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Original Article

Prognostic value of combined preoperative gamma-glutamyl transpeptidase to platelet ratio and fibrinogen in patients with HBV-related hepatocellular carcinoma after hepatectomy

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Abstract: The gamma-glutamyl transpeptidase to platelet ratio (GPR) has been reported as a non-invasive parameter for evaluating hepatic fibrosis and cirrhosis. However, only a few of studies investigated the relationship between GPR and liver cancer. Here, we sought to clarify the prognostic value of GPR as well as its combination with fibrinogen in patients with HBV-related hepatocellular carcinoma (HCC). We performed a retrospective study using data collected from 302 HCC patients, and evaluated the association between GPR, fibrinogen and clinicopathological characteristics using the chi-square test. Additionally, we assessed disease-free survival (DFS) and overall survival (OS) using the Kaplan-Meier method and log-rank test, then performed univariate and multivariate COX analyses to identify the prognostic factors. The prognostic performance of combined GPR and fibrinogen was evaluated by the receiver operating characteristic curve analysis. Results showed that GPR was associated with gender, history of smoking and drinking, cirrhosis, antiviral treatments, tumor number, and Child-Pugh grade. Univariate analysis revealed a significant correlation between tumor diameter, vascular invasion, BCLC stage, alpha-fetal protein, GPR, fibrinogen, and NLR with both DFS and OS in HCC patients. Only GPR and fibrinogen were found to be independently associated with both DFS and OS according to multivariate analysis. Furthermore, predictive capacity was enhanced by combining GPR with fibrinogen owing to a larger area under the curve than other indexes or models. Overall, preoperative GPR could be an effective non-invasive predictor for prognosis of HBV-related HCC patients, and a combination of GPR and fibrinogen improved the prognostic performance.

Keywords: Fibrinogen, gamma-glutamyl transpeptidase to platelet ratio, hepatocellular carcinoma, prognosis

Introduction

Hepatocellular carcinoma (HCC), is the most common type of primary liver cancer, and the third cause of cancer-related deaths worldwide [1]. In China, its incidence and mortality rates remain high, accounting for almost half of the new cases all over the world, due to prevalence of hepatitis and hepatitis-related liver cirrhosis [2]. Currently, surgical treatments, mainly based on resection and liver transplantation, remain first-line options for treatment of HCC patients [3]. However, high recurrence rates, both at early and advanced stages, reduce survival rates of HCC patients [1, 3]. In addition, lack of simple and effective predictors for tumor recurrence also preclude improvement of patients' long-term outcomes. It is, therefore, necessary to unravel novel and significant biomarkers, especially noninvasive parameters, for identifying and evaluating patients with the risk of recurrence and death. These could offer more options to guide development of multidisciplinary treatment strategies for improving prognosis of patients.

Inflammatory microenvironment is one of the specific features of cancer [4]. Most HCC cases develop with a background liver disease which contributes to a comprehensive inflammatory

status due to prevalence of hepatitis B and C [5-7]. In addition, various studies have reported a significant relationship between inflammation-related factors and liver cancer, although some might be first found and validated in hepatitis. Based on such findings, researchers have subsequently constructed several composite indicators and applied them to clinical practice, including neutrophil to lymphocyte ratio (NLR) [8], platelet to lymphocyte ratio (PLR) [9], lymphocyte to monocyte ratio (LMR) [10], and C-reactive protein to albumin ratio (CAR) [11]. A novel index, gamma-glutamyl transpeptidase to platelet ratio (GPR), was recently established by Lemoine and co-workers and validated with high diagnostic accuracy, enabling evaluation of the extent of liver fibrosis and cirrhosis in patients with chronic HBV infection [12]. Additionally, Wang and coworkers investigated the prognostic significance of GPR in HBV-related HCC and found that patients with high GPR had worse overall survival (OS) and diseases-free survival (DFS) [13]. Several studies have also explored the clinical relevance and prognostic impact of GPR in HCC [14-17]. Besides, fibrinogen, another inflammation-related parameter, has also been demonstrated specific relationships with many kinds of tumors, including HCC. Particularly, patients with elevated fibrinogen levels exhibited worse OS and DFS than those with low levels in HCC. Hence, both GPR and fibrinogen showed with very potential to be severed as significant prognostic markers for HCC patients.

However, most of these studies have only focused on the prognostic value of a single inflammatory parameter, which might result in insufficient evaluation and limited efficiency. In the present study, we performed a retrospective analysis from a cohort of HCC patients with HBV infection, focusing on the independent prognostic value of GPR and fibrinogen. Specifically, we investigated the prognostic value of combined GPR and fibrinogen in HBV-related HCC by stratifying patients into different subgroups, with our results showing an enhanced accuracy for risk classification of recurrence and survival.

Materials and methods

Patients

Patients with HBV-related HCC, who had liver resection as their first treatment from March 2005 to May 2013, were retrospectively enrolled at The Third Affiliated Hospital of Sun Yat-Sen University. Patients with extrahepatic metastasis, other malignancies, or those who had prior treatments were all excluded. Consequently, a total of 302 patients were enrolled in the study. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University, and written informed consent for participation was obtained from patients prior to their enrolment.

Data collection

We retrospectively reviewed electronic medical records of all patients, including demographic data with gender and age as well as their past medical history. Preoperative serological parameters were selected at the time within seven days before surgery, including neutrophil, lymphocyte and platelet count, gamma-glutamyl transpeptidase, fibrinogen, alpha-fetoprotein (AFP) and HBV-DNA. In addition, tumor characteristics were recorded using contrast-enhanced computed tomographic (CT) scans and/or magnetic resonance imaging (MRI) series, then tumor size, number, and the existence of vascular invasion all recorded. Besides, presence of cirrhosis was evaluated using radiological images and histopathological reports. And Child-Pugh grade and the Model for End-Stage Liver Disease (MELD) score were used to assess the liver function. We adopted the Barcelona Clinic Liver Cancer (BCLC) staging system to determine personalized staging for each patient. Preoperative data were used to calculate the GPR and NLR according to the following formulas: GPR = Gamma-glutamyl transpeptidase/Platelet (10^9), NLR = Neutrophil/Lymphocyte.

Follow-up

All patients were regularly followed up at the outpatient office or inpatient therapy after hepatectomy. AFP levels in serum were measured every month in the first year, then every three months for the following two years. Abdominal ultrasound and dynamic enhanced CT or MRI were also performed every three months in the first two years and followed by once every six months in the third year. The follow-up program began on the date of operation, and ended in case of death or time of the last follow-up encompassed by this study (December 2016).

OS was defined as the duration from the time of surgery to the data of HCC-related death, whereas DFS was taken to denote the time of staying free of cancer after hepatic resection for patients with HCC.

Statistical analysis

All statistical analyses were performed with SPSS software version 22.0 (SPSS Inc, Chicago, IL). Continuous variables were presented as medians and interquartile range (IQR), while categorical ones were described as frequencies and percentages, and then compared using Pearson chi-square (χ^2) or Fisher's exact (in cases of low frequency) tests. The receiver operating characteristic (ROC) curves and the highest values of the Youden index were calculated to determine the optimal cut-off point for GPR and NLR, while the upper limitation of fibrinogen (normal reference range: 2-4 g/L) was determined as its cut-off value. OS and DFS were both estimated using the Kaplan-Meier method, then compared using the log-rank test. Univariate Cox analysis was performed to identify factors potentially related to HCC recurrence or overall survival. Variables that were found to be significant ($P < 0.05$) were further subjected to a multivariate Cox regression model. A two-sided *P*-value < 0.05 was used to infer statistical significance.

Results

Patient characteristics

A total of 302 HCC patients were enrolled in the study, and all of them were positive with the hepatitis B surface antigen (HBsAg), while six (2.0%) patients were present with antibodies to hepatitis C virus concurrently, and only one (0.3%) patient was diagnosed with a coinfection of human immunodeficiency virus (HIV). Male was the majority of our HCC patients with 266 (88.1%) cases. The median age was 51 years (IQR: 42-59 years). And there were 96 (31.8%) and 58 (19.2%) patients presented with a history of smoke and drink respectively. Cirrhosis was diagnosed in 204 (67.5%) patients by pathological test of resected liver samples. And according to the BCLC staging system, 154 (51.0%) patients were classified to stage 0-A, whereas 122 (40.4%) and 26 (8.6%) patients belonged to stage B and C respectively. Most patients were presented with single tumor (213 cases, 70.5%), and the median tumor diameter was 4.3 cm (IQR: 3.0-7.5 cm). Besides, vascular invasion was found in 115 (38.1%) patients. As for preoperative blood tests, only 96 (31.8%) patients showed with obviously elevated AFP, and the median levels of GPR and NLR were 0.38 (IQR: 0.22-0.70) and 1.92 (IQR: 1.46-2.72) respectively. And the median level of fibrinogen was 2.95 g/L (IQR: 2.45-3.62 g/L). During the follow-up period, 193 (63.9%) patients progressed with tumor recurrence and 51 (16.9%) patients died from HCC-related causes. Details of these features are shown in **Table 1**.

Correlation between GPR, fibrinogen and preoperative clinicopathologic characteristics of patients with HBV-related HCC

The correlation between GPR, fibrinogen and other clinicopathologic parameters of HBV-related HCC patients were investigated. The results were presented in **Table 2**, which indicated that GPR was correlated with gender ($P = 0.004$), history of smoke ($P = 0.006$) and drink ($P = 0.007$), cirrhosis ($P < 0.001$), antiviral treatments ($P = 0.011$), tumor number ($P = 0.047$), and Child-Pugh grade ($P < 0.001$), while fibrinogen was correlated with history of smoke ($P = 0.035$), antiviral treatments ($P = 0.002$), tumor diameter ($P < 0.001$), vascular invasion ($P < 0.001$), BCLC stage ($P < 0.001$), MELD score ($P = 0.001$), pathological differentiation ($P = 0.011$), and NLR ($P < 0.001$). However, no significant associations between GPR/fibrinogen and other clinicopathologic characteristics were observed, including age, diabetes, AFP and HBV-DNA (all $P > 0.05$).

The significance of GPR and fibrinogen in univariate and multivariate analyses for prognostic factors of HBV-related HCC patients after liver resection

The median DFS of all included patients was 15.6 months (95% CI: 12.2-19.0 months). And the 1-, 3-, and 5-year DFS rates were 56.6%, 32.0%, and 25.9%, respectively. Univariate analysis showed that history of smoke ($P = 0.037$), tumor diameter ($P < 0.001$), tumor number ($P < 0.001$), vascular invasion ($P < 0.001$), BCLC stage ($P < 0.001$), pathological differentiation ($P = 0.001$), AFP ($P = 0.027$), NLR ($P = 0.015$), fibrinogen ($P < 0.001$), and GPR ($P < 0.001$) were significantly associated

Table 1. Baseline clinicopathological characteristics of 302 patients with HBV-related HCC

Category	Median (IQR)/N (%)
Gender (female/male)	36 (11.9%)/266 (88.1%)
Age (years)	51 (42-59)
Smoke (no/yes)	206 (68.2%)/96 (31.8%)
Drink (no/yes)	244 (80.8%)/58 (19.2%)
Diabetes (no/yes)	274 (90.7%)/28 (9.3%)
Cirrhosis (no/yes)	98 (32.5%)/204 (67.5%)
Antiviral treatments (no/yes)	153 (50.7%)/149 (49.3%)
Tumor diameter, cm	4.3 (3.0-7.5)
Tumor number (single/multiple)	213 (70.5%)/89 (29.5%)
Vascular invasion (no/yes)	187 (61.9%)/115 (38.1%)
BCLC stage (0-A/B/C)	154 (51.0%)/122 (40.4%)/26 (8.6%)
Child-Pugh grade (A/B)	280 (92.7%)/22 (7.3%)
MELD score	0.49 (0.30-0.69)
Pathological differentiation (well/poor-moderate)	55 (18.2%)/247 (81.8%)
AFP, ng/mL (≤ 400/> 400)	206 (68.2%)/96 (31.8%)
HBV-DNA, copies/mL (≤ 1000/> 1000)	152 (50.3%)/150 (49.7%)
Fibrinogen, g/L	2.95 (2.45-3.62)
GPR	0.38 (0.22-0.70)
NLR	1.92 (1.46-2.72)

IQR: interquartile range, BCLC: Barcelona Clinic Liver Cancer, MELD: Model for End-Stage Liver Disease, AFP: alpha fetoprotein, HBV: hepatitis B virus, GPR: gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio.

Table 2. Correlation between GPR and fibrinogen and other clinicopathological characteristics in 302 patients with HBV-related HCC

Category	Subcategory	Cases	GPR		P	Fibrinogen, g/L		P
			≤ 0.35	> 0.35		≤ 4	> 4	
Gender	Female	36	25	11	0.004	31	5	0.902
	Male	266	117	149		227	39	
Age (years)	≤ 50	151	77	74	0.167	126	25	0.328
	> 50	151	65	86		132	19	
Smoke	No	206	108	98	0.006	182	24	0.035
	Yes	96	34	62		76	20	
Drink	No	244	124	120	0.007	210	34	0.521
	Yes	58	18	40		48	10	
Diabetes	No	274	131	143	0.389	236	38	0.280
	Yes	28	11	17		22	6	
Cirrhosis	No	98	63	35	< 0.001	83	15	0.801
	Yes	204	79	125		175	29	
Antiviral treatments	No	153	83	70	0.011	121	32	0.002
	Yes	149	59	90		137	12	< 0.001
Tumor diameter, cm	≤ 5	177	90	87	0.113	169	8	
	> 5	125	52	73		89	36	
Tumor number	Single	213	108	105	0.047	187	26	0.072
	Multiple	89	34	55		71	18	
Vascular invasion	No	187	91	96	0.466	176	11	< 0.001
	Yes	115	51	64		82	33	
BCLC stage	0~A	154	80	74	0.099	145	9	< 0.001

	B-C	122	54	68		113	35	
Child-Pugh grade	A	280	140	140	< 0.001	237	43	0.220
	B	22	2	20		21	1	
MELD score	≤ 0.49	151	73	78	0.645	119	32	0.001
	> 0.49	151	69	82		139	12	
Pathological differentiation	Well	55	25	30	0.797	53	2	0.011
	Poor-Moderate	247	117	130		205	42	
AFP, ng/mL	≤ 400	206	96	110	0.831	178	28	0.481
	> 400	96	46	50		80	16	
HBV-DNA, copies/mL	≤ 1000	152	77	75	0.202	134	18	0.176
	> 1000	150	65	85		124	26	
NLR	≤ 2.5	216	109	107	0.057	195	21	< 0.001
	> 2.5	86	33	53		63	23	

BCLC: Barcelona Clinic Liver Cancer, MELD: Model for End-Stage Liver Disease, AFP: alpha fetoprotein, HBV: hepatitis B virus, GPR: gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio.

Table 3. Univariate analyses of prognostic factors for DFS and OS in patients with HBV-related HCC

Variables	DFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Gender (Male/Female)	0.780 (0.485-1.253)	0.304	0.760 (0.301-1.918)	0.562
Age, years (> 50/≤ 50)	0.851 (0.641-1.129)	0.264	1.974 (1.102-3.534)	0.022
Smoke (Yes/No)	1.371 (1.108-1.846)	0.037	1.514 (0.863-2.657)	0.148
Drink (Yes/No)	1.148 (0.805-1.638)	0.446	0.904 (0.439-1.858)	0.783
Diabetes (Yes/No)	1.416 (0.898-2.230)	0.134	0.708 (0.254-1.972)	0.509
Cirrhosis (Yes/No)	1.125 (0.826-1.533)	0.455	0.923 (0.516-1.653)	0.789
Antiviral treatments (Yes/No)	1.249 (0.938-1.663)	0.128	0.885 (0.503-1.558)	0.672
Tumor diameter, cm (> 5/≤ 5)	2.092 (1.572-2.782)	< 0.001	3.081 (1.743-5.447)	< 0.001
Tumor number (Multiple/Single)	2.184 (1.629-2.928)	< 0.001	1.416 (0.789-2.539)	0.243
Vascular invasion (Yes/No)	1.701 (1.278-2.264)	< 0.001	2.545 (1.461-4.435)	0.001
BCLC stage (B~C/0~A)	1.983 (1.488-2.643)	< 0.001	2.446 (1.372-4.361)	0.002
Child-Pugh grade (B/A)	1.138 (0.700-1.851)	0.603	0.484 (0.117-1.991)	0.314
MELD score (> 0.49/≤ 0.49)	1.047 (0.789-1.389)	0.752	0.695 (0.398-1.215)	0.202
Pathological differentiation (Poor-Moderate/Well)	1.992 (1.317-3.014)	0.001	1.852 (0.826-4.149)	0.135
AFP, ng/mL (> 400/≤ 400)	1.399 (1.039-1.884)	0.027	2.387 (1.374-4.145)	0.002
HBV-DNA, copies/mL (> 1000/≤ 1000)	1.313 (0.989-1.743)	0.059	2.478 (1.379-4.453)	0.002
Fibrinogen, g/L (> 4/≤ 4)	2.202 (1.523-3.184)	< 0.001	2.954 (1.612-5.411)	< 0.001
GPR (> 0.35/≤ 0.35)	1.702 (1.272-2.277)	< 0.001	2.152 (1.188-3.896)	0.011
NLR (> 2.5/≤ 2.5)	1.458 (1.075-1.977)	0.015	1.908 (1.077-3.380)	0.027

BCLC: Barcelona Clinic Liver Cancer, MELD: Model for End-Stage Liver Disease, AFP: alpha fetoprotein, HBV: hepatitis B virus, GPR: gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, DFS: disease-free survival, OS: overall survival, HR: hazard ratio, CI: confidence interval.

with DFS (**Table 3**). Especially, patients with higher GPR (> 0.35) showed with worse 1-, 3-, 5-year DFS (48.5%, 22.3%, and 18.3%) than those patients with lower GPR (66.0%, 44.9%, and 35.9%) (**Figure 1A**). And patients with higher fibrinogen (> 4 g/L) also showed with worse 1-, 3-, 5-year DFS (34.2%, 19.5%, and 0.0%) than those patients with lower fibrinogen (60.4%, 34.2%, and 30.2%) (**Figure 1C**). Then, the above factors were further evaluated by the multivariate analysis, and the results indicated that tumor diameter > 5 cm (P = 0.002; HR: 1.599, 95% CI: 1.180-2.167), multiple tumor nodules (P < 0.001; HR: 1.922, 95% CI: 1.430-

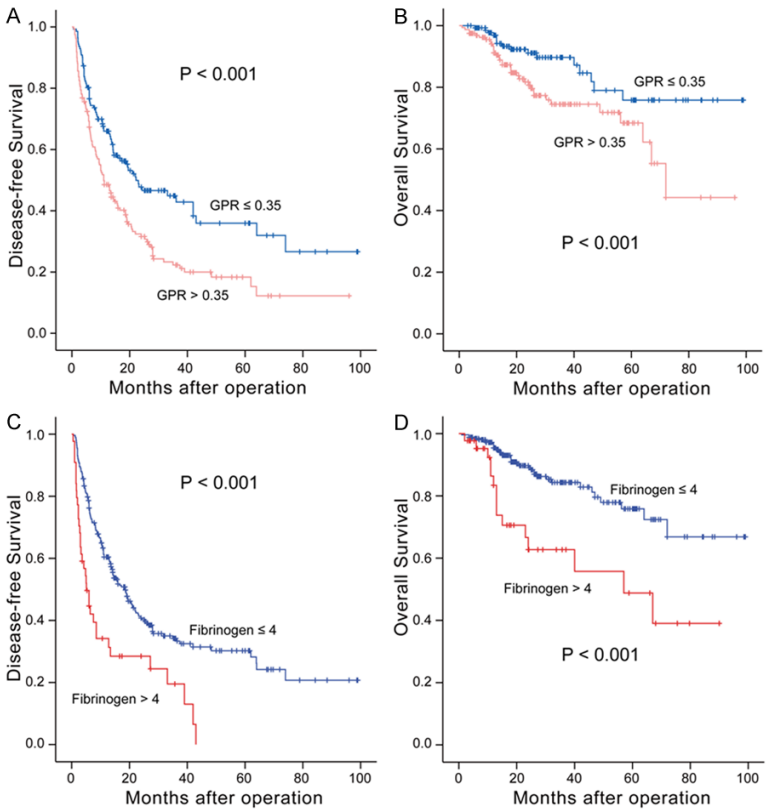

Figure 1. Comparison of the DFS and OS in HBV-related HCC patients with high and low levels of GPR and fibrinogen. A, B. DFS and OS of patients with GPR > 0.35 were significantly worse than those with GPR ≤ 0.35 (both P < 0.001). C, D. DFS and OS of patients with fibrinogen > 4 g/L were also markedly worse than those with fibrinogen ≤ 4 g/L (both P < 0.001).

2.584), poor-moderate pathological differentiation (P = 0.014; HR: 1.705, 95% CI: 1.114-2.608), higher fibrinogen (> 4 g/L) (P = 0.002; HR: 1.921, 95% CI: 1.280-2.885), and higher GPR (> 0.35) (P < 0.001; HR: 1.900, 95% CI: 1.402-2.574) were independent risk factors of DFS (**Table 4**).

The mean OS was 76.0 ± 3.0 months (95% CI: 70.2-81.9 months) for all patients. And the 1-, 3-, and 5-year OS rates were 93.8%, 81.5%, and 71.8%, respectively. Univariate analysis showed that age (P = 0.022), tumor diameter (P < 0.001), vascular invasion (P = 0.001), BCLC stage (P = 0.002), AFP (P = 0.002), HBV-DNA (P = 0.002), NLR (P = 0.027), fibrinogen (P < 0.001), and GPR (P = 0.011) were significantly associated with OS (**Table 3**). Specially, patients with higher GPR (> 0.35) showed with worse 1-, 3-, 5-year OS (91.2%, 74.5%, and 68.4%) than those patients with lower GPR (96.9%, 89.7%, and 75.8%) (**Figure 1B**). And patients with higher fibrinogen (> 4 g/L) also showed with worse 1-, 3-, 5-year OS (83.4%, 62.7%, and 48.8%) than those patients with lower NLR (95.4%, 84.3%, and 75.8%) (**Figure 1D**). Furthermore, multivariate analysis revealed that higher AFP (> 400 ng/mL) (P = 0.004; HR: 2.353, 95% CI: 1.321-4.193), higher HBV-DNA (> 1000 copies/mL) (P = 0.007; HR: 2.286, 95% CI: 1.254-4.165), higher fibrinogen (> 4 g/L) (P = 0.009; HR: 2.395, 95% CI: 1.248-4.599) and higher GPR (> 0.35) (P = 0.006; HR: 2.375, 95% CI: 1.287-4.386) were independent risk factors of OS (**Table 4**).

These results showed above suggested that both GPR and fibrinogen were independent prognostic factors for DFS and OS in patients with HBV-related HCC.

Prognostic significance of GPR in different subgroups of patients with HBV-related HCC

We further analyzed the prognostic abilities of GPR in different subgroups of HCC patients. The results showed that GPR was still significantly associated with DFS in HCC patients without cirrhosis, and the 1-, 3-, 5-year DFS of patients with higher GPR (> 0.35) were worse than those with lower GPR (38.8%, 28.8%, and 19.2% vs 62.3%, 47.0%, and 47.0%; P = 0.013) (**Figure 2A**). The similar results were also found in HCC patients with cirrhosis (51.0%, 20.0%, and 18.5% vs 68.9%, 43.6%, and 31.3%; P = 0.008) (**Figure 2B**). Both in the subgroups of tumor diameter ≤ 5 cm and > 5 cm, the 1-, 3-, 5-year DFS of HCC patients with higher GPR were also worse than those with lower GPR (≤ 5 cm: 58.6%, 27.5%, and 25.3% vs 75.0%, 54.9%, and 45.0%; P = 0.007; > 5 cm: 36.3%, 15.6%, and 8.7% vs 50.5%, 25.8%, and 19.3%; P = 0.036) (**Figure 2C**, **2D**). Based on the tumor number, GPR still showed significantly associa-

Table 4. Prognostic factors for DFS and OS in patients with HBV-related HCC by multivariate COX regression analyses

Variables	DFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Tumor diameter	1.599 (1.180-2.167)	0.002		
Tumor number	1.922 (1.430-2.584)	< 0.001		
Pathological differentiation	1.705 (1.114-2.608)	0.014		
GPR	1.900 (1.402-2.574)	< 0.001	2.375 (1.287-4.386)	0.006
Fibrinogen	1.921 (1.280-2.885)	0.002	2.395 (1.248-4.599)	0.009
AFP			2.353 (1.321-4.193)	0.004
HBV-DNA			2.286 (1.254-4.165)	0.007

AFP: alpha fetoprotein, HBV: hepatitis B virus, GPR: gamma-glutamyl transpeptidase to platelet ratio, DFS: disease-free survival, OS: overall survival, HR: hazard ratio, CI: confidence interval.

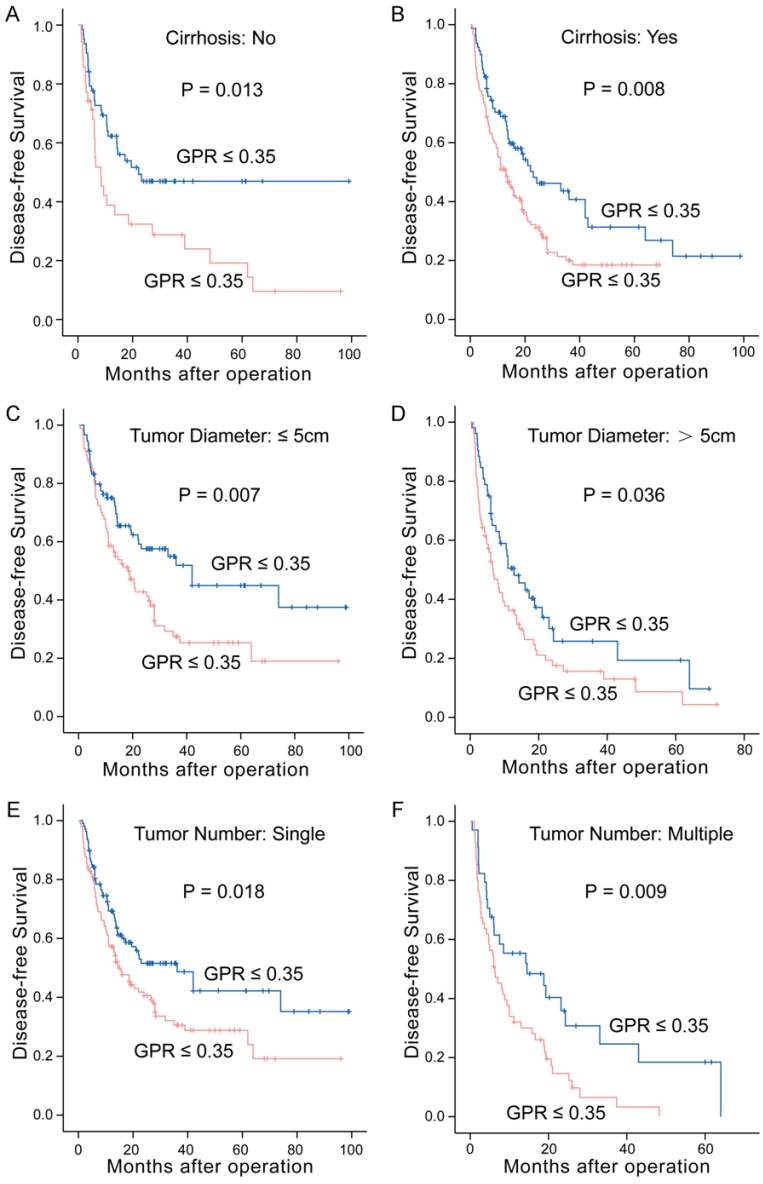

Figure 2. Comparison of the DFS in different subgroups of HBV-related HCC patients with high and low levels of GPR. Patients with GPR > 0.35 showed with worse DFS in the subgroups stratified by cirrhosis (no/yes) (A, B), tumor diameter (≤ 5/> 5 cm) (C, D) and tumor number (single/multiple) (E, F) (all P < 0.05).

tion with DFS both in patients with single (1-, 3-, 5-year DFS: 57.2%, 30.6%, and 28.8% (GPR > 0.35) vs 69.3%, 51.6%, and 42.2% (GPR ≤ 0.35); P = 0.018; **Figure 2E**) and multiple (1-, 3-, 5-year DFS: 32.1%, 6.5%, and 0.0% (GPR > 0.35) vs 55.3%, 24.6%, and 18.4% (GPR ≤ 0.35); P = 0.009; **Figure 2F**) tumors. In addition, data also displayed GPR with significant prognostic values for DFS in the subgroups classified by preoperative AFP (≤ 400/> 400 ng/mL) and BCLC stage (0-A/B-C), and higher GPR all presented with worse 1-, 3-, 5-year DFS in these subgroups (all P < 0.05; **Figure 3A-D**). When divided by pathological differentiation, GPR remained a significant prognostic ability in HCC patients with poor-moderate differentiation (P < 0.001; **Figure 3E**), while no significance was found in the subgroup with well differentiation (P = 0.128; **Figure 3F**). These findings further demonstrated that GPR was universally applicable in various subgroups of HBV-

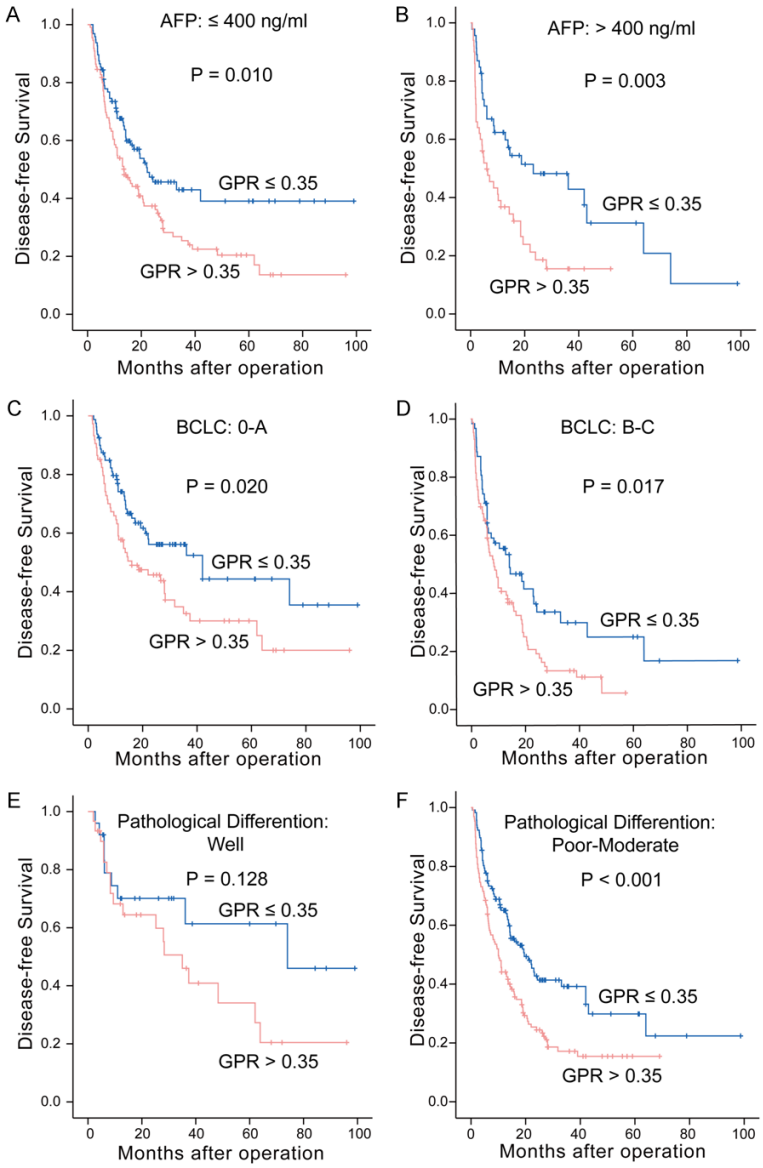

Figure 3. Comparison of the DFS in various subgroups of HBV-related HCC patients with different levels of GPR. Patients with GPR > 0.35 showed with worse DFS in the subgroups classified by AFP (≤ 400/> 400 ng/mL) (A, B), BCLC stage (0-A/B-C) (C, D) (all *P* < 0.05). And GPR also showed prognostic significance in the subgroup with poor-moderate tumor differentiation (P < 0.001), while not in the subgroup with well differentiation (P = 0.128) (E, F).

related HCC patients with robust prognostic capacity for DFS.

Prognostic significance of GPR in combination with fibrinogen for HBV-related HCC patients

GPR and fibrinogen might mainly reflect the hepatic inflammation and systematic inflammation respectively, and these two indexes has been recognized as independent prognostic factors by multivariate analysis in patients with HBV-related HCC. However, the prognostic value of combined GPR and fibrinogen in HCC has not been explored. Hence, we further evaluated the prognostic significance of the combined parameter comprised by GPR and fibrinogen in our patients' cohort. Patients were divided into three groups by the novel composite index (GPR-FIB): Group A (N = 118), patients with GPR ≤ 0.35 and fibrinogen ≤ 4 g/L; Group B (N = 164), patients with GPR > 0.35 and fibrinogen ≤ 4 g/L or with GPR ≤ 0.35 and fibrinogen > 4 g/L; Group C (N = 20), patients with GPR > 0.35 and fibrinogen > 4 g/L. We found that patients in Group A had the optimal 1-, 3-, and 5-year DFS (69.4%, 48.2%, and 43.1%) and OS (98.2%, 94.1%, and 83.2%) (**Figure 4A**, **4B**). When compared to group A, patients in group C presented with the worst 1-, 3-, and 5-year DFS (16.7%, 8.3%, and 0.0%; P < 0.001; HR: 6.515, 95% CI: 3.799-11.172) and OS (74.2%, 54.1%, and 54.1%; P = 0.002; HR: 9.179, 95% CI: 3.315-25.413) (**Figure 4A**, **4B**), while patients in group B showed with moderate 1-, 3-, and 5-year DFS (52.5%, 24.9%, and 18.9%; P = 0.001; HR: 1.736, 95% CI: 1.263-2.385) and OS (92.7%, 75.6%, and 65.8%; P = 0.002; HR: 3.350, 95% CI: 1.556-7.209) (**Figure 4A**, **4B**).

ROC curves of combined GPR and fibrinogen for DFS and OS of patients with HBV-related HCC

To evaluate the prognostic performance of combined GPR and fibrinogen for HCC patients, the ROC curve analyses were performed to

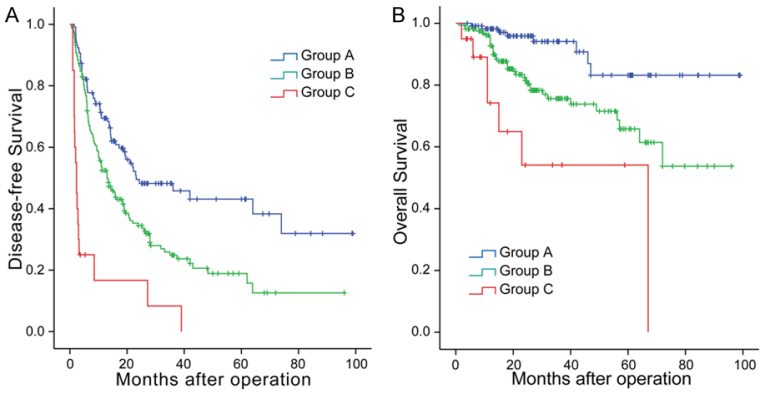

Figure 4. The prognostic significance of combined GPR and fibrinogen for DFS and OS in patients with HBV-related HCC. Patients in group A showed the optimal DFS and OS (A, B), while patients in group C possessed the worst DFS and OS (A, B). Group A: both GPR ≤ 0.35 and fibrinogen ≤ 4 g/L; Group B: both GPR > 0.35 and fibrinogen ≤ 4 g/L or with GPR ≤ 0.35 and fibrinogen > 4 g/L; Group C: both GPR > 0.35 and fibrinogen > 4 g/L.

compare the novel composite index (GPR-FIB) with other independent indexes and models. As showed in **Figure 5A**, the area under the curve (AUC) of GPR-FIB for DFS was 0.646 (95% CI: 0.582-0.711, P < 0.001), which suggested a better performance than GPR (AUC: 0.641, 95% CI: 0.576-0.705, P < 0.001) or fibrinogen (AUC: 0.559, 95% CI: 0.494-0.625, P = 0.087) alone, and other prognostic models including NLR (AUC: 0.582, 95% CI: 0.516-0.648, P = 0.018), Child-Pugh grade (AUC: 0.528, 95% CI: 0.461-0.595, P = 0.414), MELD score (AUC: 0.526, 95% CI: 0.457-0.596, P = 0.448), and BCLC stage (AUC: 0.609, 95% CI: 0.542-0.676, P = 0.002). As for the prognostic prediction for OS of HCC patients, the GPR-FIB also showed a better performance with AUC of 0.657 (95% CI: 0.580-0.735, P < 0.001), while GPR (AUC: 0.608, 95% CI: 0.526-0.690, P = 0.015), fibrinogen (AUC: 0.606, 95% CI: 0.519-0.694, P = 0.017), NLR (AUC: 0.577, 95% CI: 0.495-0.660, P = 0.082), Child-Pugh grade (AUC: 0.480, 95% CI: 0.395-0.565, P = 0.649), MELD score (AUC: 0.428, 95% CI: 0.341-0.514, P = 0.103), and BCLC stage (AUC: 0.607, 95% CI: 0.521-0.693, P = 0.016) showed with inferior prediction significance (**Figure 5B**). Therefore, the combined GPR and fibrinogen possessed an excellent capacity in prognostic prediction both for DFS and OS in HCC patients after liver resection.

Discussion

Despite recent advances in HCC prevention, diagnosis and treatments, the disease is still one of the leading causes of cancer-related deaths worldwide [1]. In China, HCC-related morbidity and mortality remains high, mainly due to prevalence of viral hepatitis (especially hepatitis B) [2]. Persistence of hepatitis and liver cirrhosis promotes development and progression of HCC, while its recurrence severely hampers the prognosis of HCC patients. It is, therefore, important to stratify patients using different risk scores by identifying novel and effective biomarkers to guide personalized surveillance, treatment, and recurrence prevention of HCC.

Inflammation-related biomarkers are considered useful predictors for prognosis of many kinds of cancers [10, 11, 18, 19]. And the relationship between inflammation and HCC has also been comprehensively investigated in experimental and clinical studies [14, 20]. Recently, a new simple model, gamma-glutamyl transpeptidase to platelet ratio (GPR), which is calculated by the gamma-glutamyl transpeptidase and platelet count and relates to inflammation, was put forward by Lemoine and co-workers [12]. The model was first proposed as a new, simple and noninvasive laboratory parameter for detecting liver cirrhosis in patients with chronic HBV (CHB) infection [12]. In a patient cohort from west Africa, GPR revealed excellent diagnostic accuracy for fibrosis and cirrhosis than aspartate transaminase-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4). This diagnostic performance was further validated in cohorts from France and Senegal, indicating that GPR might serve as a stable and highly cost-effective index for predicting cirrhosis. Similarly, Boyd and co-workers [21] demonstrated that GPR could be adopted as a non-invasive indicator for predicting fibrosis in HIV-HBV co-infected subjects. And Shimakawa and co-workers [22] also validated the comparative performance of GPR in HCV-infected patients. However, Li and co-workers [23, 24], while comparing GPR with APRI and FIB-4 in Chinese patients with chronic HBV infection, found the model had no such advantages in the overall cohort, although it exhibited diagnostic superiority in certain populations with positive HBeAg, high HBV-DNA and normal or mildly elevated

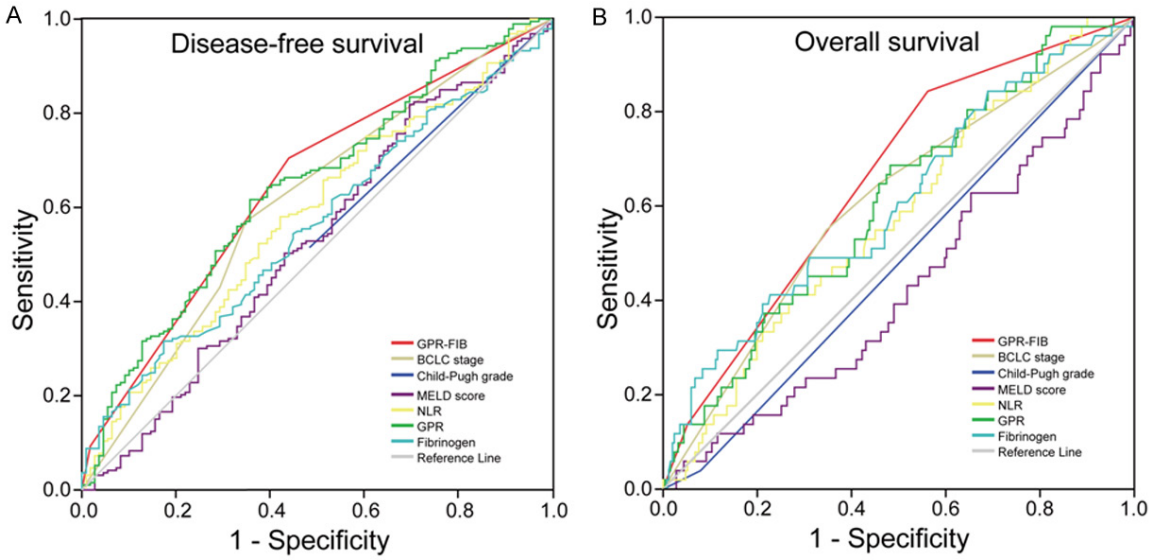

Figure 5. The ROC curves of GPR, fibrinogen, and other indexes for DFS (A) and OS (B) in patients with HBV-related HCC after hepatectomy. The composite index with combination of GPR and fibrinogen (GPR-FIB) showed superior prediction performance both for DFS (Area under the curve, AUC: 0.646) and OS (AUC: 0.657), which was better than GPR, fibrinogen, NLR, Child-Pugh grade, MELD score and BCLC stage.

alanine transaminase (ALT). In another study using a large cohort, Zhang and co-workers [25] reassessed GPR's performance and recommended it as a suitable noninvasive marker for diagnosing liver fibrosis as well as dynamic evaluation of treatment response in Chinese patients with CHB. A recent meta-analysis further validated the GPR model, and found moderate diagnostic accuracy for predicting HBV-related significant fibrosis, severe fibrosis, and cirrhosis [26]. Based on results of the aforementioned studies, GPR has the potential as a reliable index for evaluating the extent of liver fibrosis and cirrhosis.

Considering prevalence of background liver disease with viral hepatitis in HCC patients, it is possible that factors associated with cirrhosis might also play a role in the development of liver cancer. GGT, one of the key enzymes involved in glutathione synthesis and metabolism, has also been revealed to participate in the oxidant reactions and act as an oxidative stress marker, which is closely related to tumor formation, cell proliferation and apoptosis [27]. Besides, GGT is also correlated with inflammation as it could be induced by some inflammatory cytokines [28]. Consequently, an increasing number of studies demonstrated the close relationships between GGT and various tumors as a diagnostic or prognostic biomarker [27, 29]. And some studies also found HCC patients with elevated level of GGT presented with worse DFS and OS [27, 30, 31]. With reference to platelet, a great deal of evidence shows that it plays an important role in the occurrence and development of tumor [32-35]. It was demonstrated that platelet and its lysates could promote the proliferation and invasion of hepatoma cells, and the synthesis of some growth factors and cytokines could also been promoted by platelet to help the tumor growth [33, 35, 36]. Clinical studies also found that cancer patients with elevated platelet levels usually have worse prognosis [37, 38]. Therefore, based on the pathological and clinical significance of GGT and platelet in HCC, several researchers evaluated the predictive power of GPR in predicting HCC development in patients with CHB. For instance, Park and co-workers [17] found significantly higher GPR in patients with HCC, indicating that it was an independent predictor for HCC development. Besides, the predictive value of GPR was found to be maintained in different subgroups stratified by antiviral treatments and cirrhosis. Recently, Hu and co-workers [15] compared GPR in a large cohort of patients with HCC (N = 565) and cirrhosis (N = 441), and found an elevated GPR in HCC patients. Moreover, GPR was correlated with the BCLC stage, Child-Pugh grade, as well as tumor size, while its AUC in predicting HCC diag-

nosis was 0.853 (95% CI: 0.830-0.875). This indicates GPR's potential in diagnostic prediction of HBV-related HCC.

In addition, several studies have also reported the prognostic significance of GPR in prognosis of HCC patients. For instance, Ke and co-workers [16] investigated the prognostic value of GPR for short-term outcomes in 275 HCC patients who received anatomical minor liver resection and found it could be a promising predictor for overall and major complications after hepatectomy. Apart from its application in predicting short-term prognosis, several researchers have also accessed GPR's influence on the long-term outcomes of HCC patients. Consequently, several studies have reported that GPR is an independent prognostic factor for both DFS and OS in patients with HBV-related HCC [13, 39]. And a recent study also revealed that GPR had superior capacity in predicting prognosis of HBV-related HCC patients than many other inflammation-related scores [14]. In fact, those with higher GPR exhibited worse DFS and OS, which was consistent with our results. In this study, patients with HBV-related HCC were divided into two groups, of high and low GPR, using a cut-off value of 0.35 determined by the ROC curve. High GPR was associated with gender, history of smoking and drinking, cirrhosis, Child-Pugh grade, as well as tumor number, suggesting that GPR could predict certain medical history, liver function and tumor characteristics. Results from univariate and multivariate analyses revealed that patients with high GPR exhibited worse 1-, 3-, 5-year DFS and OS rates, indicating that high GPR was a prognostic risk factor.

Furthermore, comprehensive subgroup analyses within the cohort revealed that GPR possessed a reliable and effective strength in prognosis prediction for various HCC subgroups. Notably, in the present study, GPR showed a significant prognostic value for DFS in the subgroups of patients with and without cirrhosis. This was contrary to the study by Pang and co-workers [39], who found GPR to be a useful indicator of OS and RFS in patients without cirrhosis, but not in subjects with cirrhosis. This discrepancy may be partially explained by a difference in sample sizes between the two studies. Our study cohort comprised 204 (67.5%) cirrhosis patients, relative to only 86 (47.3%) in theirs. In addition, their study employed a higher cut-off value (0.76) which could have affected the prognostic significance. A large study cohort is, therefore, needed to validate these results. Furthermore, we also found a significant GPR in the subgroups with regards to tumor size (>/≤ 5 cm), tumor number (single/multiple), AFP (>/≤ 400 ng/mL), and BCLC stage (0-A/B-C), indicating that GPR could act as an effective prognostic marker for predicting long-term outcomes in patients with HBV-related HCC following hepatectomy, and across various HCC subgroups.

Fibrinogen, a soluble glycoprotein synthesized by hepatocytes, plays an important role in the coagulation system. Several studies have reported a relationship between fibrinogen and tumor progression and prognosis [40]. Particularly, elevated levels of fibrinogen were usually associated with poor outcomes in cancer patients, including HCC [41, 42]. In the present study, we found a correlation between fibrinogen and various tumor characteristics, including tumor diameter, vascular invasion, pathological differentiation, as well as BCLC stage. In addition, multivariate analysis revealed that the fibrinogen was also an independent prognostic factor for DFS and OS, which was consistent with previous studies. Recently, several researchers have attempted to extend fibrinogen's prognostic efficiency and accuracy by combining it with other parameters, including NLR, and C-reactive protein among others [43-46]. However, the prognostic value of combined GPR and fibrinogen has not been reported. In the current study, we hypothesized that the combination of GPR and fibrinogen could improve the prognosis prediction.

To investigate this, we combined GPR with fibrinogen and divided patients into three groups using the composite index. Results indicated that this combination resulted in a better prognostic prediction accuracy, suggesting that it could serve as a significant prognostic factor. Patients with GPR ≤ 0.35 and fibrinogen ≤ 4 g/L had the optimal 1-, 3-, 5-year DFS and OS rates, while those with GPR > 0.35 and fibrinogen > 4 g/L exhibited the worst rates. Furthermore, when compared with other prognostic models or indexes, the composite index (GPR-FIB) also showed superior prognostic predictions for both DFS and OS rates, owing to larger AUCs of ROC curves. Therefore, a combination of GPR and fibrinogen showed an advantage in

predicting long-term outcomes of patients with HBV-related HCC.

There are several limitations in the present study. Firstly, this was designed as a single-center retrospective study, which made it prone to inherent limitations including confounding, and selection bias, as well as missing values. Secondly, although all enrolled patients had a HBV infection background, a number of them exhibited HCV or HIV coinfections, which might introduce some biases in subsequent analyses. Thirdly, our results and conclusions lacked internal and external validation. Therefore, larger multi-center prospective studies in patients with different etiologies of hepatitis are needed during future investigations.

In conclusion, GPR could serve as a simple and effective predictor of DFS and OS in patients with HBV-related HCC following liver resection. In addition, a combination of GPR and fibrinogen improved prognostic accuracy in these patients.

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Disclosure of conflict of interest

None.

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