years)	50.23 ± 12.28	48.34 ± 11.00	0.221
Drinking: absent / present (n)	57 / 58	52 / 63	0.509
Smoking : absent / present (n)	73 / 42	66 / 49	0.345
HBsAg: negative / positive (n)	27 / 88	17 / 98	0.094
HCVAb: negative / positive (n)	109 / 6	113 / 2	0.280
Family history: absent/present (n)	99 / 16	95 / 20	0.468
Tumor number: single/multiple (n)	86 / 29	72 / 43	**0.047**
Tumor size (cm)	6.08 ± 3.32	8.53 ± 3.78	**< 0.001**
Liver cirrhosis: absent / present (n)	9 / 106	7 / 108	0.796
NEUT ($\times 10^9$/L)	3.71 ± 1.50	4.52 ± 2.24	**0.001**
LYMPH ($\times 10^9$/L)	1.77 ± 0.61	1.58 ± 0.59	**0.012**
WBC ($\times 10^9$/L)	6.17 ± 1.85	6.87 ± 2.50	**0.017**
Platelets ($\times 10^9$/L)	172.43 ± 72.73	180.14 ± 82.65	0.453
Albumin (g/L)	41.32 ± 4.01	39.47 ± 4.62	**0.002**
Globulin (g/L)	29.83 ± 4.79	31.34 ± 6.52	**0.045**
TBIL (μmol/L)	13.22 ± 4.93	15.07 ± 12.61	0.146
DBIL (μmol/L)	4.47 ± 2.32	5.48 ± 4.10	**0.022**
ALT (U/L)	37.38 ± 30.49	44.05 ± 33.32	0.115
AST (U/L)	39.33 ± 30.06	55.15 ± 35.29	**< 0.001**
ALP (U/L)	81.45 ± 87.65	102.22 ± 50.98	**0.030**
GGT (U/L)	59.17 ± 40.61	114.51 ± 64.46	**< 0.001**
AFP (ng/ml): median, range	44.60, 1.18-24200	457.80, 0.61-25410	0.271
GLR level	38.42 ± 33.52	84.83 ± 61.84	**< 0.001**

*Data presented as mean ± SD or proportions.
N, number of patients; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; NEUT, neutrophil cell count; LYMPH, lymphocyte count; WBC, white blood cell; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AFP, alpha-fetoprotein; GLR, GGT to lymphocyte ratio.

Table 2. Analysis predictors of progression-free survival and overall survival in patients with HCC.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	*p* value
Progression-free survival						
Gender (male *vs* female)	1.27	0.73-2.37	0.507			
Age, y (> 50 *vs* ≤ 50)	1.16	0.78-1.72	0.446			
Drinking (present *vs* absent)	0.95	0.64-1.42	0.832			
HBsAg (positive *vs* negative)	0.82	0.49-1.37	0.469			
Tumor number (multiple *vs* single)	1.78	1.16-2.80	**0.007**			
Tumor size, cm (> 5 *vs* ≤ 5)	2.61	1.73-3.37	**< 0.001**	1.75	1.23-2.67	**0.003**
Liver cirrhosis (present *vs* absent)	1.33	0.65-2.75	0.429			
MVI (MVI *vs* non-MVI)	2.58	1.86-3.58	**< 0.001**	1.91	1.35-2.71	**< 0.001**
AFP, ng/ml (> 20 *vs* ≤ 20)	1.59	1.12-2.26	**0.010**			
GLR (> 56 *vs* ≤ 56)	2.36	1.53-3.08	**< 0.001**	1.56	1.18-2.36	**0.017**
Overall survival						
Gender (male *vs* female)	1.13	0.62-2.09	0.716			
Age, y (> 50 *vs* ≤ 50)	1.08	0.73-1.61	0.671			
Drinking (present *vs* absent)	0.83	0.56-1.24	0.371			
HBsAg (positive *vs* negative)	0.72	0.43-1.21	0.224			
Tumor number (multiple *vs* single)	1.83	1.20-2.66	**0.004**			
Tumor size, cm (> 5 *vs* ≤ 5)	2.87	2.10-3.76	**< 0.001**	2.11	1.48-3.07	**< 0.001**
Liver cirrhosis (present *vs* absent)	1.13	0.55-2.33	0.732			
MVI (MVI *vs* non-MVI)	2.83	2.05-3.61	**< 0.001**	2.00	1.41-2.84	**< 0.001**
AFP, ng/ml (> 20 *vs* ≤ 20)	1.64	1.15-2.33	**0.006**			
GLR (> 56 *vs* ≤ 56)	2.47	1.80-3.40	**< 0.001**	1.63	1.28-2.31	**0.006**

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; MVI, Microvascular invasion; AFP, alpha-fetoprotein; GLR, GGT to lymphocyte ratio.

Figures

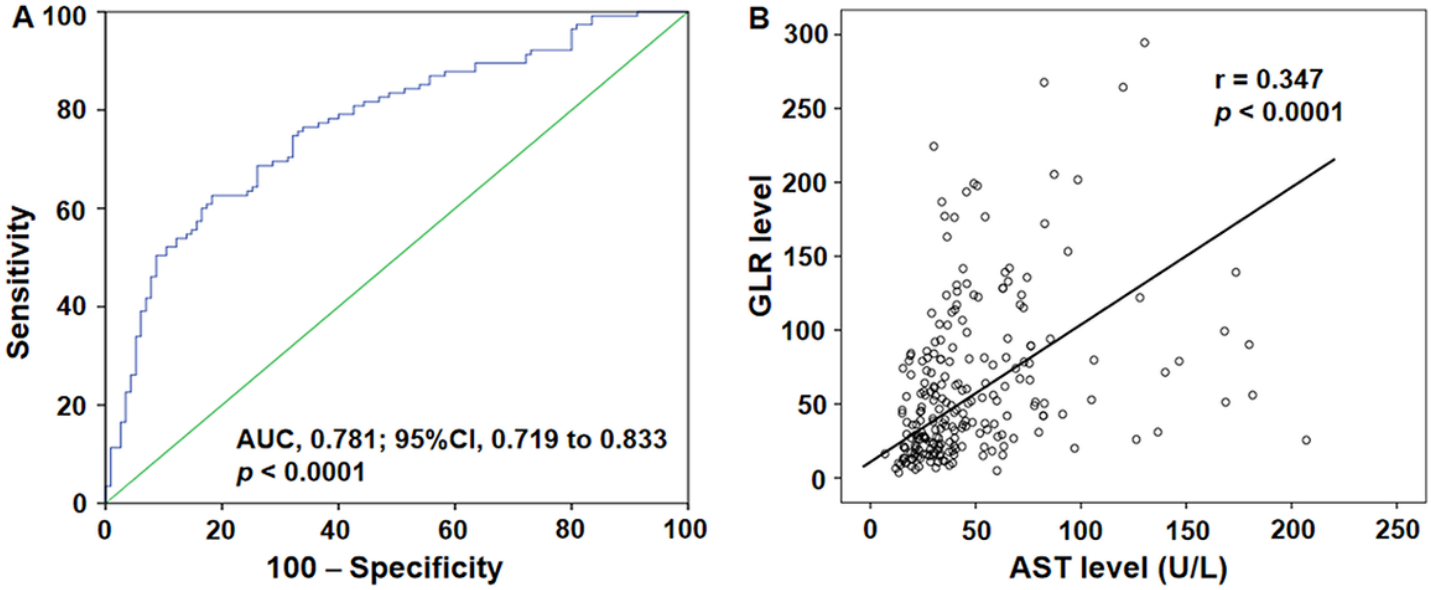

Figure 1

GLR acts as an inflammatory factor in HCC patients combined with MVI. A: The ROC curve of GLR in patients with HCC; B: The positive relation between GLR level and AST level. MVI, Microvascular invasion; GLR, gamma-glutamyl transpeptidase to lymphocyte ratio; AST, aspartate aminotransferase; ROC, receiver operating characteristic.

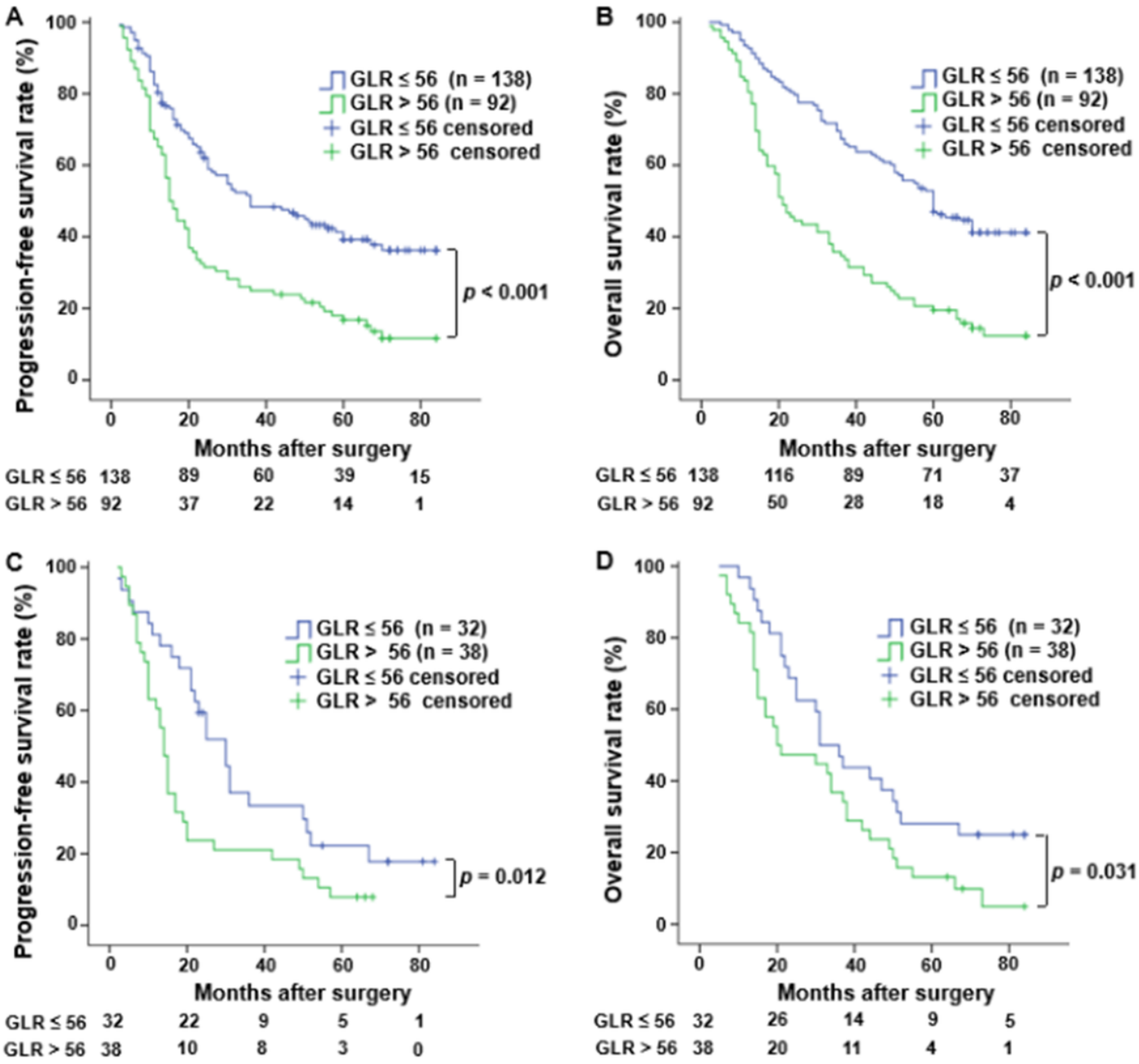

Figure 2

The relationship between MVI groups and prognosis of patients with hepatocellular carcinoma. The PFS (A) and OS (B) of HCC patients with MVI were shorter than those without MVI; C and D showed the PFS and OS of HCC patients with different groups of MVI respectively. PFS, progression-free survival; OS, overall survival.

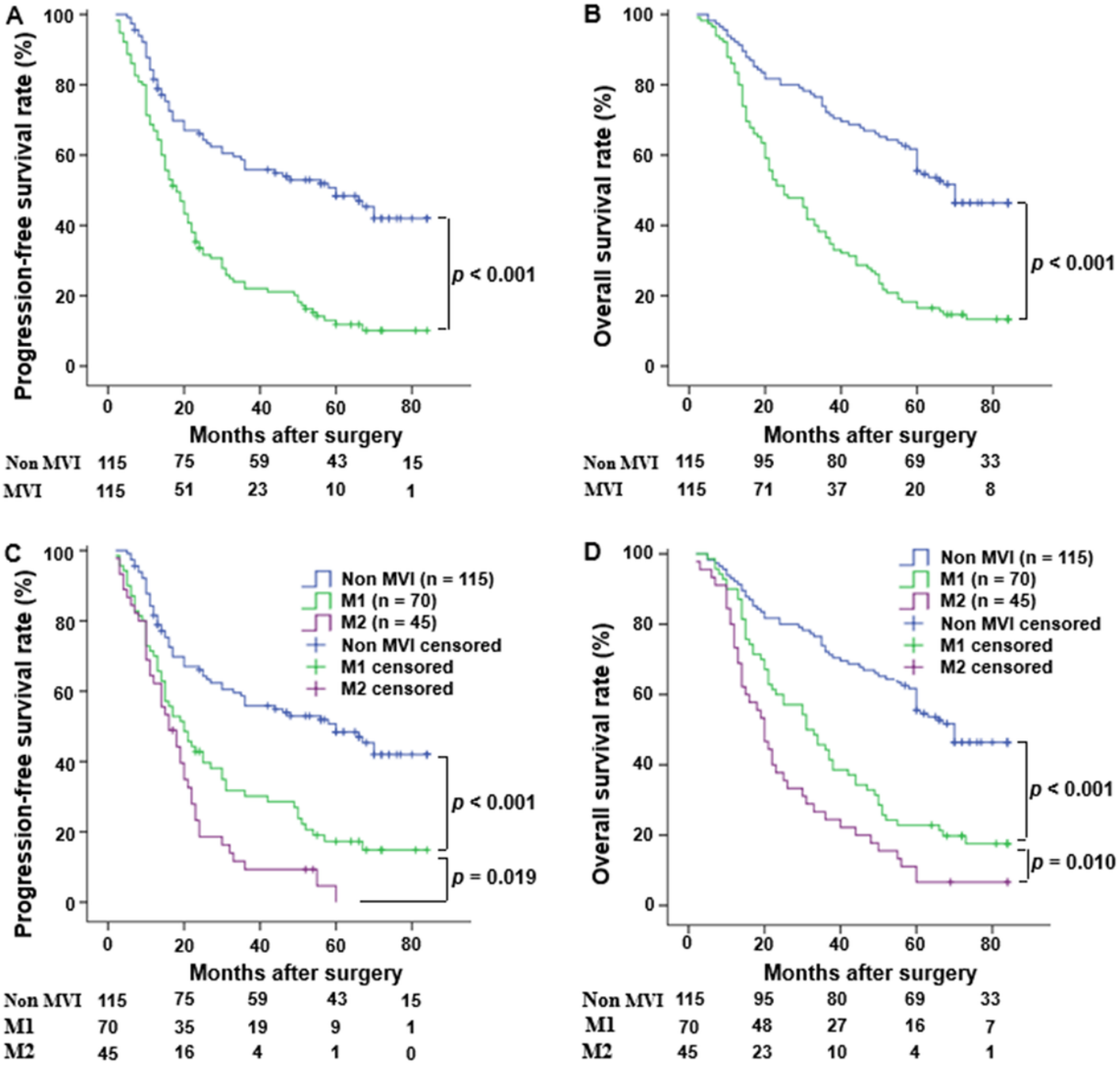

Figure 3

The relationship between GLR and prognosis of patients with HCC. The PFS (A) and OS (B) of HCC patients with GLR > 56 were significantly shorter than those in GLR ≤ 56 HCC patients; in the M1 group HCC patients, the PFS (C) and OS (D) of GLR > 56 patients were shorter than GLR ≤ 56 patients. PFS, progression-free survival; OS, overall survival.