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

Qing Pang
Jian-Bin Bi
Zhi-Xin Wang
Xin-Sen Xu
Kai Qu
Run-Chen Miao
Wei Chen
Yan-Yan Zhou
Chang Liu

Department of Hepatobiliary Surgery, the First Affiliated Hospital of Medical College, Xi’an Jiaotong University, Shaanxi Province, People’s Republic of China

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. Until 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. Persistent infection with HBV can evolve into cirrhosis, and then into hepatocellular carcinoma (HCC), a leading cause of cancer-related deaths worldwide. It is reported that as many as 40% of men and 15% of women with perinatally acquired HBV die of liver cirrhosis or HCC.

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...
have shown an unsatisfactory survival, mainly due to a high risk of tumor recurrence, especially in patients with chronic hepatitis B (CHB). 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, have been proposed to stratify HCC and for evaluating the prognosis. However, these models are limited in clinical use; 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. Numerous studies have verified several noninvasive models as significant predictors for cirrhosis in patients with CHB, with a high diagnostic potential. Subsequently, several of these models were found to be accurate predictors of HCC formation. Recently, partial cirrhosis-derived models have been found to be excellent tools for predicting survival of HCC. Two routine clinical parameters, gamma-glutamyl transpeptidase (GGT) and platelets, are independent risk factors for HCC in CHB and are independent predictors of survival in patients with HBV-related HCC. 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. 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, 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: GPR = GGT/PLT; S-index = 1,000×GGT/(PLT×ALB).

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 χ² 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 <0.76 (n=89)** | **GPR ≥0.76 (n=93)** | **P-value** |
| Sex, male/female | 140/42 | 66/23 | 74/19 | 0.386 |
| Age (years), mean ± SD | 52.1±10.4 | 51.6±10.7 | 51.6±10.3 | 0.986 |
| ALT (U/L), median (min–max) | 52 (7–1,315) | 39 (7–934) | 58 (15–1,315) | 0.003 |
| AST (U/L), median (min–max) | 48 (11–1,075) | 40 (11–891) | 60 (20–1,075) | <0.001 |
| ALP (U/L), median (min–max) | 104 (1–872) | 89 (1–344) | 118 (30–872) | <0.001 |
| GGT (U/L), median (min–max) | 76 (12–1,830) | 42 (12–155) | 134 (20–1,830) | <0.001 |
| PLT (10^9/L), median (min–max) | 112 (3–486) | 132 (46–486) | 85 (3–287) | <0.001 |
| INR (U/L), median (min–max) | 1.1 (0.8–8.09) | 1.1 (0.8–1.6) | 1.1 (0.9–8.09) | 0.048 |
| ALB, median (min–max) | 38 (14–54) | 39 (14–54) | 38 (24–51) | 0.136 |
| aFP, alpha-fetoprotein | 84/85 | 41/45 | 43/40 | 0.591 |
| Ascites: yes/no | 25/157 | 11/78 | 14/79 | 0.598 |
| Cirrhosis: yes/no | 86/96 | 35/54 | 51/42 | 0.036 |
| Tumor size: ≥5/≤5 cm | 89/87 | 35/51 | 54/36 | 0.010 |
| Tumor no: multiple/single | 43/135 | 19/68 | 24/67 | 0.480 |
| Child–Pugh: A/B/C | 155/27 | 78/11 | 77/16 | 0.358 |
| Vascular invasion: yes/no | 20/162 | 3/86 | 17/76 | 0.003 |
| BCLC stage: A1/A2/A3+ | 66/187/120 | 44/6/33/3 | 22/12/39/7 | <0.001 |
| A4/B/C/D | 119/63 | 67/22 | 52/41 | 0.006 |
| Resection/RFA | 88/94 | 34/55 | 54/39 | 0.007 |
| Death: yes/no | 79/103 | 32/57 | 47/46 | 0.047 |
| Recurrence: yes/no | 0.79 (0.05–18.83) | 0.38 (0.05–0.75) | 1.45 (0.76–18.83) | <0.001 |
| 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 |

Notes: * χ² test, 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; ASAT, 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.
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 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 singular          | 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; 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.

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.19,19 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 al28 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
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 size, 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.
advances in fibrosis stage estimated by Forns index, one of cirrhosis-related models, affected OS and RFS, independent of tumor characteristics.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 heptectomy is associated with higher complication and longer hospital duration, it is still proposed as the frontline treatment for HCC.\textsuperscript{36,37} RFA may be an alternative to heptectomy because of its comparable long-term efficacy in partial HCC patients.\textsuperscript{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

**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.
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.

Acknowledgment
This study was supported by the Clinical Research Award of the First Affiliated Hospital of Xi’an Jiaotong University, People’s Republic of China (No. XJTU1AF-CRF-2015-003), and National Natural Science Foundation of China, No. 81272644 and No. 81072051.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907–1917.
2. Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014; 384(9959):2053–2063.
3. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142(6):1264–1273 e1261.
4. Lee TY, Lin JT, Zeng YS, Chen YJ, Wu MS, Wu CY. Association between nucleos(t)ide analogue and tumor recurrence in HBV-related hepatocellular carcinoma after radiofrequency ablation. Hepatology. In press 2015.
5. Kim BK, Park JY, Kim do Y, et al. Persistent hepatitis B viral replication affects recurrence of hepatocellular carcinoma after curative resection. Liver Int. 2008;28(3):393–401.
6. Lei HJ, Chau GY, Lui WY, et al. Prognostic value and clinical relevance of the 6th Edition 2002 American Joint Committee on Cancer staging system in patients with resectable hepatocellular carcinoma. J Am Coll Surg. 2006;203(4):426–435.
7. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–338.
8. Pang Q, Bi JB, Xu XS, et al. King’s score as a novel prognostic model for patients with hepatitis B-associated hepatocellular carcinoma. Eur J Gastroenterol Hepatol. 2015;27(11):1337–1346.
9. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol. 2003;38(2):200–207.
10. Li J, Gordon SC, Rupp LB, et al. The validity of serum markers for fibrosis staging in chronic hepatitis B and C. J Viral Hepat. 2014;21(12):930–937.
11. Suh B, Park S, Shin DW, et al. High liver fibrosis index FIB-4 is highly predictive of hepatocellular carcinoma in chronic hepatitis B carriers. Hepatol. 2015;61(4):1261–1268.
12. Hann HW, Wan S, Lai Y, et al. Aspartate aminotransferase to platelet ratio index as a prognostive predictor of hepatocellular carcinoma risk in patients with chronic hepatitis B virus infection. J Gastroenterol Hepatol. 2015;30(1):131–138.
13. Pang Q, Xu XS, Zhang JY, Yu K, Chen W, Liu C. FIB-4 as a prognostic model for patients with hepatitis B-associated hepatocellular carcinoma. Hepatol. 2015;62(4):1325–1326.
14. Choi WM, Lee JH, Ahn H, et al. Forns index predicts recurrence and death in patients with hepatitis B-related hepatocellular carcinoma after curative resection. Liver Int. 2015;35(8):1992–2000.
15. Jun CH, Hong HJ, Chung MW, et al. Risk factors for hepatocellular carcinoma in patients with drug-resistant chronic hepatitis B. World J Gastroenterol. 2013;19(40):6834–6841.
16. Lin YJ, Lee MH, Yang HL, et al. Predictability of liver-related seromarkers for the risk of hepatocellular carcinoma in chronic hepatitis B patients. PLoS One. 2013;8(4):e61448.
17. Nishikawa H, Nishijima N, Arimoto A, et al. Prognostic factors in patients with hepatitis B virus-related hepatocellular carcinoma undergoing nucleoside analog antiviral therapy. Oncol Lett. 2013;6(5):1213–1218.
18. Lemoine M, Shimakawa Y, Nagayama S, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut. In press 2015.
19. Zhou K, Gao CF, Zhao YP, et al. Simpler score of routine laboratory tests predicts liver fibrosis in patients with chronic hepatitis B. J Gastroenterol Hepatol. 2010;25(9):1569–1577.
20. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–2194.
21. Park YH, Kim BK, Kim JK, et al. Long-term outcomes of chronic hepatitis B virus infection in the era of antiviral therapy in Korea. J Gastroenterol Hepatol. 2014;29(5):1005–1011.
22. Asahina Y, Tsuchiya K, Nishimura T, et al. Alpha-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology. 2013;58(4):1253–1262.
23. Fu SC, Huang YW, Wang TC, Hu JT, Chen DS, Yang SS. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with new onset diabetes: a nationwide cohort study. Aliment Pharmacol Ther. 2015;41(11):1200–1209.
24. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–662.
25. Bruix J, Gores GJ, Mazzaferrro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut. 2014;63(5):844–855.
26. Ko S, Kanehiro H, Hisanaga M, Nagao M, Ikeda N, Nakajima Y. Liver fibrosis increases the risk of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. Br J Surg. 2002;89(1): 57–62.
27. Gassmann P, Spieker T, Haier J, Schmidt F, Mardin WA, Senninger N. Prognostic impact of underlying liver fibrosis and cirrhosis after curative resection of hepatocellular carcinoma. World J Surg. 2010;34(10):2442–2451.
28. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer. 1985;56(4):918–928.
29. Llovet JM, Bruix J. Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology. 2000;32(3):679–680.
30. Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer. 2002;94(6):1760–1769.
31. Kobayashi T, Itamoto T, Tashiro H, et al. Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy. J Hepatobiliary Pancreat Sci. 2011;18(5):689–699.
32. Yan X, Fu X, Cai C, Zi X, Yao H, Qiu Y. Validation of models in patients with hepatocellular carcinoma: comparison of Hong Kong Liver Cancer with Barcelona Clinic Liver Cancer staging system in a Chinese cohort. Eur J Gastroenterol Hepatol. 2015;27(10):1180–1186.
33. Wang Q, Fiel MI, Blank S, et al. Impact of liver fibrosis on prognosis following liver resection for hepatitis B-associated hepatocellular carcinoma. Br J Cancer. 2013;109(3):573–581.
34. Yao M, Zhao J, Lu F. Alpha-fetoprotein still is a valuable diagnostic and prognosis predicting biomarker in hepatitis B virus infection-related hepatocellular carcinoma. Oncotarget. 2016;7(4):3702–3708.
35. Bruix J, Sherman M; American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–1022.
36. Xu Q, Kobayashi S, Ye X, Meng X. Comparison of hepatic resection and radiofrequency ablation for small hepatocellular carcinoma: a meta-analysis of 16,103 patients. Sci Rep. 2014;4:7252.
37. Qi X, Tang Y, An D, et al. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2014;48(5):450–457.