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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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ORIGINAL ARTICLE

Case Control Study

Prognostic utility of gamma-glutamyl transpeptidase to platelet ratio in patients with solitary hepatitis B virus-related hepatocellular carcinoma after hepatectomy

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Abstract

BACKGROUND

The prognostic impact of preoperative gamma-glutamyl transpeptidase to platelet ratio (GPR) levels in patients with solitary hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) following radical resection has not been established.

AIM

To examine the clinical utility of GPR for prognosis prediction in solitary HBV-related HCC patients.

METHODS

A total of 1167 solitary HBV-related HCC patients were retrospectively analyzed. GPR levels were compared with 908 non-HCC individuals. Overall survival (OS) and recurrence-free survival (RFS) were evaluated, and cox proportional hazard model analyses were performed to identify independent risk factors. Differences in characteristics were adjusted by propensity score matching (PSM). Subgroup and stratified survival analyses for HCC risks were performed, and a linear trend

of the hazard ratio (HR) according to GPR levels was constructed.

RESULTS

GPR levels of patients with solitary HBV-related HCC were higher than those with hepatic hemangiomas, chronic hepatitis B and healthy control (adjusted $P < 0.05$). Variable bias was diminished after the PSM balance test. The low GPR group had improved OS ($P < 0.001$) and RFS ($P < 0.001$) in the PSM analysis and when combined with other variables. Multivariate cox analyses suggested that low GPR levels were associated with a better OS (HR = 0.5, 95%CI: 0.36-0.7, $P < 0.001$) and RFS (HR = 0.57, 95%CI: 0.44-0.73, $P < 0.001$). This same trend was confirmed in subgroup analyses. Prognostic nomograms were constructed and the calibration curves showed that GPR had good survival prediction. Moreover, stratified survival analyses found that GPR > 0.6 was associated with a worse OS and higher recurrence rate (P for trend < 0.001).

CONCLUSION

Preoperative GPR can serve as a noninvasive indicator to predict the prognosis of patients with solitary HBV-related HCC.

Key Words: Gamma-glutamyl transpeptidase to platelet ratio; Hepatitis B virus; Hepatocellular carcinoma; Prognosis; Propensity score matching

Core Tip: In this study, we assessed the prognostic value of gamma-glutamyl transpeptidase to platelet ratio (GPR) in early hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) patients. We evaluated the clinical utility of preoperative GPR in predicting outcomes for solitary HBV-related HCC patients using propensity score matching, restricted cubic spline, survival analyses and stratified analyses. Preoperative GPR levels facilitate recurrence monitoring and inform treatment strategies, potentially enhancing the quality of life for HCC patients.

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INTRODUCTION

Worldwide there are 782500 new cases and 745500 deaths per year due to hepatocellular carcinoma (HCC), the most common primary liver cancer[1]. Environmental and individual risk factors include male sex, advanced age, obesity, type 2 diabetes, infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), cirrhosis, aflatoxin B1 exposure, alcohol abuse, smoking, and several metabolic factors[2,3]. Chronic HBV infection is an important risk factor for HCC, especially in Asia-Pacific regions, and accounts for > 50% of newly diagnosed HCC cases[4]. Although HBV can become inactive, chronic HBV infections can cause progressive liver fibrosis, which may evolve into HCC in patients with cirrhosis[5]. The annual incidence of HBV-related HCC in patients with chronic HBV infection ranges from 2% to 5% when cirrhosis is already established[6].

Surgical resection is regarded as a standard curative treatment for early and intermediate stages of HCC among appropriately selected patients[7]. However, 5-year recurrence rates of HCC patients after curative hepatectomy are as high as 70%–80%, which hinders their long-term survival[8,9]. Clinical outcomes following surgery differ widely and such large variation is mostly unexplained. This variation becomes an obstacle to finding effective therapies and strategies for cancer management. Therefore, it is important to identify risk factors associated with postoperative recurrence and death to avoid subsequent consequences after HCC resection.

Liver puncture biopsy is an invasive procedure and the gold standard for ascertaining the degree of liver fibrosis and damage. Previous studies have found that various non-invasive methods based on routine laboratory tests can predict liver fibrosis, cirrhosis, and even the risk of developing HCC, including the fibrosis-4 index[10], aspartate aminotransferase-platelet index[11], and albumin-bilirubin score[12]. Interestingly, a previous study demonstrated that the gamma-glutamyl transpeptidase to platelet ratio (GPR) is an accurate indicator of chronic hepatic fibrosis in patients with chronic HBV infection[13]. In addition, the relative risk of HCC development was significantly increased within chronic HBV patients with high GPR levels[14]. Dai *et al*[15] reported that preoperative GPR could be an effective non-invasive predictor for the prognosis of HCC patients after hepatectomy[15]. A meta-analysis encompassing 10 studies with 4706 patients indicated that HCC patients with higher GPR exhibited poorer clinical outcomes compared to those with lower GPR, suggesting that GPR is a valid prognostic biomarker for HCC. Furthermore, elevated GPR may signal a deteriorating prognosis in postoperative HCC patients[16]. According to the Chinese guidelines for the diagnosis and treatment

of primary liver cancer[17], Chinese patients with single nodule liver cancer are considered to be in the early stage, and surgical resection is the preferred treatment method. Previous research has demonstrated that the GPR value is a potential prognostic indicator for the occurrence of both overall postoperative and major complications following minor hepatectomy in patients with HCC[18]. However, no study has investigated the prognostic effect of preoperative GPR levels in patients with solitary HBV-related HCC after radical resection.

In the present study, we explored the critical importance of preoperative GPR as a prognosis factor for HBV-related HCC through propensity score matching (PSM), and survival and stratified analyses.

MATERIALS AND METHODS

Study population

We enrolled patients who underwent curative HCC resection between January 2012 and December 2018 at the Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University.

Inclusion criteria were as follows: (1) The 18 years of age or older; (2) Medical history of chronic HBV infection; (3) HBV-related HCC was confirmed histopathologically after initial hepatectomy, without previous treatment; (4) Patients presented solitary HCC without gross vascular invasion, bile duct tumor thrombosis, satellite nodules or extrahepatic metastasis upon preoperative clinical imaging and histopathological examination; (5) Child-Pugh classification A or B; and (6) Negative surgical margin observed microscopically or macroscopically upon resection.

Exclusion criteria: (1) Patients with concurrent malignancies; (2) Patients deemed unsuitable for surgery due to either poor tolerance or insufficient residual liver volume to ensure surgical feasibility; (3) Patients diagnosed with hepatic neoplasms of mixed histology; (4) Recurrent HCC; and (5) Non-HBV infection. A total of 1167 patients were enrolled, of whom 172 patients were Barcelona Clinic Liver Cancer (BCLC) stage 0, and 995 patients were BCLC stage A.

To evaluate GPR levels, a total of 908 participants (age ≥ 18 years and ≤ 80 years, males and females) were enrolled from the First Affiliated Hospital of Guangxi Medical University, including 28 patients with hepatic hemangiomas, 242 healthy control, 67 patients with nonalcoholic fatty liver, 224 patients with chronic hepatitis B, 84 patients with chronic hepatitis C, 245 patients with post-hepatitis cirrhosis, and 18 patients with alcoholic cirrhosis. Eligibility criteria were as follows: (1) Liver cirrhosis detected by liver biopsy or supported by two imaging techniques, with chronic hepatitis infection or alcoholism history; (2) Chronic hepatitis defined as hepatitis B surface antigen or hepatitis C antibodies positive for at least 6 months, with confirmed of HBV or HCV infection; (3) Nonalcoholic fatty liver and hepatic hemangiomas were diagnosed by two clinical imaging methods, in patients with no history of hepatitis infection; and (4) Healthy individuals were confirmed to have no liver or gastrointestinal diseases, no history of other malignancies, and were serologically negative for hepatitis viruses.

This study was approved by The Ethics Committee of The First Affiliated Hospital of Guangxi Medical University, China, No. 2024-E638-01. All participants signed written informed consent before study commencement.

Data acquisition and pre-processing

Medical records of HBV-related HCC were reviewed to extract information on baseline characteristics and pathological variables. Histopathological examination confirmed the diagnosis of cirrhosis. Tumor stage after operation was determined following the BCLC staging system. Cutoff values of continuous variables were based on those used commonly in upper and lower clinical limits or median values of subjects. GPR was defined as gamma-glutamyl transpeptidase (GGT) (U/L)/platelet count (× 10^9/L). The above indicators are derived from the latest preoperative clinical data of each patient. The x-tile program[19] was used to generate the optimal GPR cutoff point with minimum P values from χ^2 tests. Therefore, the cutoff value of GPR was set as 0.2. In particular, the tercile stratification thresholds for GPR were set at 0.2 and 0.6.

Follow-up

After surgery, all patients were followed-up for at least one year. During the first postoperative year, outpatient surveillance was conducted at 3-month intervals, and then every 6-month thereafter by outpatient visits or telephone calls until death or up to January 31, 2022. Serum alpha-fetoprotein (AFP) assay, ultrasonography, and chest radiography were routinely performed. Enhanced computed tomography was performed every 6 months. Based on this surveillance, the overall survival (OS) time was defined as the time from surgery to death (any cause) or to the interruption of follow-up. The recurrence-free survival (RFS) time was defined as the time from surgery to HCC recurrence, including the appearance of intrahepatic tumor nodule(s) with radiologic features consistent with HCC, with or without a rise in serum AFP levels, or follow-up interruption.

PSM

PSM analysis was used to adjust for differences in baseline characteristics and to minimize biases of variable selection. With a 0.05 standardized difference as the caliper, a 1:1 matching was performed using the nearest neighbor method. Standardized mean differences were used to assess the balanced distribution of matched patients within each group. A mean difference value higher than 0.1 was considered imbalanced. Matching variables included sex, age, body mass index, smoking history, drinking history, history of liver fluke disease, liver cirrhosis, alpha-fetoprotein, tumor size, liver function grade, microvascular imaging (MVI), *etc.* After PSM, both low and high GPR groups included 328 patients

(Figure 1). Three groups of PSM analysis were further matched by R packet TriMatch[20].

Statistical analysis

Descriptive analysis of clinicopathological features was assessed using Pearson's χ^2 and Wilcoxon rank sum tests, as appropriate. Survival analysis was performed through the Kaplan-Meier method to estimate the survival rates for different groups. The log-rank test was used to evaluate the statistical significance of the equivalences of the survival curves. To evaluate the association between variables and endpoints, a cox proportional hazards model was constructed for univariate and multivariate survival analyses to calculate the hazard ratio (HR) and 95%CI. In multivariable analyses, we used forward stepwise selection of covariates that were $P < 0.05$ in the univariate regression. Restricted cubic spline (RCS) analyses were performed to determine the association between continuous GPR levels and death/recurrence risks. Interaction analyses, combined analyses, and nomograms were utilized to explore the comprehensive effects of GPR levels and subgroup parameters on the prognosis of HCC. Statistical significance for a linear trend of HR across stratified GPR levels and clinical outcomes of patients was tested. $P < 0.05$ indicated a statistically significant difference.

All analyses were performed in x-tile (version 3.6.1), R (version 3.6.2, https://www.r-project.org/) and Statistical Package for the Social Sciences version 24.0 (IBMCorp., Chicago, IL, United States).

RESULTS

A flow diagram summarizing the present work is shown in Figure 1.

GPR level comparisons

Pairwise comparison of GPR levels revealed that GPR levels of solitary HBV-related HCC patients were higher than those of patients with hepatic hemangiomas, chronic hepatitis B and healthy controls (adjusted $P < 0.05$) (Figure 2). However, no significant difference was found between patients with HBV-related HCC and post-hepatitis cirrhosis.

PSM balance test

To adjust for differences in baseline characteristics, associated covariates were entered into the propensity model. After the PSM balance test, the distribution of propensity scores in the high and low GPR groups were similar (Figure 3A). Moreover, all variables were within a reasonable range (overall distance fell within the caliper) after adjusting for solitary HCC patients with GPR ≤ 0.2 and GPR > 0.2 (Figure 3B).

Characteristics of the study population

Comparisons of baseline characteristics and clinicopathological features among early-stage solitary HCC patients with GPR ≤ 0.2 and GPR > 0.2 before and after PSM are presented in Table 1. Before PSM, there were differences between the groups in several variables, including sex, smoking, drinking, liver flukes, cirrhosis, serum AFP level, total bilirubin, albumin, GGT, HBV DNA, tumor size and infiltrative growth ($P < 0.05$) (Table 1). After PSM, the clinicopathological variables of the two groups were balanced, and the two groups were comparable (Table 1). Although some differences in the serum AFP and total bilirubin, the overall distance of propensity scores is still within a reasonable range (Figure 3B).

Survival analysis

Survival curve and Cox proportional hazards model analyses showed that, compared with the high GPR group (GPR > 0.2), low GPR patients had a better OS time and risk value upon univariate analyses (log-rank $P < 0.001$, HR = 0.48, 95%CI: 0.36-0.64, $P < 0.001$) (Figure 3C and Table 2). After matching, the low GPR group was shown to have a better OS and risk than the high GPR group of patients with early-stage solitary HCC (log-rank $P < 0.001$, HR = 0.49, 95%CI: 0.35-0.69, $P < 0.001$) (Figure 3D and Table 2). Similarly, compared with the high GPR group (GPR > 0.2), patients in the low GPR group had improved RFS and risk values (log-rank $P < 0.001$, HR = 0.49, 95%CI: 0.4-0.6, $P < 0.001$) (Figure 3E and Table 3). Indeed, after matching, the low GPR group had improved RFS and risk (log-rank $P < 0.001$; HR = 0.56, 95%CI: 0.44-0.71, $P < 0.001$) (Figure 3F and Table 3). Moreover, some clinical features were related to tumor prognosis, such as tumor size, cirrhosis, and HBV-DNA (Table 2 and Table 3). Results from the multivariate analysis suggest that preoperative low GPR levels were independently associated with a better OS (HR = 0.5, 95%CI: 0.36-0.7, $P < 0.001$) and RFS (HR = 0.57, 95%CI: 0.44-0.73, $P < 0.001$) (Table 3).

Subgroup and combined analyses by baseline characteristics

To explore more deeply the predictive value of GPR levels for the prognosis of early-stage solitary HBV-related HCC patients, we performed subgroup analyses based on baseline characteristics. Patients in each group were divided into subgroups with low and high GPR levels. Among subgroups, low preoperative GPR levels were significantly associated with an improved OS when compared to those that had high GPR levels (Figure 4A). A strong interaction was found between GPR and HBV-DNA copies (P for interaction = 0.015) (Figure 4A). Indeed, the forest plot depict that the risk of RFS was improved in patients with low GPR values among each subgroup of baseline characteristics (Figure 4A). Importantly, a significant interaction between GPR and tumor size was observed (P for interaction = 0.032) (Figure 4A). Combined analyses showed that a low GPR coupled with a tumor size ≤ 5 cm, absence of cirrhosis, AFP < 200 ng/mL, and no MVI predicted a favorable OS after PSM (Figure 4B). Conversely, high GPR levels coupled with tumor size > 5 cm, AFP ≥ 200 ng/mL, the presence of cirrhosis and MVI predicted a shorter recurrence time (Figure 4C).

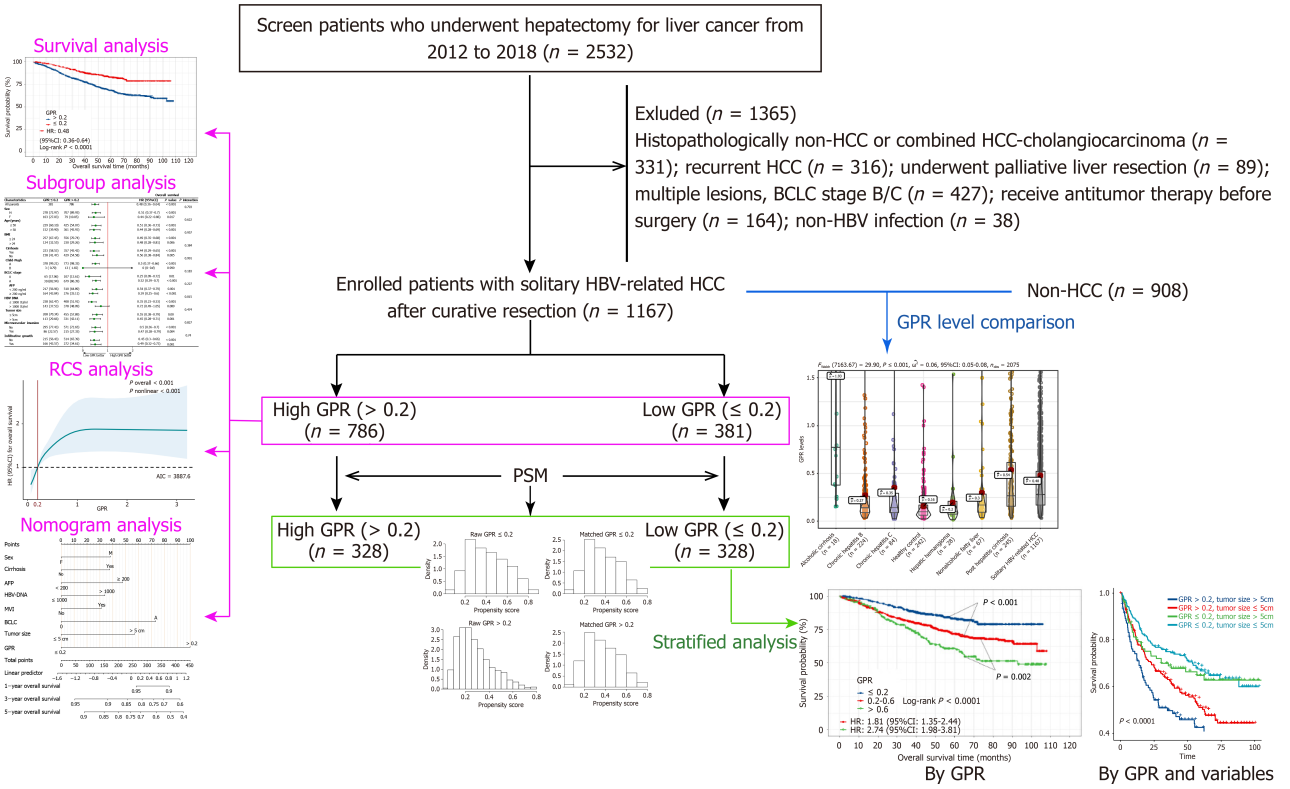


Figure 1 Flow diagram of the propensity score analysis for this study. GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; RCS: Restricted cubic spline; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer.

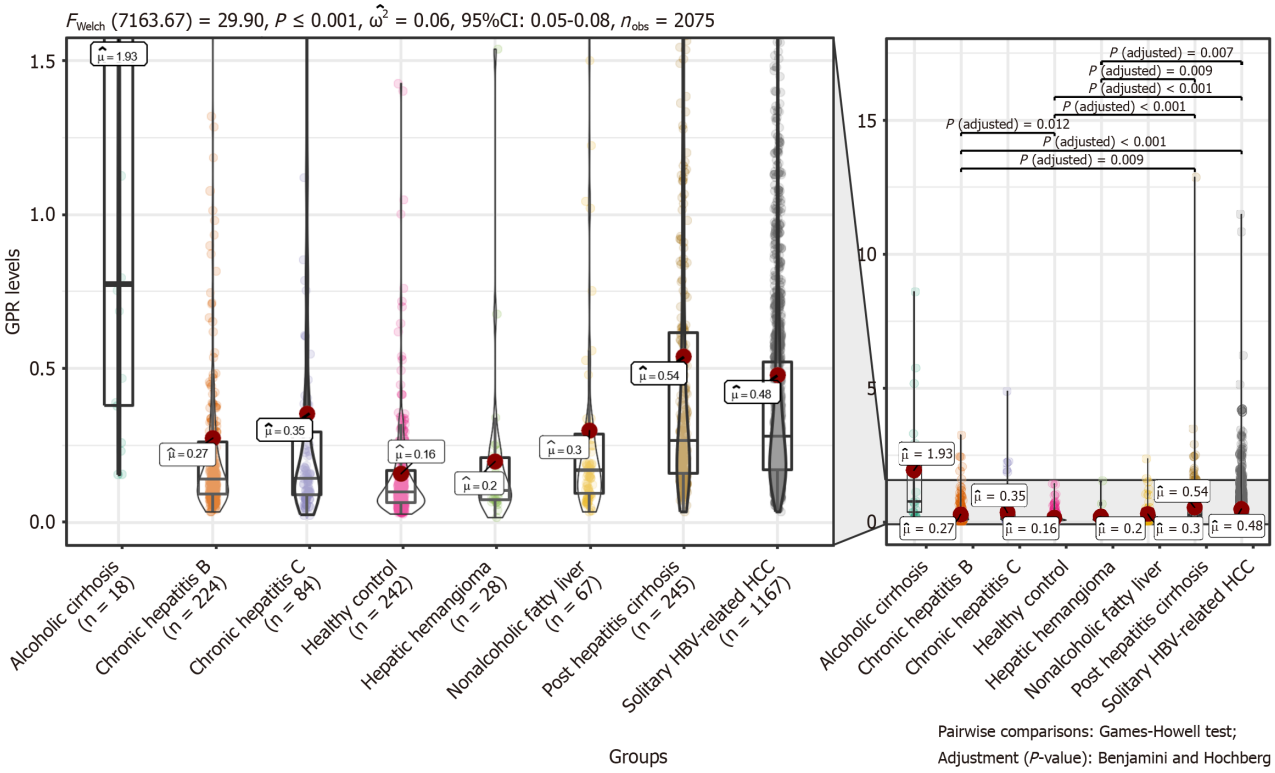
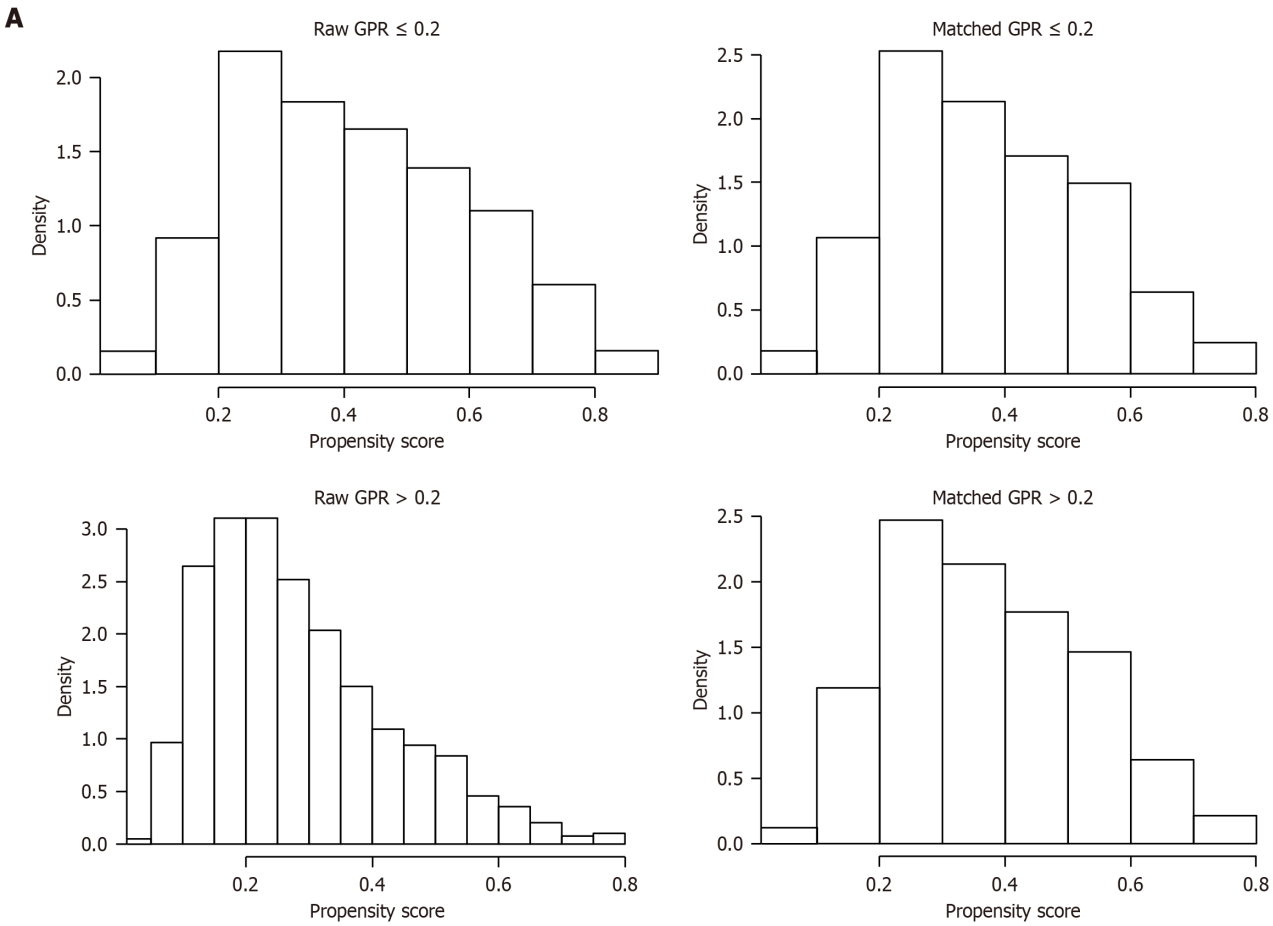
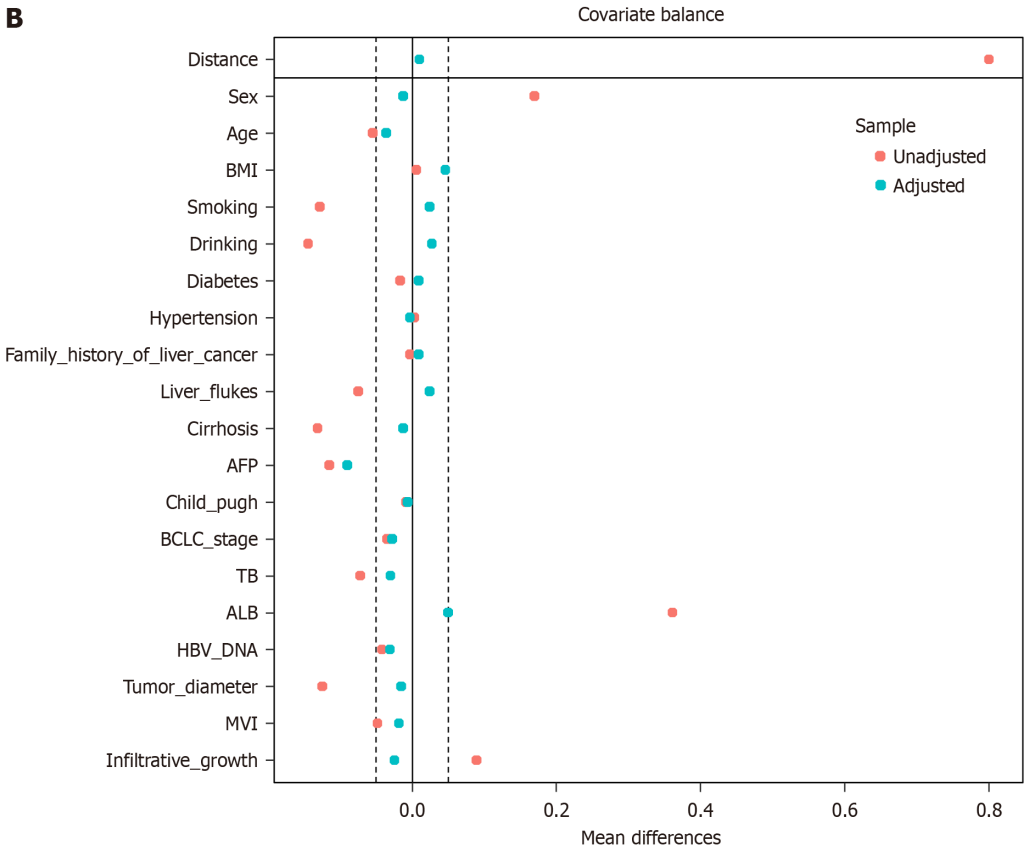


Figure 2 Violin plot analysis comparing the gamma-glutamyl transpeptidase-to-platelet ratio levels among hepatitis B virus-related hepatocellular carcinoma and other 7 non-hepatocellular carcinoma groups. Pairwise comparisons were performed by Games-Howell test, and *P* value was adjusted by Benjamini-Hochberg methods.


A
Raw GPR ≤ 0.2
Matched GPR ≤ 0.2
Raw GPR > 0.2
Matched GPR > 0.2
Density
Propensity score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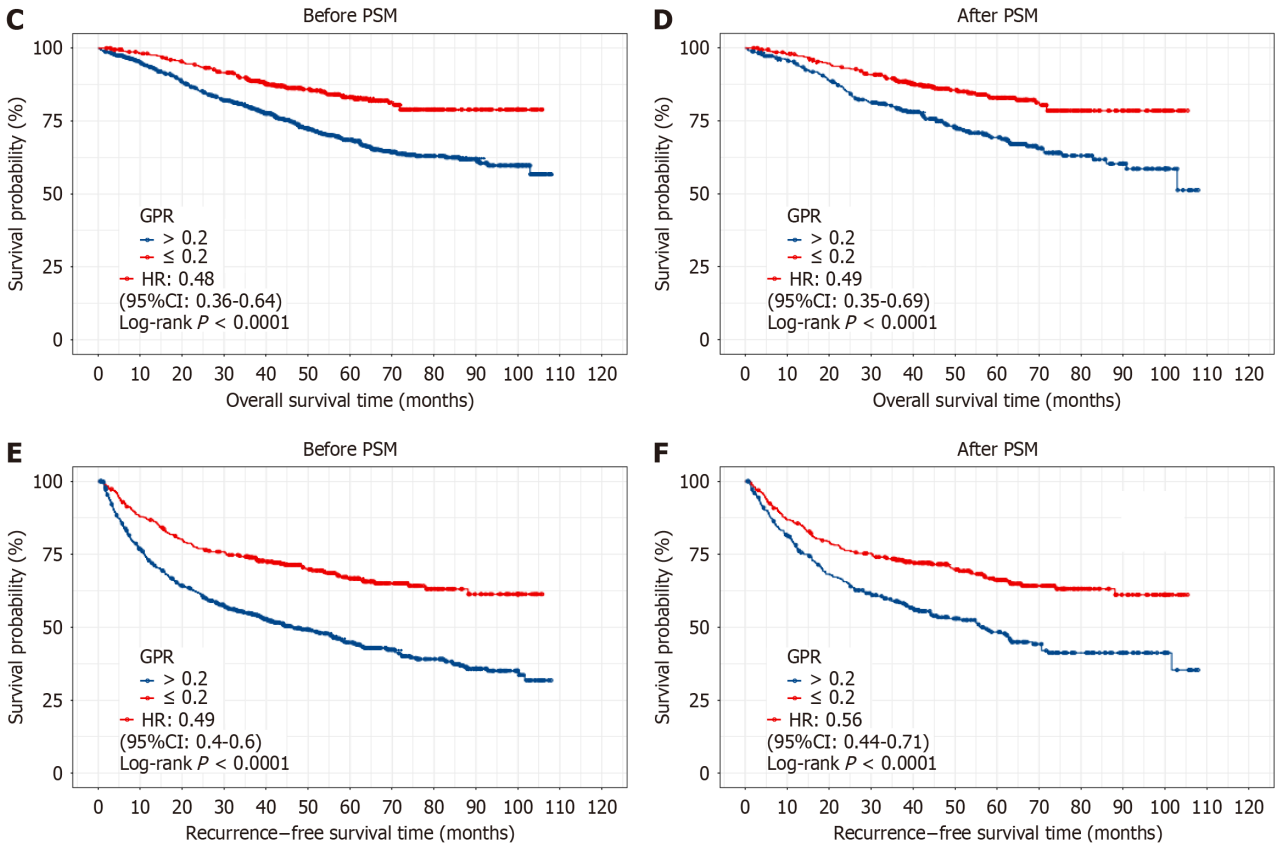


Figure 3 The balance test of propensity score matching and KaplanMeier analysis between gamma-glutamyl transpeptidase-to-platelet ratio level and prognosis of solitary hepatitis B virus-related hepatocellular carcinoma cohort. A: Distribution of propensity values before and after propensity score matching (PSM); B: Absolute standardized differences in covariates between solitary hepatocellular carcinoma (HCC) patients with gamma-glutamyl transpeptidase-to-platelet ratio (GPR) ≤ 0.2 and GPR > 0.2, before and after PSM; C and D: Kaplan-Meier survival curves of overall survival in patients with solitary HCC before and after PSM; E and F: Kaplan-Meier survival curves of RFS in patients with solitary HCC before and after PSM. PSM: Propensity score matching; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; BMI: Body mass index; HR: Hazard ratio; AFP: Alpha-fetoprotein; TB: Total bilirubin; ALB: Albumin; HBV: Hepatitis B virus; MVI: Microvascular imaging.

Stratified and RCS analyses by GPR levels

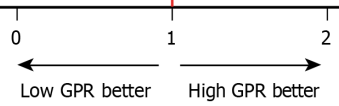
RCS curves demonstrated that the association between continuous GPR levels and death/recurrence risks presented as a non-linear trend, with or without variables adjustments ($P < 0.001$) (Figure 5A). Per standardized difference increased in GPR levels were associated with a 1.29 (1.18-1.42) HR increase in OS after PSM (Table 4). Moreover, the HR for RFS of HCC patients after hepatectomy was positively correlated with elevated GPR level per standardized difference change (HR = 1.20, 95%CI: 1.11-1.31, $P < 0.001$) (Table 4). To verify if GPR levels could predict the prognosis of patients with solitary HBV-related HCC, a GPR-based risk assessment divided patients into three groups, namely the GPR > 0.2 group was stratified as intermedial GPR levels (0.2 < GPR ≤ 0.6) and high GPR levels (GPR > 0.6). Compared with patients at the bottom tercile for preoperative GPR (GPR ≤ 0.2), patients in the middle tercile had worse OS and RFS ($P < 0.001$) (Figure 5B). Moreover, those in the top tercile group had even lower OS (HR = 2.74; 95%CI: 1.98–3.81, P for trend < 0.001) and RFS values (HR = 2.60; 95%CI: 2.04–3.31, P for trend < 0.001) (Figure 5B and Table 4). After matching analysis, the triangle chart showed the correlation among the matching items in each group, and the absolute standard deviation was well adjusted (Figure 5C). Indeed, after PSM, intermedial GPR level was associated with worse prognosis in terms of OS (HR = 1.52, 95%CI: 1.08–2.14, log-rank $P < 0.001$) and RFS (HR = 1.69, 95%CI: 1.25–2.17, log-rank $P < 0.001$) (Figure 5D). Furthermore, high GPR levels were associated with worse prognosis of postoperative patients with HCC, including shorter OS (HR = 2.33, 95%CI: 1.60–3.39, P for trend < 0.001) and RFS (HR = 2.35, 95% CI: 1.77–3.13, P for trend < 0.001) (Figure 5D and Table 4). We detected an increased linear trend for HR in patients stratified according to their GPR levels (P for trend < 0.001) (Table 4). Besides, Kaplan-Meier curves of OS and RFS were statistically different among GPR-stratified patients with or without adjusting for PSM (all $P < 0.05$) (Figure 5). Therefore, a high GPR level is enough to warrant HCC surveillance before liver resections.

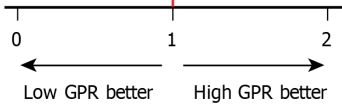
Construction of prognostic nomograms

According to the univariate Cox analysis results of the variables and clinical prognosis before PSM, clinical variables that may be associated factors ($P < 0.05$) were included in the model construction. Thus, we developed two survival nomograms to predict OS (Figure 6A) and RFS (Figure 6B). The c-indexes of the OS and RFS nomograms were respectively 0.732 (95%CI: 0.669-0.795) and 0.756 (95%CI: 0.723-0.785). Moreover, calibration curves demonstrated that the nomograms predicted the 1-year, 3-years, and 5-years OS and RFS with a high resolution and accuracy.

A

Characteristics	GPR ≤ 0.2	GPR > 0.2	Overall survival HR (95%CI)	*P* value	*P* interaction	Recurrence-free survival HR (95%CI)	*P* value	*P* interaction
All parents	381	786	0.48 (0.36–0.64)	< 0.001		0.49 (0.4–0.6)	< 0.001	
Sex					0.793			0.359
M	278 (72.97)	707 (89.95)	0.51 (0.37–0.7)	< 0.001		0.47 (0.37–0.6)	< 0.001	
F	103 (27.03)	79 (10.05)	0.44 (0.22–0.86)	0.017		0.6 (0.38–0.95)	0.03	
Age (years)					0.622			0.849
≤ 50	229 (60.10)	425 (54.07)	0.51 (0.36–0.73)	< 0.001		0.5 (0.39–0.65)	< 0.001	
> 50	152 (39.90)	361 (45.93)	0.44 (0.28–0.69)	< 0.001		0.47 (0.34–0.64)	< 0.001	
BMI					0.957			0.473
≤ 24	257 (67.45)	556 (70.74)	0.49 (0.35–0.68)	< 0.001		0.47 (0.37–0.59)	< 0.001	
> 24	124 (32.55)	230 (29.26)	0.48 (0.28–0.81)	0.006		0.54 (0.38–0.78)	0.001	
Cirrhosis					0.384			0.15
Yes	223 (58.53)	357 (45.42)	0.44 (0.29–0.65)	< 0.001		0.43 (0.33–0.58)	< 0.001	
No	158 (41.47)	429 (54.58)	0.56 (0.38–0.84)	0.005		0.58 (0.44–0.77)	< 0.001	
Child-Pugh					0.991			0.987
A	378 (99.21)	773 (98.35)	0.5 (0.37–0.66)	< 0.001		0.49 (0.4–0.6)	< 0.001	
B	3 (0.79)	13 (1.65)	0 (0–Inf)	0.999		0 (0–Inf)	0.999	
BCLC stage					0.183			0.464
0	65 (17.06)	107 (13.61)	0.25 (0.09–0.72)	0.01		0.57 (0.34–0.96)	0.034	
A	316(82.94)	679 (86.39)	0.52 (0.39–0.7)	< 0.001		0.48 (0.38–0.59)	< 0.001	
AFP					0.227			0.339
< 200 ng/ml	217 (56.96)	510 (64.89)	0.54 (0.37–0.79)	0.001		0.51 (0.39–0.67)	< 0.001	
≥ 200 ng/ml	164 (43.04)	276 (35.11)	0.39 (0.25–0.6)	< 0.001		0.43 (0.32–0.58)	< 0.001	
HBV DNA					0.015			0.062
≤ 1000 IU/ml	238 (62.47)	408 (51.91)	0.35 (0.23–0.53)	< 0.001		0.42 (0.32–0.55)	< 0.001	
> 1000 IU/ml	143 (37.53)	378 (48.09)	0.72 (0.49–1.05)	0.089		0.61 (0.46–0.83)	0.001	
Tumor size					0.474			0.032
≤ 5cm	268 (70.34)	455 (57.89)	0.55 (0.38–0.79)	0.00		0.59 (0.46–0.76)	< 0.001	
> 5cm	113 (29.66)	331 (42.11)	0.45 (0.28–0.71)	0.001		0.39 (0.28–0.56)	< 0.001	
Microvascular invasion					0.827			0.476
No	295 (77.43)	571 (72.65)	0.5 (0.36–0.7)	< 0.001		0.47 (0.37–0.59)	< 0.001	
Yes	86 (22.57)	215 (27.35)	0.47 (0.28–0.79)	0.004		0.56 (0.39–0.81)	0.002	
Infiltrative growth					0.74			0.872
No	215 (56.43)	514 (65.39)	0.45 (0.3–0.66)	< 0.001		0.47 (0.35–0.61)	< 0.001	
Yes	166 (43.57)	272 (34.61)	0.49 (0.32–0.73)	0.001		0.48 (0.36–0.65)	< 0.001	





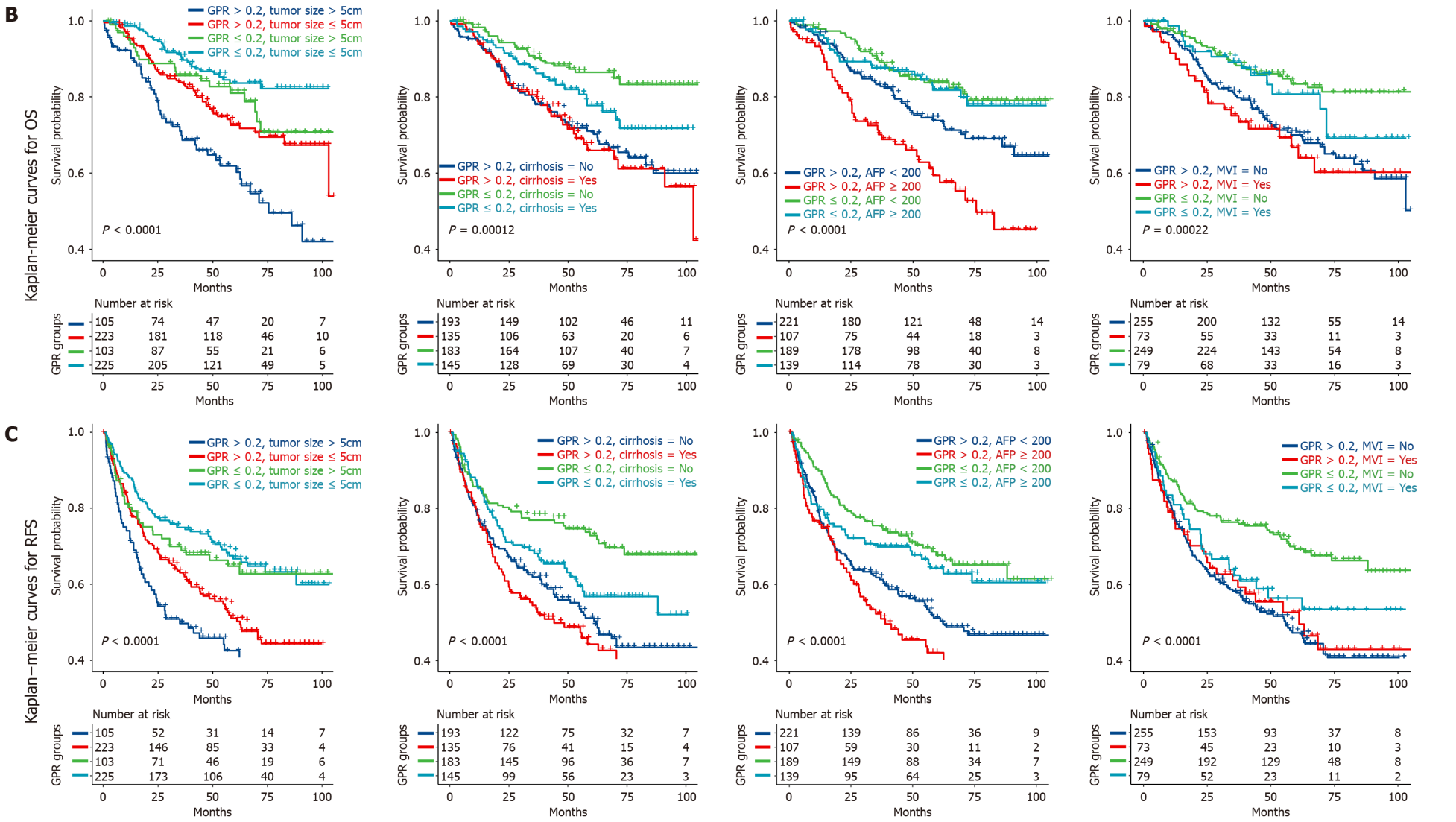
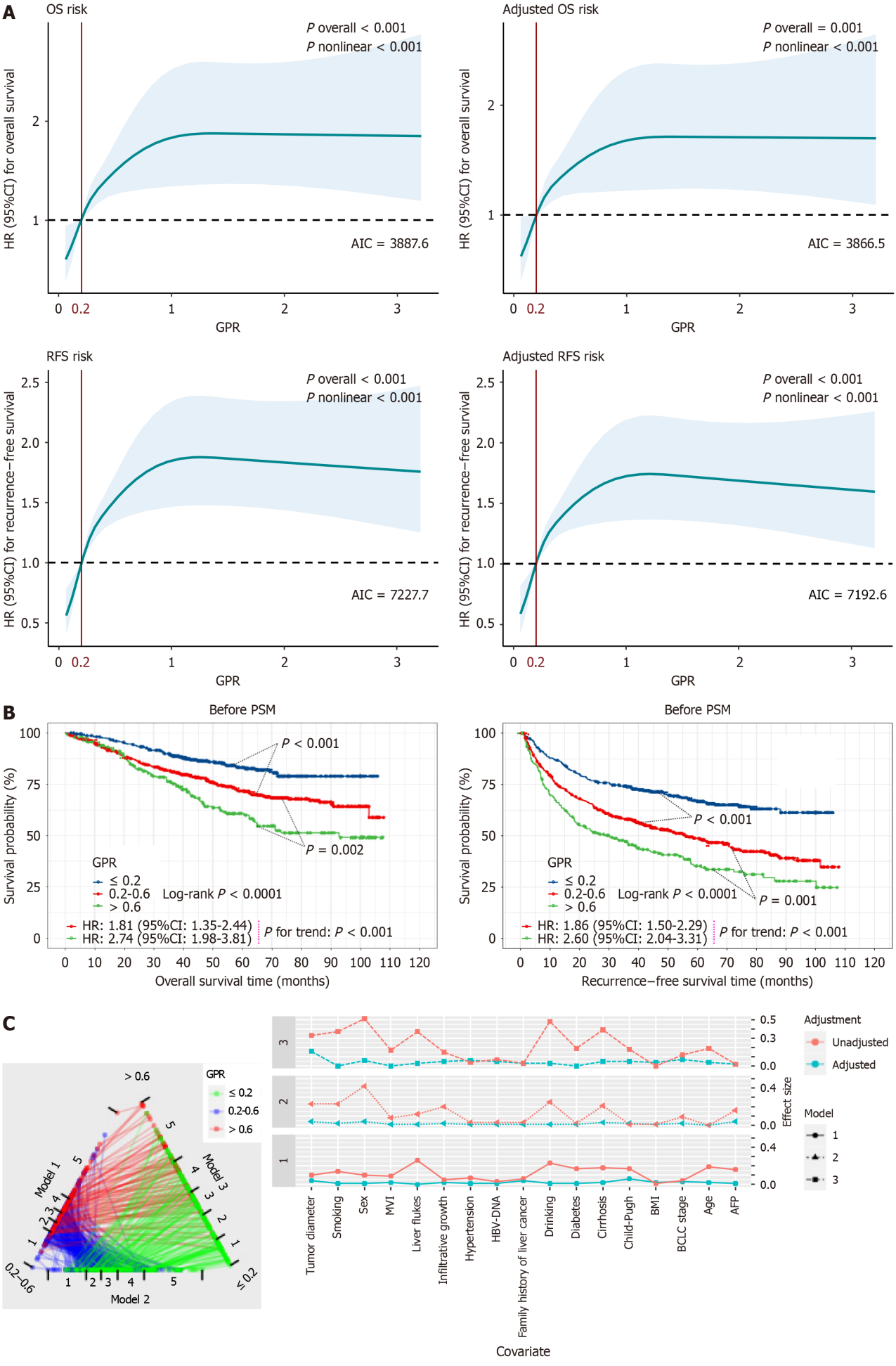


Figure 4 Subgroup analyses for gamma-glutamyl transpeptidase-to-platelet ratio level and combined analyses of gamma-glutamyl transpeptidase-to-platelet ratio levels and variables in overall survival and recurrence-free survival of solitary hepatitis B virus-related hepatocellular carcinoma. A: Subgroup analyses for overall survival (OS) and recurrence-free survival (RFS); B: Combined analyses with tumor size, cirrhosis, alpha-fetoprotein (AFP), and microvascular imaging (MVI) for OS; C: Combined analyses with tumor size, cirrhosis, AFP, and MVI for RFS. GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; HR: Hazard ratio; OS: Overall survival; BMI: Body mass index; HR: Hazard ratio; AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; BCLC: Barcelona Clinic Liver Cancer; F: Female; M: Male.


A
OS risk
P overall < 0.001
P nonlinear < 0.001
HR (95%CI) for overall survival
AIC = 3887.6
GPR
Adjusted OS risk
P overall = 0.001
P nonlinear < 0.001
AIC = 3866.5
RFS risk
P overall < 0.001
P nonlinear < 0.001
HR (95%CI) for recurrence−free survival
AIC = 7227.7
Adjusted RFS risk
P overall < 0.001
P nonlinear < 0.001
AIC = 7192.6
B
Before PSM
Survival probability (%)
P < 0.001
P = 0.002
GPR
≤ 0.2
0.2-0.6
> 0.6
Log-rank P < 0.0001
HR: 1.81 (95%CI: 1.35-2.44)
HR: 2.74 (95%CI: 1.98-3.81)
P for trend: P < 0.001
Overall survival time (months)
Before PSM
P < 0.001
P = 0.001
Log-rank P < 0.0001
HR: 1.86 (95%CI: 1.50-2.29)
HR: 2.60 (95%CI: 2.04-3.31)
P for trend: P < 0.001
Recurrence−free survival time (months)
C
GPR
≤ 0.2
0.2-0.6
> 0.6
Model 1
Model 2
Model 3
Adjustment
Unadjusted
Adjusted
Model
Effect size
Tumor diameter
Smoking
Sex
MVI
Liver flukes
Infiltrative growth
Hypertension
HBV-DNA
Family history of liver cancer
Drinking
Diabetes
Cirrhosis
Child-Pugh
BMI
BCLC stage
Age
AFP
Covariate

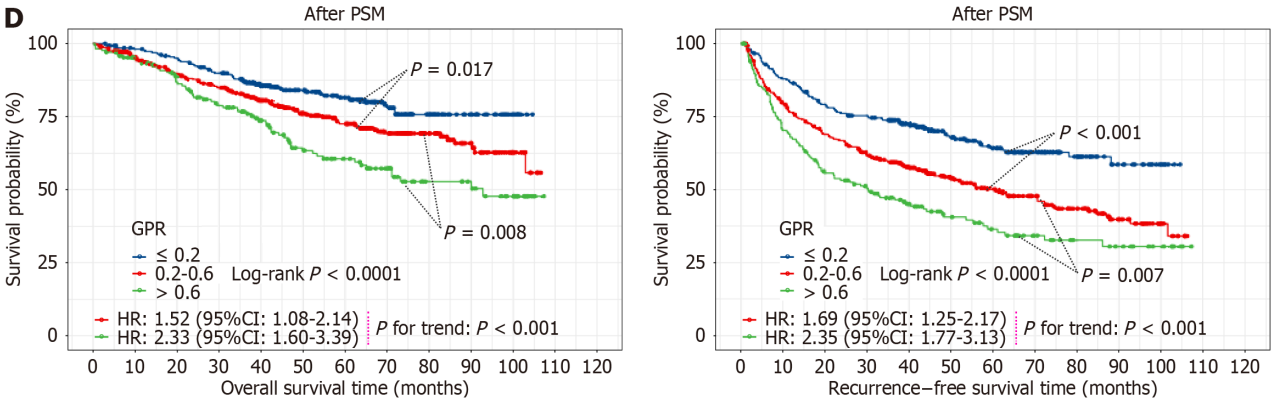


Figure 5 The association between gamma-glutamyl transpeptidase-to-platelet ratio and death/recurrence risk and Kaplan-Meier stratified analysis between gamma-glutamyl transpeptidase-to-platelet ratio levels and prognosis in the solitary hepatitis B virus-related hepatocellular carcinoma cohort. A: The restricted cubic spline curves of gamma-glutamyl transpeptidase-to-platelet ratio levels. The risk was adjusted by age, cirrhosis, hepatitis B virus-DNA, tumor size, microvascular imaging, and infiltrative growth; B: Kaplan-Meier survival curves of overall survival (OS) and recurrence-free survival (RFS) in patients with solitary hepatocellular carcinoma (HCC) before propensity score matching (PSM); C: Triangle plot and absolute standardized differences adjustment of three groups; D: Kaplan-Meier survival curves of OS and RFS in patients with solitary HCC after PSM. OS: Overall survival; PSM: Propensity score matching; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; MVI: Microvascular imaging; HBV: Hepatitis B virus; BCLC: Barcelona Clinic Liver Cancer; BMI: Body mass index; HR: Hazard ratio; AFP: Alpha-fetoprotein.

DISCUSSION

HCC is a common malignant tumor with high recurrence rates and cancer mortality. Previous studies have found that the ratio of routine blood tests and liver function tests have a good predictive value on the prognosis of liver cancer. In the current study, we explored the value of GPR to clinical prognosis by screening early HBV-related HCC patients. GPR levels were higher in these patients than in those with hepatic hemangiomas, chronic hepatitis B and healthy controls. Of note, when the preoperative GPR cutoff value was set at 0.2, HCC patients with high GPR levels had a poorer prognosis. In the entire cohort, patients in the high GPR group had a significantly increased risk after hepatectomy. We used PSM to balance baseline and clinicopathological characteristics. This analysis corroborated the correlation between GPR levels and clinical prognosis for HBV-related HCC patients. Subgroup and combined analyses suggested that, low GPR levels had a protective effect on patient prognosis after liver resection. These findings were supported when patients were stratified according to GPR terciles (*P* for trend < 0.001). Prognostic nomograms were constructed and the calibration curves showed that GPR can predict the OS and RFS well. This is the first study to examine the relationship between the GPR and surgical outcomes in solitary HBV-related HCC patients. Our results could provide useful information for preoperative planning and postoperative surveillance in these patients.

In this study, multivariate analyses before and after PSM found that, in patients with a single nodule HBV-related HCC, the tumor diameter was associated with OS after radical resection. In addition, the tumor size, aggressive tumor growth, and the presence of liver cirrhosis were associated with tumor recurrence. A Korean study noted that a tumor size > 3 cm, and microvascular invasion were closely associated with early recurrence after liver resection for solitary HCC[21]. A previous study noted that cancer recurrence and long-term survival were independently associated with a tumor size > 5 cm in cirrhotic patients undergoing curative hepatectomy for solitary HCC without macrovascular invasion[22]. Besides, compared with patients who underwent curative hepatectomy without liver cirrhosis, HCC patients with liver cirrhosis had a 6% to 15% higher annual risk of de novo recurrence[23]. Patients with HBV-related HCC often have a background of liver cirrhosis, so it is particularly important to evaluate the prognosis of patients before surgery. Some study suggested that GPR can be a good predictor for HCC development in chronic hepatitis B patients[14, 24]. A study has demonstrated that HBV-associated HCC patients with high GPR levels had significantly poorer survival outcomes, regardless of the specific treatment approaches administered[25].

GGT as a cell-membrane-bound enzyme plays a crucial role in modulating the metabolic process of glutathione, involved in nucleic acid metabolism and carcinogenesis. Previous study suggested that serum GGT levels strongly predicted HCC development in patients with chronic HBV infection who underwent nucleotide/nucleoside analogues, particularly non-cirrhotic patients[26]. The detection of serum GGT was previously reported to be associated with the prognosis of HCC patients who underwent hepatectomy[27], radiofrequency-ablation[28], adjuvant transarterial chemoembolization[29], and liver transplantation[30]. A plausible mechanism underlying the prognostic significance of GPR could involve its correlation with inflammatory processes. GGT, a constituent of the GPR, serves as a biomarker for hepatic injury and is indicative of the ongoing inflammatory response in HCC. Elevated GGT levels have been observed in individuals with conditions such as hepatitis, liver fibrosis, cirrhosis, and hepatic malignancies[16]. Elevated levels of GGT have been significantly associated with the presence of multiple intrahepatic micrometastases and vascular invasion in HCC[28,30]. Certain serum inflammatory cytokines, notably tumor necrosis factor-alpha and interferon-alpha, which are closely associated with the prognosis of HCC, may contribute to the upregulation of GGT expression[31]. Furthermore, GGT participates in oxidative reactions and serves as a biomarker for oxidative stress, which is an essential component of numerous chronic inflammation-associated responses[32-34]. Platelets, which are anuclear cytoplasmic

Table 1 Preoperative clinicopathologic data of patients with solitary hepatitis B virus-related hepatocellular carcinoma

Variables		Before PSM				After PSM			
		N (1167)	GPR ≤ 0.2 (*n* = 381)	GPR > 0.2 (*n* = 786)	*P* value	*N* (656)	GPR ≤ 0.2 (*n* = 328)	GPR > 0.2 (*n* = 328)	*P* value
Sex	Male	985	278	707	< 0.001	533	266	267	1
	Female	182	103	79		123	62	61	
Age (years)	≤ 50	654	229	425	0.059	377	196	181	0.269
	> 50	513	152	361		279	132	147	
Body mass index	> 24	354	124	230	0.282	205	107	98	0.5
	≤ 24	813	257	556		451	221	230	
Smoking	Yes	407	100	307	< 0.001	190	97	93	0.796
	No	760	281	479		466	231	235	
Drinking	Yes	386	89	297	< 0.001	179	87	92	0.726
	No	781	292	489		477	241	236	
Diabetes mellitus	Yes	59	15	44	0.284	33	15	18	0.721
	No	1108	366	742		623	313	310	
Hypertension	Yes	114	38	76	0.953	67	33	34	1
	No	1053	343	710		589	295	294	
Family history of liver cancer	Yes	128	41	87	0.954	72	39	33	0.532
	No	1039	340	699		584	289	295	
Liver flukes	Yes	221	53	168	0.003	112	51	61	0.35
	No	946	328	618		544	277	267	
Cirrhosis	Yes	587	158	429	< 0.001	280	145	135	0.477
	No	580	223	357		376	183	193	
Serum alpha-fetoprotein (ng/mL)	≥ 200	440	164	276	0.011	246	139	107	0.012
	< 200	727	217	510		410	189	221	
Child-Pugh	A	1151	378	773	0.355	649	325	324	1
	B	16	3	13		7	3	4	
Barcelona Clinic Liver Cancer stage	0	172	65	107	0.142	103	53	50	0.83
	A	995	316	679		553	275	278	
Total bilirubin (μmol/L)	> 20.5	128	31	97	0.04	73	28	45	0.047
	≤ 20.5	1039	350	689		583	300	283	
Albumin (g/L)	> 40	534	223	311	< 0.001	354	184	170	0.309
	≤ 40	633	158	475		302	144	158	
Gamma-glutamyl transpeptidase (U/L)	> 50	557	18	539	< 0.001	221	18	203	< 0.001
	≤ 50	610	363	247		435	310	125	
Hepatitis B virus DNA (IU/mL)	> 1000	521	143	378	0.001	277	126	151	0.058
	≤ 1000	646	238	408		379	202	177	
HBeAg status	-	299	619	918	0.914	259	252	511	0.510
	+	82	167	249		69	76	145	
Antiviral therapy	No	265	521	786	0.264	233	221	454	0.310

	Yes	116	265	381		95	107	202	
Surgical margin (cm)	< 2	169	308	477	0.092	146	127	273	0.132
	≥ 2	212	478	690		182	201	383	
Tumor size (cm)	> 5	444	113	331	< 0.001	208	103	105	0.933
	≤ 5	723	268	455		448	225	223	
Microvascular invasion	Yes	301	86	215	0.093	152	79	73	0.644
	No	866	295	571		504	249	255	
Infiltrative growth	Yes	438	166	272	0.004	270	137	133	0.812
	No	729	215	514		386	191	195	

P value: Calculated by Pearson's χ^2 test. PSM: Propensity score matching; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio.

Table 2 Univariate and multivariate Cox-regression analyses predicting overall survival before and after propensity score matching

Variables	Before propensity matching				After propensity matching			
	Uni-HR (95%CI)	*P* value	Multi-HR (95%CI)	*P* value	Uni-HR (95%CI)	*P* value	Multi-HR (95%CI)	*P* value
Sex (male/female)	1.44 (1.01-2.05)	0.043	1.3 (0.9-1.87)	0.159	1.22 (0.79-1.87)	0.364		
Age (years) (> 50/≤ 50)	1.02 (0.81-1.29)	0.85			0.86 (0.63-1.19)	0.362		
Body mass index (> 24/≤ 24)	1.16 (0.9-1.49)	0.255			1.25 (0.88-1.79)	0.218		
Smoking (yes/no)	1.05 (0.83-1.34)	0.672			1.04 (0.74-1.48)	0.81		
Drinking (yes/no)	0.9 (0.7-1.15)	0.412			0.85 (0.59-1.23)	0.388		
Diabetes mellitus (yes/no)	0.75 (0.4-1.41)	0.372			0.46 (0.15-1.45)	0.186		
Hypertension (yes/no)	0.82 (0.54-1.24)	0.345			0.66 (0.36-1.23)	0.192		
Family cases (yes/no)	0.79 (0.53-1.17)	0.234			0.61 (0.34-1.1)	0.098		
Liver flukes (yes/no)	0.88 (0.65-1.19)	0.392			0.75 (0.47-1.18)	0.214		
Cirrhosis (yes/no)	1.21 (0.96-1.53)	0.1			1.24 (0.9-1.71)	0.18		
Child-Pugh (B/A)	2.16 (1.07-4.36)	0.032	1.78 (0.87-3.63)	0.115	1.34 (0.33-5.42)	0.679		
Barcelona Clinic Liver Cancer stage (A/0)	1.93 (1.31-2.83)	< 0.001	1.51 (1-2.26)	0.048	2.03 (1.19-3.45)	0.009	1.64 (0.94-2.86)	0.082
Total bilirubin (μmol/L) (> 20.5/≤ 20.5)	0.85 (0.6-1.21)	0.37			0.9 (0.55-1.45)	0.651		
Albumin (g/L) (> 40/≤ 40)	1.35 (1.07-1.71)	0.012	1.16 (0.91-1.48)	0.229	1.2 (0.87-1.65)	0.26		
Alpha-fetoprotein (ng/mL) (≥ 200/< 200)	1.38 (1.09-1.74)	0.006	1.35 (1.06-1.72)	0.013	1.37 (0.99-1.89)	0.055		
Hepatitis B virus DNA (IU/mL) (> 1000/≤ 1000)	0.73 (0.58-0.92)	0.008	0.83 (0.66-1.05)	0.123	0.72 (0.52-0.99)	0.042	0.82 (0.59-1.12)	0.213
Tumor size (cm) (≤ 5/> 5)	0.57 (0.46-0.72)	< 0.001	0.74 (0.57-0.95)	0.019	0.6 (0.43-0.82)	0.002	0.66 (0.48-0.93)	0.017
Microvascular invasion (yes/no)	1.55 (1.21-1.99)	< 0.001	1.19 (0.92-1.55)	0.186	1.2 (0.83-1.74)	0.322		
Infiltrative growth (yes/no)	1.29 (1.02-1.63)	0.032	1.35 (1.06-1.7)	0.014	1.2 (0.87-1.65)	0.272		
Gamma-glutamyl transpeptidase-to-platelet ratio (≤ 0.2/> 0.2)	0.48 (0.36-0.64)	< 0.001	0.52 (0.39-0.69)	< 0.001	0.49 (0.35-0.69)	< 0.001	0.5 (0.36-0.7)	< 0.001

Uni-HR: Hazard ratio for univariable Cox-regression analyses; Multi-HR: Hazard ratio for multivariable Cox-regression analyses.

fragments derived from bone marrow megakaryocytes, serve as critical agents in hemostasis. Upon vascular injury, they swiftly accumulate at the site of damage and discharge granule contents, including platelet-activating factors, to facilitate thrombus formation[35]. Additionally, platelets are implicated in multiple stages of tumorigenesis, including the promotion of tumor growth, intravasation of tumor cells, and metastatic spread. Furthermore, their ability to secrete substantial amounts of microparticles and exosomes is crucial for orchestrating effective communication between the

Table 3 Univariate and multivariate Cox-regression analyses predicting recurrence-free survival before and after propensity score matching

Variables	Before propensity matching				After propensity matching			
	Uni-HR (95%CI)	*P* value	Multi-HR (95%CI)	*P* value	Uni-HR (95%CI)	*P* value	Multi-HR (95%CI)	*P* value
Sex (male/female)	1.32 (1.03-1.69)	0.028	1.19 (0.92-1.54)	0.176	1.09 (0.8-1.49)	0.574		
Age (years) (> 50/≤ 50)	1.03 (0.87-1.22)	0.756			0.93 (0.73-1.19)	0.575		
Body mass index (> 24/≤ 24)	1.13 (0.94-1.36)	0.185			1 (0.77-1.29)	0.989		
Smoking (yes/no)	1.11 (0.93-1.32)	0.244			1.01 (0.78-1.31)	0.93		
Drinking (yes/no)	1 (0.84-1.2)	0.972			0.85 (0.64-1.11)	0.23		
Diabetes mellitus (yes/no)	1.4 (0.98-2)	0.067			1.22 (0.71-2.1)	0.461		
Hypertension (yes/no)	0.81 (0.6-1.09)	0.165			0.83 (0.54-1.26)	0.38		
Family cases (yes/no)	0.89 (0.68-1.16)	0.384			0.76 (0.51-1.14)	0.192		
Liver flukes (yes/no)	1.14 (0.93-1.4)	0.204			1.01 (0.74-1.38)	0.945		
Cirrhosis (yes/no)	1.27 (1.08-1.5)	0.005	1.25 (1.05-1.49)	0.012	1.3 (1.03-1.65)	0.03	1.33 (1.04-1.68)	0.021
Child-Pugh (B/A)	1.08 (0.54-2.18)	0.823			1.01 (0.32-3.14)	0.99		
Barcelona Clinic Liver Cancer stage (A/0)	1.4 (1.09-1.8)	0.008	1.14 (0.87-1.49)	0.348	1.39 (0.98-1.97)	0.061		
Total bilirubin (μmol/L) (> 20.5/≤ 20.5)	0.87 (0.67-1.13)	0.292			0.85 (0.6-1.22)	0.386		
Albumin (g/L) (> 40/≤ 40)	1.36 (1.15-1.61)	< 0.001	1.17 (0.98-1.4)	0.084	1.21 (0.96-1.54)	0.112		
Alpha-fetoprotein (ng/mL) (≥ 200/< 200)	1.31 (1.1-1.55)	0.002	1.29 (1.08-1.54)	0.005	1.22 (0.96-1.55)	0.111		
Hepatitis B virus DNA (IU/mL) (> 1000/≤ 1000)	0.8 (0.68-0.95)	0.009	0.9 (0.76-1.06)	0.214	0.76 (0.6-0.96)	0.023	0.8 (0.63-1.02)	0.067
Tumor size (cm) (≤ 5/> 5)	0.6 (0.51-0.71)	< 0.001	0.67 (0.55-0.81)	< 0.001	0.79 (0.62-1.02)	0.07		
Microvascular invasion (yes/no)	1.4 (1.16-1.68)	< 0.001	1.1 (0.9-1.33)	0.359	1.18 (0.9-1.56)	0.233		
Infiltrative growth (yes/no)	1.24 (1.05-1.47)	0.013	1.28 (1.08-1.53)	0.005	1.24 (0.97-1.57)	0.082		
Gamma-glutamyl transpeptidase-to-platelet ratio (≤ 0.2/> 0.2)	0.49 (0.4-0.6)	< 0.001	0.53 (0.43-0.65)	< 0.001	0.56 (0.44-0.71)	< 0.001	0.57 (0.44-0.73)	< 0.001

Uni-HR: Hazard ratio for univariable Cox-regression analyses; Multi-HR: Hazard ratio for multivariable Cox-regression analyses.

Table 4 Stratified analysis between gamma-glutamyl transpeptidase-to-platelet ratio levels and prognosis in the solitary hepatitis B virus-related hepatocellular carcinoma

Variables	Before propensity matching				After propensity matching			
	OS-HR (95%CI)	*P* value	RFS-HR (95%CI)	*P* value	OS-HR (95%CI)	*P* value	RFS-HR (95%CI)	*P* value
As continuous	1.12 (1.04-1.20)	0.002	1.11 (1.06-1.17)	< 0.001	1.29 (1.18-1.42)	< 0.001	1.20 (1.11-1.31)	< 0.001
By GPR cut-off								
GPR ≤ 0.2								
GPR > 0.2	2.07 (1.56-2.74)	< 0.001	2.05 (1.68-2.51)	< 0.001	2.04 (1.46-2.84)	< 0.001	1.79 (1.40-2.28)	< 0.001
By GPR tercile								
Bottom (≤ 0.2)								
Middle (> 0.2, ≤ 0.6)	1.81 (1.35-2.44)	< 0.001	1.85 (1.50-2.29)	< 0.001	1.52 (1.08-2.14)	0.017	1.69 (1.25-2.17)	< 0.001
Top (> 0.6)	2.74 (1.98-3.81)	< 0.001	2.60 (2.04-3.31)	< 0.001	2.33 (1.60-3.39)	< 0.001	2.35 (1.77-3.13)	< 0.001
P for trend[1]	< 0.001		< 0.001		< 0.001		< 0.001	
By interquartile								

Q1								
Q2	1.42 (0.98-2.06)	0.061	1.43 (1.10-1.86)	< 0.001	0.75 (0.43-1.28)	0.288	0.88 (0.60-1.29)	0.514
Q3	1.72 (1.20-2.46)	0.003	1.74 (1.35-2.24)	< 0.001	1.45 (0.90-2.34)	0.125	1.58 (1.12-2.23)	0.009
Q4	2.34 (1.66-3.29)	< 0.001	2.29 (1.79-2.93)	< 0.001	2.08 (1.33-3.24)	0.001	1.79 (1.27-2.51)	0.001
P for trend[1]	< 0.001		< 0.001		< 0.001		< 0.001	

[1]Test for trend based on variable containing median value for each classification.
HR: Hazard ratio; OS: Overall survival; RFS: Recurrence-free survival; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio.

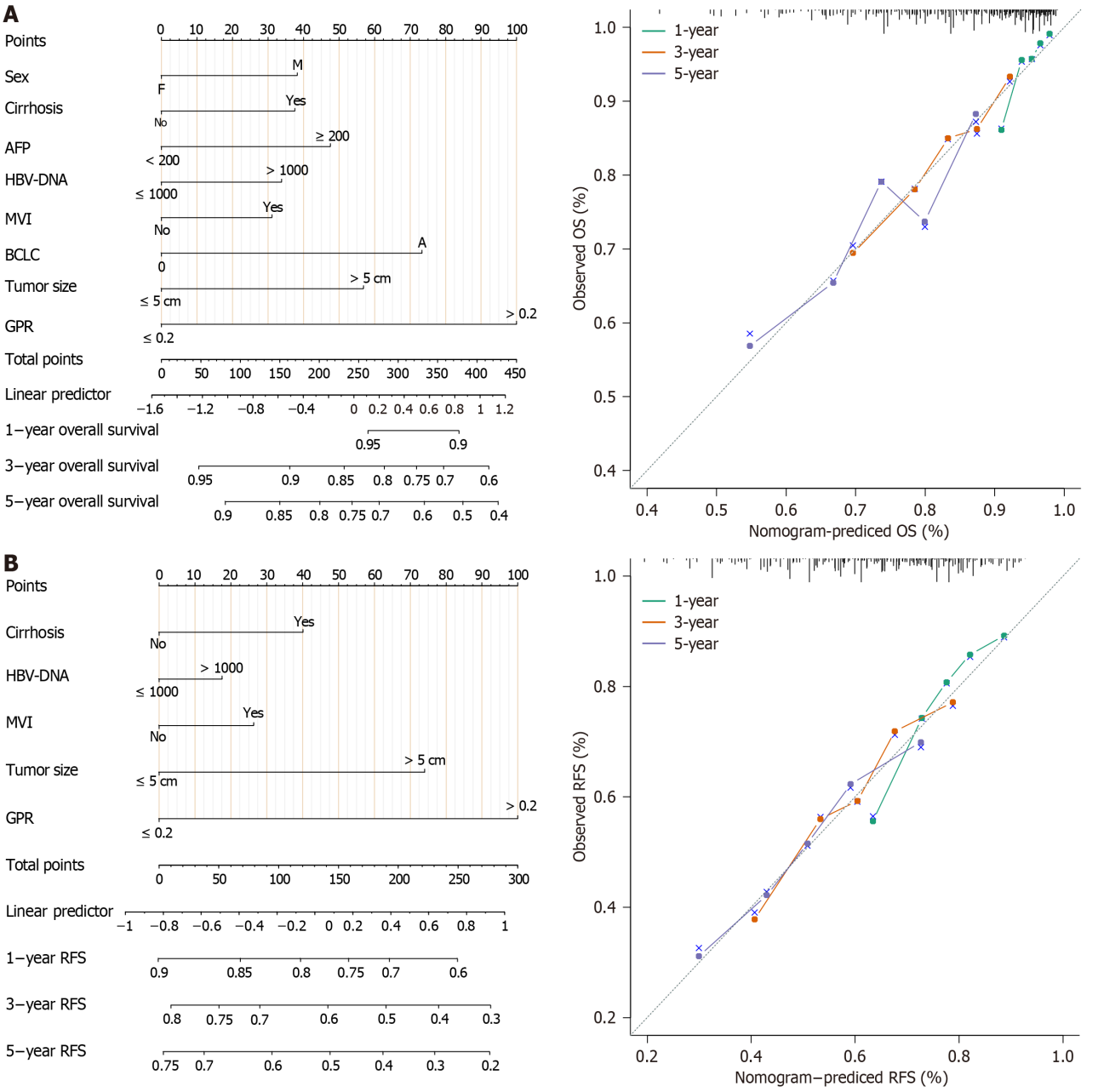


Figure 6 Prognostic nomograms for solitary hepatitis B virus-related hepatocellular carcinoma. A: Nomogram plot and calibration curves for overall survival; B: Nomogram plot and calibration curves for recurrence-free survival. AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; MVI: Microvascular imaging; BCLC: Barcelona Clinic Liver Cancer; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; RFS: Recurrence-free survival; OS: Overall survival; F: Female; M: Male.

tumor and its host environment[36,37]. A study has explored the correlation between the GPR and inflammation-related signaling pathways, revealing that the expression of p38 mitogen-activated protein kinase exhibited a significant negative correlation with both the GPR and GGT[38]. In the present study, we explored the association of preoperative GPR and the prognosis of patients with single-lesion HBV-related HCC. First, we compared the enrolled subjects with the control group in different physiological states. The results showed that the GPR level of HCC patients was at the same level as that of post-hepatitis cirrhosis patients, and was at a high level compared with healthy subjects and patients with benign liver diseases. The above findings can more intuitively show the evaluation of the prognostic value of GPR level. We set a GPR cutoff value of 0.2 to distinguish the above-mentioned patients into high-risk and low-risk groups. After adjusting for baseline characteristics by PSM, HCC patients who underwent hepatectomy had a poor OS and elevated RFS rate when their preoperative GPR was > 0.2. Previously published studies[15,25,39,40] found that an increased GPR was associated with the prognosis of HCC patients, but the cutoff values varied widely, ranging from 0.3 to 0.84. These differences could be explained by different inclusion and exclusion criteria, differences in tumor staging, and background of liver cirrhosis and hepatitis. Indeed, some researchers have shown that GPR levels have a good prognostic value in HCC patients[41-43], even in AFP-negative HCC[44]. In this study, through subgroup and stratification analyses, we confirmed that a low preoperative GPR level predicts a good prognosis for HCC patients. Therefore, GPR may be a good noninvasive index to guide clinician decision-making.

Although preoperative GPR levels were shown to accurately predict surgical outcomes in patients with HBV-related HCC, the present study has several limitations. First, data were collected from one center in a confined area where HBV is prevalent, and only patients with solitary HCC who received curative resection were included. Although the sample size was modest and potential selection bias should be considered in subsequent analyses, further external validation by multicenter, large-sample, prospective studies is essential to determine the robustness of our findings in different patient populations. Our study is still unclear about the mechanisms linking GPR levels to tumor progression. Further research could provide additional insights to better understand the role of GPR in HCC progression. This study has preliminarily illuminated the role of GPR in predicting outcomes for HCC patients undergoing liver resection; the relationship between various noninvasive blood fibrosis indices and postoperative outcomes warrants further investigation. Moreover, it is unclear if preoperative GPR is useful for HCV-related HCC or nonalcoholic fatty liver disease-related HCC patients receiving radical resection.

CONCLUSION

GPR levels before surgery can be used as a new indicator to predict surgical outcomes in patients with solitary HBV-related HCC. This is a potentially helpful tool to monitor the recurrence and OS in clinical practice. A prognostic risk stratification based on GPR can objectively and accurately predict the postoperative prognosis of HCC patients. Therefore, preoperative GPR levels can be used for recurrence monitoring and treatment strategy based on risk stratification, and may contribute to improve the quality of life of solitary nodule HCC patients.

FOOTNOTES

Author contributions: Yang CK and Peng T designed the study; Yang CK, Wei ZL, Shen XQ, Jia YX, and Wu QY performed research; Yang CK, Wei ZL, Shen XQ, Jia YX, Wu QY and Wei XL provided sample collection and clinical support; Yang CK, Wei YG, Su H, Liao XW, Zhu GZ and Qin W contributed to data interpretation; Yang CK and Wei ZL wrote the manuscript; Peng T critically revised the manuscript and participated in the analysis and interpretation of the data; all of the authors read and approved the final version of the manuscript to be published.

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