ORIGINAL RESEARCH

Simple models based on gamma-glutamyl transpeptidase and platelets for predicting survival in hepatitis B-associated hepatocellular carcinoma

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Background: Several hepatic cirrhosis-derived noninvasive models have been developed to predict the incidence and outcomes of hepatocellular carcinoma (HCC). We aimed to investigate the prognostic significance of the two novel established cirrhosis-associated models based on gamma-glutamyl transpeptidase (GGT) and platelets in hepatitis B-associated HCC.

Methods: We retrospectively evaluated 182 HCC patients with positive hepatitis B surface antigen who received radical therapy at a single institution between 2002 and 2012. Laboratory data prior to operation were collected to calculate the GGT to platelets ratio (GPR) and the S-index. Predictive factors associated with overall survival and recurrence-free survival were assessed using log-rank test and multivariate Cox analysis. Additional analyses were performed after patients were stratified based on cirrhosis status, tumor size, therapy methods, and so forth, to investigate the prognostic significance in different subgroups.

Results: During a median follow-up time of 45.0 months, a total of 88 (48.4%) patients died and 79 (43.4%) patients recurred. The cut-off points for GPR and S-index in predicting death were determined to be 0.76 and 0.56, respectively. Compared with patients with a lower GPR, those with GPR ≥0.76 had a higher probability of cirrhosis and a larger tumor (both $P<0.05$). GPR and S-index were both found to be significantly associated with survival by univariate log-rank test. Multivariate analysis identified tumor size ≥5 and high level of GPR, but not high Barcelona Clinic Liver Cancer stage or S-index, as independent factors for predicting poor overall survival and recurrence-free survival.

Conclusion: The GPR is an effective preoperative predictor for outcomes in hepatitis B-associated HCC.

Keywords: hepatocellular carcinoma, cirrhosis, hepatitis B virus, GPRs, platelets, gamma-glutamyl transpeptidase, survival

Introduction

Hepatitis B virus (HBV) infection threatens 350 million people worldwide, particularly in East Asia.[1] Till date, there is no effective cure for HBV. Currently prevalent medical drug therapy, such as interferons and nucleos(t)ide analogs, is used to suppress viral replication, but cannot eradicate the virus.[2] Persistent infection with HBV can evolve into cirrhosis, and then into hepatocellular carcinoma (HCC), a leading cause of cancer-related deaths worldwide.[3] It is reported that as many as 40% of men and 15% of women with perinatally acquired HBV die of liver cirrhosis or HCC.[2]

Partial hepatectomy remains the best choice for HCC treatment. In contrast, radiofrequency ablation (RFA) is an alternative choice to curative treatment of HCC cases not suitable for resection. However, till date, both the two curative methods

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have shown an unsatisfactory survival, mainly due to a high risk of tumor recurrence,[4] especially in patients with chronic hepatitis B (CHB).[5] It is urgent to establish several significant and simple models to predict outcomes in hepatitis B-related HCC. Accordingly, several prognostic stage systems, such as Tumor-Node-Metastasis, Barcelona Clinic Liver Cancer (BCLC) staging systems,[6,7] have been proposed to stratify HCC and for evaluating the prognosis. However, these models are limited in clinical use;[8] therefore, there is an urgent need for hepatologists to seek novel tools to evaluate the outcomes of HCC.

Hepatic cirrhosis is a crucial factor associated with the incidence, recurrence, and survival of HCC.[9] Numerous studies have verified several noninvasive models as significant predictors for cirrhosis in patients with CHB, with a high diagnostic potential.[10] Subsequently, several of these models were found to be accurate predictors of HCC formation.[11,12] Recently, partial cirrhosis-derived models have been found to be excellent tools for predicting survival of HCC.[8,13,14] Two routine clinical parameters, gamma-glutamyl transpeptidase (GGT) and platelets, are independent risk factors for HCC in CHB[15,16] and are independent predictors of survival in patients with HBV-related HCC.[8,17] The GGT to platelet ratio (GPR) and the S-index, which combines GGT and platelets, have been recently validated to be accurate markers of cirrhosis in CHB.[18,19] However, the predictive significance of GPR and S-index in evaluating outcomes in HCC has never been investigated. Herein, we retrospectively analyzed hepatitis B-related HCC patients and evaluated the performance of the two models in predicting survival and the presence of cirrhosis.

Materials and methods
Study population
Patients with hepatitis B-related HCC who were treated by curative therapy, such as partial hepatectomy and RFA, at our institute between December 2002 and July 2012 were retrospectively analyzed in this study. Patients with positive anti-hepatitis C virus antibody, coinfection with human immunodeficiency virus, patients with hematologic diseases, those who had received previous treatment for HCC, patients with intrahepatic cholangiocarcinoma, and those with extrahepatic spread, or on other treatments were all excluded. Finally, 182 patients were involved in this cohort. This study was performed in compliance with the Declaration of Helsinki,[20] and the protocol was approved by the Ethical Committee of the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine. Written informed patient consent was obtained.

Data collection
The electronic medical record was reviewed to collect the following information: demographic data (age, sex), cirrhosis status, ascites, preoperative platelet count (PLT), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, GGT, international normalized ratio, albumin (ALB), alpha-fetoprotein (AFP), tumor number and size, and pathologic results. Preoperative data were used to calculate the GPR and S-index according to the following formulas:[18,19] GPR = GGT/PLT; S-index $=1,000\times$GGT/(PLT$\times$ALB^2).

HCC diagnosis, treatment, and follow-up
HCC was preoperatively diagnosed by computed tomography or magnetic resonance imaging. HCC diagnosis was further verified by histopathological examination of tumor samples removed from patients who underwent liver resection.

After discharge, patients were regularly followed up by computed tomography/magnetic resonance imaging, abdominal ultrasound, and serologic tests. Postoperative recurrence during follow-up was treated by salvage treatments, such as second hepatic surgery, transcatheter arterial chemoembolization, and so forth.

Statistical analysis
Predictive Analytics Software (Version 18.0) (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Different groups were compared by using the two-sample t-test or Wilcoxon test for continuous variables and the χ^2 test for categorical data. The receiver operating characteristic (ROC) curve and the highest value of Youden index were adopted to determine the optimal cut-off point of the GPR and S-index.

The primary outcomes we analyzed were overall survival (OS) and recurrence-free survival (RFS), which were both estimated by the Kaplan–Meier method, and differences in survival were analyzed by the univariate log-rank test. All variables that were found to be significant ($P<0.05$) were further entered into a multivariate Cox regression model. A P-value <0.05 was considered statistically significant.

Results
Patient characteristics
Based on the selection criteria, we finally included a total of 182 patients, 119 of whom received partial hepatectomy and 63 underwent RFA. Also, 140 patients were male and 42 were female, with a mean age 51.6±10.4 years. Eighty-six patients were cirrhotic by pathology and 25 presented with ascites. There were 155 patients with Child–Pugh A stage and others belonged to Child–Pugh B/C stage. During

a median follow-up of 45 months, 88 (48.4%) patients died and 79 (43.4%) experienced postoperative recurrence.

Determination of the cut-off values for GPR and S-index

The ROC curve of GPR and S-index for detecting death indicated that 0.76 and 0.56 were the optimal cut-off values with 61.4% and 62.5% sensitivity and 58.5% and 56.4% specificity, respectively. Both GPR and S-index were significant indicators for determining death in living patients, with area under the curve values of 0.586 (95% confidence interval [CI]: 0.503–0.669) and 0.584 (95% CI: 0.501–0.667), respectively.

The associations between GPR, S-index, and clinical variables

Demographic data, serologic tests, and tumor characteristics of patients stratified by the GPR and S-index are summarized in Table 1. Of these clinical factors, cirrhosis status, tumor size, vascular invasion, and BCLC stage were significantly different between 93 patients with GPR ≥0.76

and 89 patients with GPR <0.76. In contrast, cirrhosis status, ascites, and Child–Pugh class were significantly different between different S-index levels.

Then we further evaluated the associations between the two models and cirrhosis. The area under the ROC curve was 0.639 (95% CI: 0.558–0.720, P=0.001) and 658 (95% CI: 0.579–0.737, P<0.001) for GPR and S-index, respectively, in detecting cirrhosis (Figure 1). Also, on comparing with these single parameters included in the models, they both showed a higher accuracy in predicting the presence of cirrhosis (Figure 1).

Figure 2A and B further indicated that GPR score was positively related with tumor size, and Figure 2C and D showed that patients with Child–Pugh B/C stage had a high level of S-index, compared to patients with Child–Pugh A stage.

Predictors of survival

The median survival time of all included patients was 52 months, with 1-, 3-, and 5-year OS rates of 73.6%, 55.7%, and 46.0%, respectively. The log-rank test demonstrated that

Table 1 Basic characteristics of hepatitis B-related HCC patients stratified according to level of the GPR

Variables	Overall	GPR			S-index		
		<0.76 (n=89)	≥0.76 (n=93)	*P*-value	<0.56 (n=86)	≥0.56 (n=96)	*P*-value
Sex, male/female	140/42	66/23	74/19	0.386[a]	69/19	73/23	0.766[a]
Age (years), mean ± SD	52.1±10.4	51.6±10.7	51.6±10.3	0.986[b]	50.5±10.8	52.6±10.0	0.187[b]
ALT (U/L), median (min–max)	52 (7–1,315)	39 (7–934)	58 (15–1,315)	**0.003[b]**	39 (7–934)	58 (16–1,315)	**0.004[b]**
AST (U/L), median (min–max)	48 (11–1,075)	40 (11–891)	60 (20–1,075)	**<0.001[b]**	40 (11–891)	59 (20–1,075)	**<0.001[b]**
ALP (U/L), median (min–max)	104 (1–872)	89 (1–344)	118 (30–872)	**<0.001[b]**	88 (1–344)	119 (30–872)	**<0.001[b]**
GGT (U/L), median (min–max)	76 (12–1,830)	42 (12–155)	134 (20–1,830)	**<0.001[b]**	43 (12–155)	131 (20–1,830)	**<0.001[b]**
PLT (10⁹/L), median (min–max)	112 (3–486)	132 (46–486)	85 (3–287)	**<0.001[b]**	136 (62–486)	84 (3–287)	**<0.001[b]**
INR (U/L), median (min–max)	1.1 (0.8–80.9)	1.1 (0.8–1.6)	1.1 (0.9–80.9)	**0.048[b]**	1.1 (0.8–1.6)	1.1 (0.9–80.9)	**<0.001[b]**
ALB, median (min–max)	38 (14–54)	39 (14–54)	38 (24–51)	0.136[b]	40 (27–54)	386 (14–51)	**<0.001[b]**
AFP: ≥200/<200	84/85	41/45	43/40	0.591[a]	42/42	42/43	0.939[a]
Ascites: yes/no	25/157	11/78	14/79	0.598[a]	7/79	18/78	**0.038[a]**
Cirrhosis: yes/no	86/96	35/54	51/42	**0.036[a]**	31/55	55/42	**0.004[a]**
Tumor size: ≥5/<5 cm	89/87	35/51	54/36	**0.010[a]**	39/45	50/42	0.294[a]
Tumor no: multiple/single	43/135	19/68	24/67	0.480[a]	18/67	25/68	0.374[a]
Child–Pugh: A/B+C	155/27	78/11	77/16	0.358[a]	81/5	74/22	**0.001[a]**
Vascular invasion: yes/no	20/162	3/86	17/76	**0.003[a]**	6/80	14/82	0.101[a]
BCLC stage: A1+A2/A3+A4/B/C+D	66/18/72/120	44/6/33/3	22/12/39/7	**<0.001[a]**	39/6/33/6	27/12/39/14	0.057[a]
Resection/RFA	119/63	67/22	52/41	**0.006[a]**	70/16	49/47	**<0.001[a]**
Death: yes/no	88/94	34/55	54/39	**0.007[a]**	33/53	55/41	**0.011[a]**
Recurrence: yes/no	79/103	32/57	47/46	**0.047[a]**	31/55	48/48	0.058[a]
GPR, median (min–max)	0.79 (0.05–18.83)	0.38 (0.05–0.75)	1.45 (0.76–18.83)	**<0.001[b]**			
S-index, median (min–max)	0.62 (0.03–16.86)				0.23 (0.03–0.55)	1.06 (0.56–16.86)	**<0.001[b]**

Notes: [a]χ^2 test, [b]Wilcoxon test. The bold font represents a *P*-value less than 0.05 and the relevant variables are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase to platelet ratio; HCC, hepatocellular carcinoma; INR, international normalized ratio; PLT, platelet count; RFA, radiofrequency ablation.
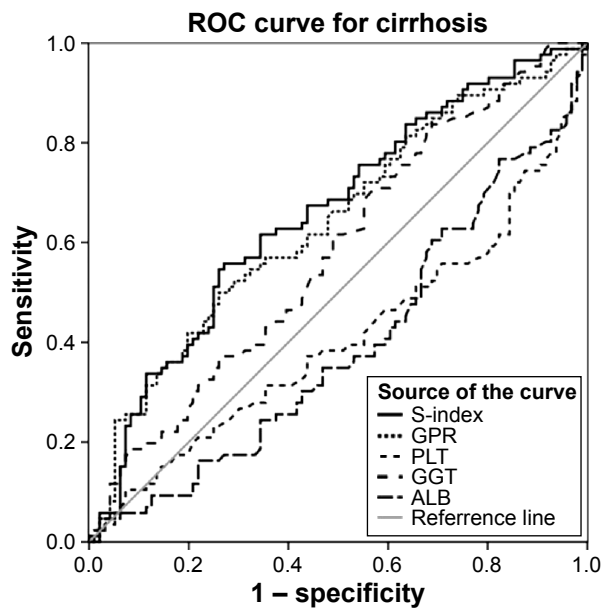
Figure 1 Diagnostic performance of GPR, S-index, and contained variables in detecting the presence of cirrhosis.
Abbreviations: ALB, albumin; GGT, gamma-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase to platelet ratio; PLT, platelet count; ROC, receiver operating characteristic.

the OS and RFS varied significantly in different GPR levels (Figure 3A and B), S-index levels (Figure 3C and D), and BCLC stages (Figure 3E and F).

Univariate analysis showed that aspartate aminotransferase, tumor size, tumor number, vascular invasion, BCLC stage, GPR, and S-index were significantly associated with OS as well as RFS (Table 2). Specifically, patients with a lower level of GPR or S-index had a significantly longer survival than patients with a higher level. Furthermore, multivariate analysis revealed that tumor size and GPR, but not BCLC stage and S-index, were independent predictors of OS and RFS (Figure 4).

Subgroup analyses according to cirrhosis status, methods of treatment, and other variables

As shown in Table 1, the GPR was significantly different in patients with different status of cirrhosis, different tumor size, and on different treatments. Our current results and previous studies showed that age, AFP, cirrhosis, ascites,
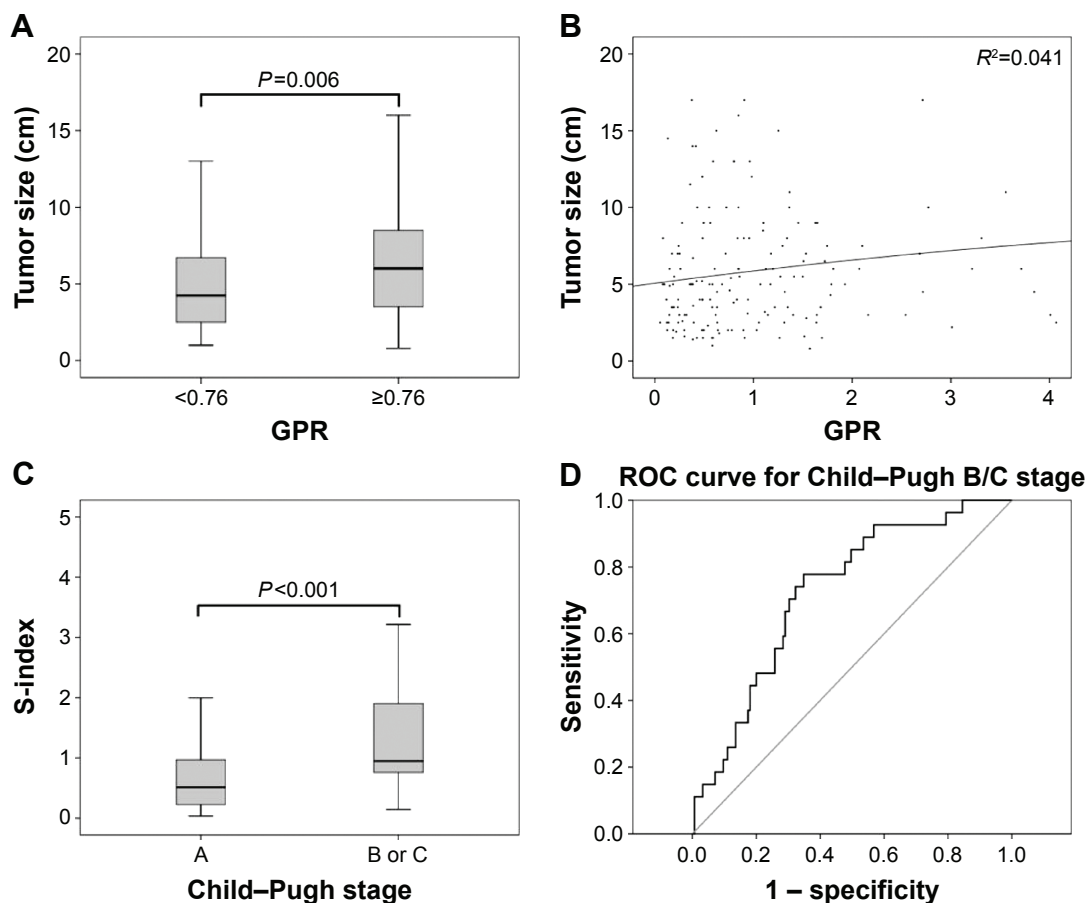

Figure 2 The box plots reflect the associations between GPR and tumor size (**A** and **B**) and between S-index and Child–Pugh stage (**C** and **D**).
Notes: Scatter plot (**C**) reflects the associations between GPR and tumor size, and the diagnostic performance of S-index (**D**) in detecting the Child-Pugh B/C stage. The *P*-values in (**A**) and (**C**) were calculated by Wilcoxon test.
Abbreviations: GPR, gamma-glutamyl transpeptidase to platelet ratio; ROC, receiver operating characteristic.
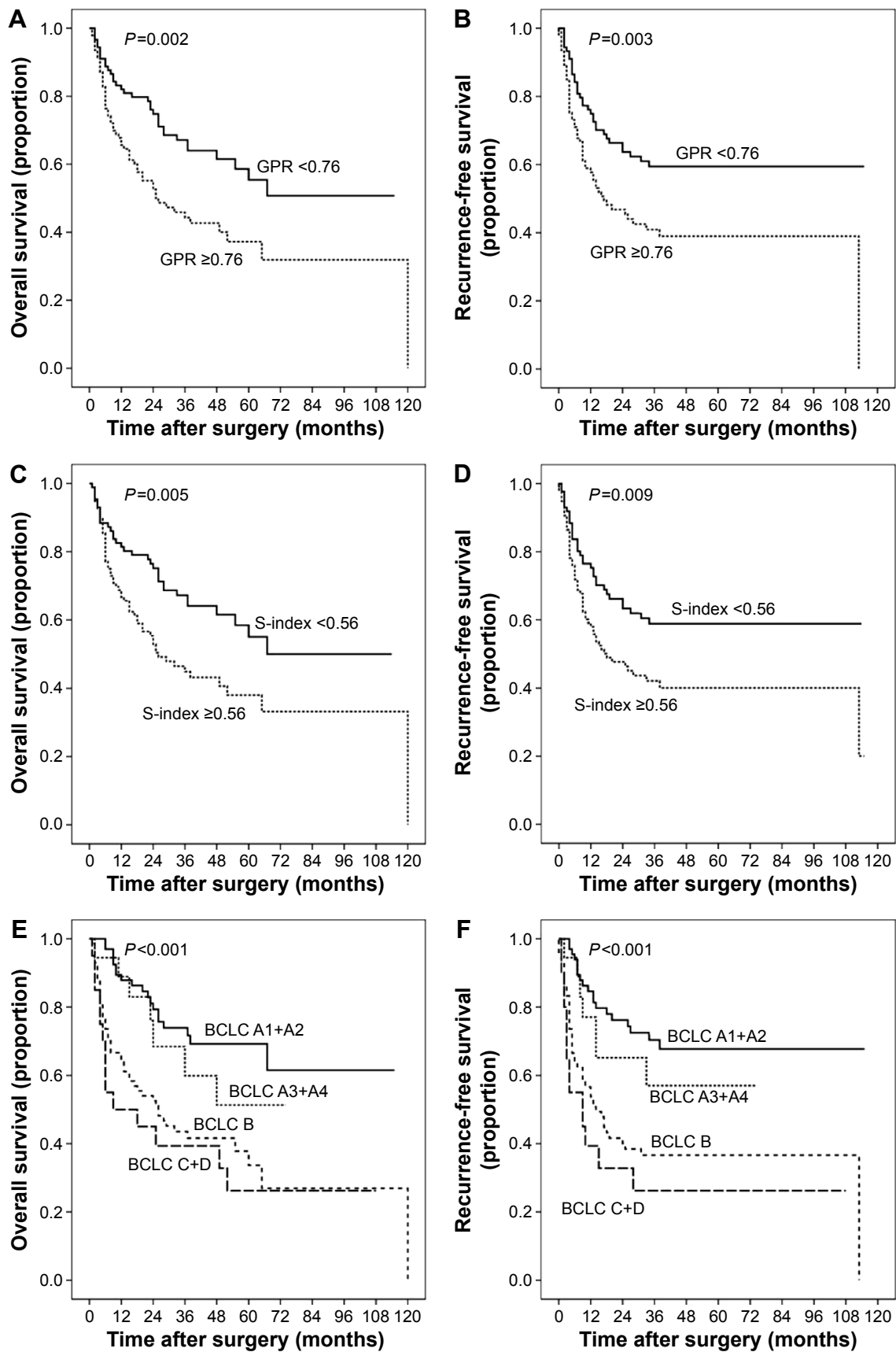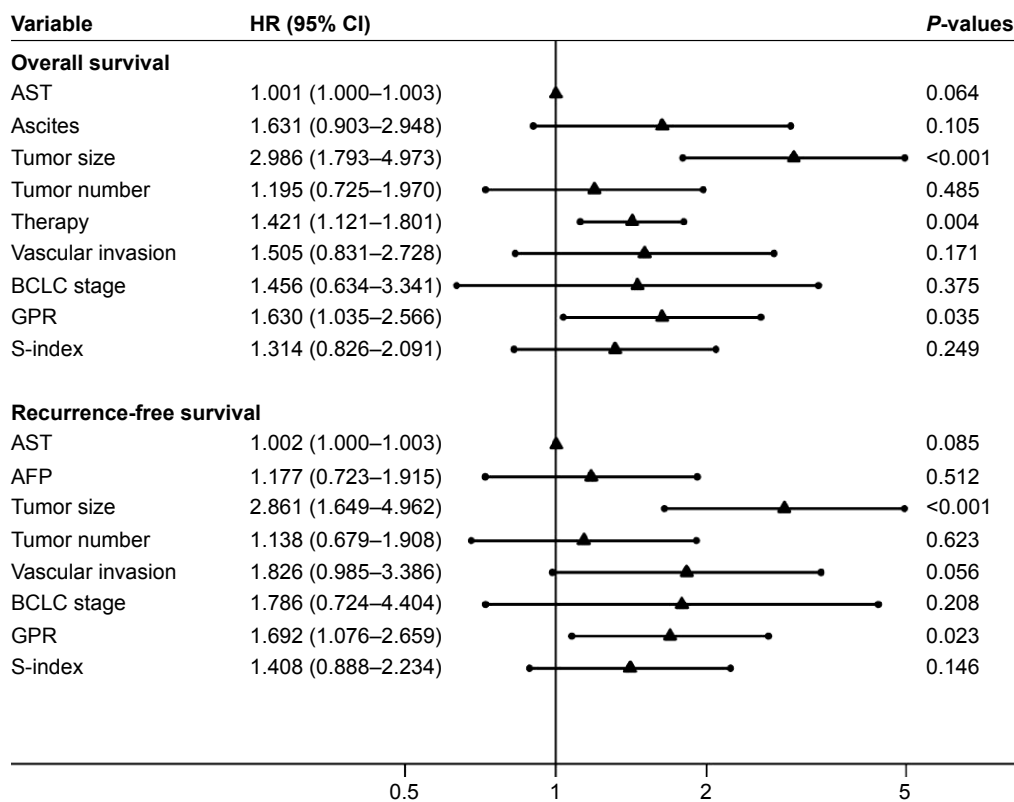
Figure 3 Kaplan–Meier cumulative overall survival and recurrence-free survival curves of patients stratified according to the GPR (**A**, **B**), S-index (**C**, **D**), and BCLC stage (**E**, **F**).
Note: The *P*-values were calculated by log-rank test.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; GPR, gamma-glutamyl transpeptidase to platelet ratio.

Table 2 The results of univariate analysis of the factors associated with overall survival and recurrence-free survival in hepatitis B-related HCC patients

Variables	Overall survival		Recurrence-free survival	
	Crude HR (95% CI)	*P*-value	Crude HR (95% CI)	*P*-value
Sex, male versus female	0.905 (0.553–1.479)	0.689	0.900 (0.550–1.471)	0.674
Age (years)	1.017 (0.996–1.038)	0.112	1.014 (0.994–1.034)	0.183
ALT (U/L)	1.001 (1.000–1.002)	0.067	1.001 (1.000–1.002)	0.076
AST (U/L)	1.002 (1.000–1.003)	**0.008**	1.002 (1.000–1.003)	**0.011**
ALP (U/L)	1.001 (0.999–1.003)	0.323	1.001 (0.999–1.003)	0.442
GGT (U/L)	1.001 (1.000–1.001)	0.098	1.001 (1.000–1.001)	0.178
PLT (10^9/L)	1.002 (0.999–1.005)	0.240	1.002 (0.999–1.004)	0.244
INR	1.013 (0.988–1.038)	0.317	1.009 (0.985–1.035)	0.454
ALB	0.986 (0.953–1.020)	0.421	0.989 (0.957–1.023)	0.539
AFP, ≥200 versus <200 (ng/mL)	1.424 (0.912–2.224)	0.120	1.619 (1.038–2.526)	**0.034**
Ascites, yes versus no	1.811 (1.051–3.120)	**0.032**	1.696 (0.985–2.919)	0.057
Cirrhosis, yes versus no	1.148 (0.751–1.754)	0.524	0.987 (0.648–1.505)	0.953
Tumor size, ≥5 versus <5 cm	2.872 (1.814–4.548)	**<0.001**	3.093 (1.953–4.898)	**<0.001**
Tumor number, multiple versus singlular	1.644 (1.035–2.611)	**0.035**	1.644 (1.035–2.612)	**0.035**
Child–Pugh, B+C versus A	1.431 (0.819–2.500)	0.208	1.299 (0.744–2.265)	0.358
Treatment, RFA versus resection	1.250 (1.004–1.556)	**0.046**	1.172 (0.943–1.456)	0.152
Vascular invasion: yes versus no	2.442 (1.397–4.267)	**0.002**	2.781 (1.588–4.873)	**<0.001**
BCLC stage: B–D versus A	2.700 (1.698–4.292)	**<0.001**	2.976 (1.872–4.732)	**<0.001**
GPR, high versus low	1.929 (1.251–2.975)	**0.003**	1.872 (1.217–2.880)	**0.004**
S-index, high versus low	1.843 (1.192–2.849)	**0.006**	1.749 (1.134–2.693)	**0.011**

Note: The bold font represents a *P*-value less than 0.05 and the relevant variables are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; GGT, gamma-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase to platelet ratio; HCC, hepatocellular carcinoma; INR, international normalized ratio; PLT, platelet count; RFA, radiofrequency ablation; HR, hazard ratio.

Variable	HR (95% CI)		P-values
Overall survival			
AST	1.001 (1.000–1.003)		0.064
Ascites	1.631 (0.903–2.948)		0.105
Tumor size	2.986 (1.793–4.973)		<0.001
Tumor number	1.195 (0.725–1.970)		0.485
Therapy	1.421 (1.121–1.801)		0.004
Vascular invasion	1.505 (0.831–2.728)		0.171
BCLC stage	1.456 (0.634–3.341)		0.375
GPR	1.630 (1.035–2.566)		0.035
S-index	1.314 (0.826–2.091)		0.249
Recurrence-free survival			
AST	1.002 (1.000–1.003)		0.085
AFP	1.177 (0.723–1.915)		0.512
Tumor size	2.861 (1.649–4.962)		<0.001
Tumor number	1.138 (0.679–1.908)		0.623
Vascular invasion	1.826 (0.985–3.386)		0.056
BCLC stage	1.786 (0.724–4.404)		0.208
GPR	1.692 (1.076–2.659)		0.023
S-index	1.408 (0.888–2.234)		0.146

Figure 4 Forest plot based on the results of multivariate analysis of the factors associated with overall survival and recurrence-free survival of hepatitis B-related HCC patients.
Note: The factors that were found to be significant (*P*<0.05) in univariate analysis were entered into a multivariate Cox regression models.
Abbreviations: AFP, alpha-fetoprotein; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; GPR, gamma-glutamyl transpeptidase to platelet ratio; HCC, hepatocellular carcinoma; HR, hazard ratio.

tumor size, tumor number, vascular invasion, and methods of treatment were significant prognostic factors of HCC. Therefore, these factors might be critical confounders in our cohort. To investigate whether they influenced the significance of GPR, we performed subgroup analyses accordingly, and the forest plots based on the results are shown in Figure 5. GPR was a useful indicator of OS and RFS in patients without cirrhosis, but not in patients with cirrhosis. Patients with a high level of GPR had a significantly poor survival, no matter what kinds of treatments they received and whether they had ascites. In addition, GPR was found to be more significant in the subgroups of older age and decreased level of AFP.

Stratification of patients according to the GPR and tumor size

In our cohort, the GPR and tumor size were two crucial independent prognostic factors. The combination of GPR and tumor size showed a higher diagnostic accuracy in predicting postoperative death than BCLC stage (Table 3) (area under the curve: 0.696, 95% CI: 0.619–0.774 vs 0.666, 95% CI: 0.585–0.746). Accordingly, the study further stratified the patients as three groups: Group A (GPR <0.76 and tumor size <5 cm, n=57), Group B (GPR <0.76 but tumor size ≥5 cm, or tumor size <5 cm but GPR ≥0.76, n=71), and Group C (GPR ≥0.76 and tumor size ≥5 cm, n=54).

The 1-, 3-, and 5-year OS rates were 92.2%, 79.7%, and 73.1% versus 74.6%, 55.6%, and 40.3% versus 55.6%, 33.5%, and 25.1% for groups A, B, and C, respectively (P<0.001) (Figure 6A). Similarly, Group A showed significantly higher RFS rates compared with groups B or C (P<0.001) (Figure 6B).

Discussion

HBV infection is the leading cause of HCC in the People's Republic of China. Liver cirrhosis, as an intermediate disease that links all risk factors with HCC, is an independent predictor for HCC.[21–23] Despite great advances in the treatment of HCC in recent years, the prognosis of this malignancy remains poor. One of the greatest problems plaguing potential curative treatment for HCC is the high risk of postoperative recurrence.

Chronic necroinflammation and hepatocellular regeneration in the setting of cirrhosis lead to the production of reactive oxygen species, chromosomal mutations, and eventually malignant transformation of proliferating hepatocytes.[24] Intrahepatic recurrence following curative hepatic resection of HCC may not be metastasis from the original tumor, but rather de novo cancers from the cirrhotic liver.[25] Thus,

liver cirrhosis significantly increases the risk of postoperative recurrence and is an established prognostic factor for HCC.[26,27]

Apart from liver biopsy, several noninvasive models have been proposed and validated to assess cirrhosis with a high accuracy. Similar to cirrhosis, these noninvasive models were further identified as good predictors for HCC development and outcomes.[8,13,14] Recent studies have shown that both GPR and S-index are significant predictors for cirrhosis in patients with chronic HBV, with a high degree of accuracy.[18,19] In our present study, we found that although both GPR and S-index had a low ability in assessing the presence of cirrhosis in CHB-related HCC, they both were identified as significant prognostic markers.

In 1985, Okuda et al[28] designed a prognostic stage model for HCC, and several other prognostic systems based on clinical variables, such as Tumor-Node-Metastasis stage,[6] Cancer of the Liver Italian Program,[29] Chinese University Prognostic Index,[30] BCLC stage,[7] and so forth, were subsequently proposed to stratify HCC. Meanwhile, they have also been identified as significant prognostic tools of HCC in numerous studies. However, there are still some limitations for the use of these models. Firstly, they mainly focus on tumor characteristics, such as tumor diameter, which cannot be reversed before surgery. In addition, tumor size and vascular invasion were found to be not associated with survival in partial HCC patients.[31] Secondly, to date, the optimal staging system for HCC remains under intense debate. Among these systems, the BCLC stage has been validated by numerous studies and populations, and has been adopted worldwide.[32] In our study, we found that the typical BCLC stage was really statistically significant in predicting HCC survival by log-rank test, but it was not independent of other variables. In contrast, the cirrhosis-derived model GPR was an independent prognostic index.

One major criticism of the present study was that the survival rates of HCC patients with cirrhosis and those without cirrhosis were not statistically different. It was inconsistent with a previous report which showed that patients with histological fibrosis F4 had a higher risk of death than patients with histological fibrosis F0–2.[14] This may be due to the limited sample and the lack of information of cirrhosis stage in our study. In fact, to date, whether the degree of background liver fibrosis significantly influences survival is still controversial. One single-institution cohort study found that progressive advances in fibrosis stages did not affect OS or RFS following HBV–HCC resection, till complete cirrhosis was developed.[33] Another cohort study from Keron showed that progressive
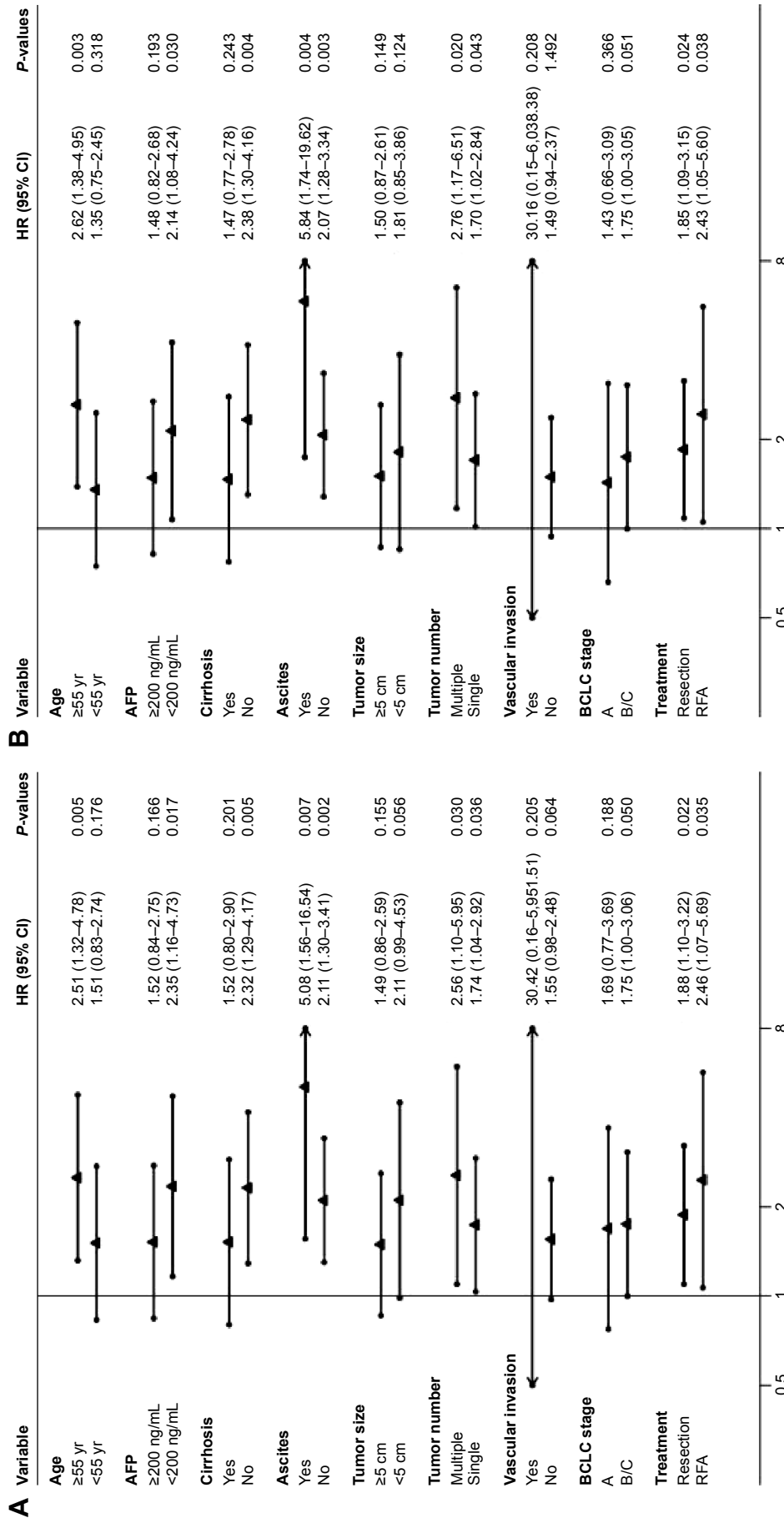
A

Variable	HR (95% CI)	P-values
Age		
≥55 yr	2.51 (1.32–4.78)	0.005
<55 yr	1.51 (0.83–2.74)	0.176
AFP		
≥200 ng/mL	1.52 (0.84–2.75)	0.166
<200 ng/mL	2.35 (1.16–4.73)	0.017
Cirrhosis		
Yes	1.52 (0.80–2.90)	0.201
No	2.32 (1.29–4.17)	0.005
Ascites		
Yes	5.08 (1.56–16.54)	0.007
No	2.11 (1.30–3.41)	0.002
Tumor size		
≥5 cm	1.49 (0.86–2.59)	0.155
<5 cm	2.11 (0.99–4.53)	0.056
Tumor number		
Multiple	2.56 (1.10–5.95)	0.030
Single	1.74 (1.04–2.92)	0.036
Vascular invasion		
Yes	30.42 (0.16–5,951.51)	0.205
No	1.55 (0.98–2.48)	0.064
BCLC stage		
A	1.69 (0.77–3.69)	0.188
B/C	1.75 (1.00–3.06)	0.050
Treatment		
Resection	1.88 (1.10–3.22)	0.022
RFA	2.46 (1.07–5.69)	0.035

B

Variable	HR (95% CI)	P-values
Age		
≥55 yr	2.62 (1.38–4.95)	0.003
<55 yr	1.35 (0.75–2.45)	0.318
AFP		
≥200 ng/mL	1.48 (0.82–2.68)	0.193
<200 ng/mL	2.14 (1.08–4.24)	0.030
Cirrhosis		
Yes	1.47 (0.77–2.78)	0.243
No	2.38 (1.30–4.16)	0.004
Ascites		
Yes	5.84 (1.74–19.62)	0.004
No	2.07 (1.28–3.34)	0.003
Tumor size		
≥5 cm	1.50 (0.87–2.61)	0.149
<5 cm	1.81 (0.85–3.86)	0.124
Tumor number		
Multiple	2.76 (1.17–6.51)	0.020
Single	1.70 (1.02–2.84)	0.043
Vascular invasion		
Yes	30.16 (0.15–6,038.38)	0.208
No	1.49 (0.94–2.37)	1.492
BCLC stage		
A	1.43 (0.66–3.09)	0.366
B/C	1.75 (1.00–3.05)	0.051
Treatment		
Resection	1.85 (1.09–3.15)	0.024
RFA	2.43 (1.05–5.60)	0.038

Figure 5 Forest plots based on the results of subgroup analyses of the GPR for overall survival (**A**) and recurrence-free survival (**B**) in patients with hepatitis B-related HCC.
Note: The subgroup analyses were based on the following variables: age, level of AFP, status of cirrhosis, ascites, tumor number, vascular invasion, BCLC stage, and treatment method.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; GPR, gamma-glutamyl transpeptidase to platelet ratio; HCC, hepatocellular carcinoma; HR, hazard ratio; RFA, radiofrequency ablation.

Table 3 Ranking of discriminatory ability of the prognostic systems on the basis of C-index

Rank	System	C-index	95% CI
1	GPR + tumor size	0.696	0.619–0.774
2	BCLC	0.666	0.585–0.746
3	GPR	0.608	0.525–0.692

Note: C-index reflects the ability to predict survival: the greater the C-index, the more accurate the prognostic prediction.
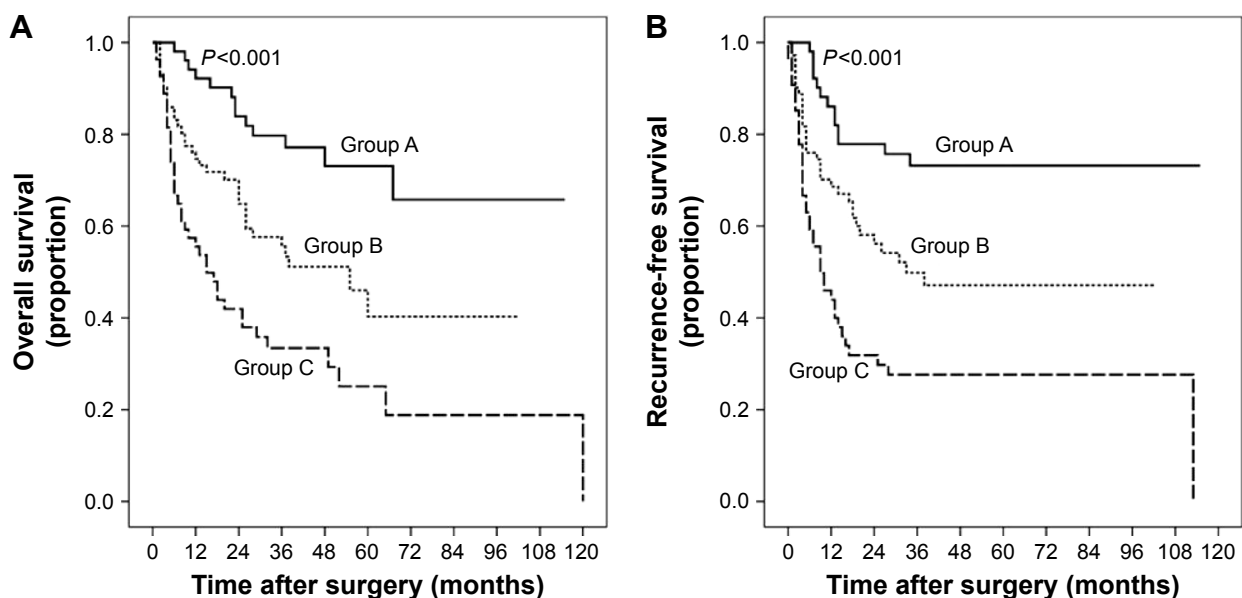**Abbreviations:** BCLC, Barcelona Clinic Liver Cancer; C-index, concordance index; CI, confidence interval; GPR, gamma-glutamyl transpeptidase to platelet ratio.

advances in fibrosis stage estimated by Forns index, one of cirrhosis-related models, affected OS and RFS, independent of tumor characteristics.[14] In our study, the GPR score, which also reflects the degree of cirrhosis, was a significant prognostic index, independent of tumor characteristics. Thus, cirrhosis stage may pose more significance in HCC outcomes than cirrhosis status. This might partly explain why the GPR was a significant prognostic index in subgroups without cirrhosis, but not in those with cirrhosis.

Besides the association between noninvasive cirrhosis indices and prognosis, other predictors in our study are consistent with preceding studies. A recent retrospective cohort study highlighted that lower preoperative AFP level implicated a much higher survival rate only in chronic HBV-related HCC patients, but not among the HCC patients etiologically irrelevant to HBV infection.[34] In our present study, AFP was significantly associated with OS as well as RFS in HBV-related HCC patients. In the multivariate analysis, in addition to GPR index, tumor size was another

significant predictor for OS and RFS after curative therapy. In a previous report, tumor size was a well-known risk factor for recurrence after treatment for HCC.[35] The combination of GPR and tumor size may pose greater significance in estimating postoperative outcomes than any single variable. Compared with RFA, liver resection had a significantly longer OS, while the RFS between the two curative therapies was not significant different. In fact, controversy still exists in regards to the effectiveness of RFA versus resection. Though partial hepatectomy is associated with higher complication and longer hospital duration, it is still proposed as the first-line treatment for HCC.[36,37] RFA may be an alternative to hepatectomy because of its comparable long-term efficacy in partial HCC patients.[36] No matter what kind of treatment was followed, the GPR was found to be a valuable predictor for HCC survival in our study.

There is no doubt that some other limitations in the present study should be realized. Firstly, our study was designed as a retrospective cohort study. The inherent limitations of the retrospective study included confounding, selection bias, information bias, and some missing values. Therefore, our results should be validated by prospective and multiple center study. Secondly, only patients with HCC caused by chronic HBV infection were involved in the study and the impact of GPR in HCV-related HCC patients should be further investigated. Thirdly, GPR was a novel index, and before we put it into practice, the significance of GPR in detecting

Figure 6 Cumulative overall survival (**A**) and recurrence-free survival (**B**) curves of the subgroup study stratification of patients according to GPR and tumor size.
Notes: Group A (GPR <0.76 and tumor size <5 cm), Group B (GPR <0.76 but tumor size ≥5 cm, or tumor size <5 cm but GPR ≥0.76), and Group C (GPR ≥0.76 and tumor size ≥5 cm). The *P*-values were calculated by log-rank test.
Abbreviation: GPR, gamma-glutamyl transpeptidase to platelet ratio.

cirrhosis and HCC in CHB should be further investigated in the setting of research.

Nevertheless, our study had significant advantages that might balance the above limitations. To the best of our knowledge, it was the first study to evaluate the association between GPR and S-index, and survival in HCC. We compared the two models with BCLC stage, one of the most widely used HCC stage models worldwide, and found that GPR index, but not BCLC stage or S-index, was the most meaningful index to predict OS and RFS. Also, we firstly estimated the diagnostic capability of the two models for cirrhosis in these patients. The long-term follow-up and homogeneity of the study population (limited to the patients' HBV infection and curative therapy) were additional strengths of this study.

In conclusion, the results of our study demonstrated that patients with a high preoperative GPR index may have a poor OS and RFS after curative therapy of HBV-related HCC. GPR can be applied to evaluate liver function, stage of liver fibrosis, and to predict prognosis in these patients.

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Disclosure

The authors report no conflicts of interest in this work.

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