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Preoperative γ-glutamyl transpeptidase to platelet ratio (GPR) is an independent prognostic factor for HBV-related hepatocellular carcinoma after curative hepatic resection

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Abstract

Liver fibrosis and cirrhosis is associated with the prognosis of patients with hepatocellular carcinoma (HCC) after treatment. The γ-glutamyl transpeptidase to platelet ratio (GPR) is reported to predict significant liver fibrosis and cirrhosis. The aim of this study was to investigate the predictive value of preoperative GPR on the recurrence and survival of patients with HCC who underwent curative hepatectomy.

A retrospective review of demographics, medical records, and prognosis of patients with hepatitis B virus (HBV)–related HCC was performed. Overall survival (OS) and disease-free survival (DFS) were evaluated using Kaplan–Meier method, and the log-rank test was used to analyze differences in recurrence and survival. Univariate and multivariate analyses were used for significance of prognostic factor.

A total of 357 patients with HBV-related HCC were included in this analysis. The preoperative GPR was associated with recurrence and survival rates, independent of HCC progression or tumor marker levels, in a multivariate analysis. OS was higher in patients with a GPR <0.84 versus ≥084 (5-year survival rates 58.6% vs. 38.5%; $P<0.001$). DFS was also worse in patients with a GPR ≥0.84 than in those with GPR <0.84 (5-year recurrence rates 42.8% vs. 22.8%; $P<0.001$).

GPR score of ≥0.84 represents a major risk factor for the poor prognosis for HBV-related HCC after hepatic resection, and GPR served as an independent predictive factor for HBV-related HCC OS.

Abbreviations: AFP = α-fetoprotein, DFS = disease-free survival, GGT = γ-glutamyl transferase, GGT = γ-glutamyl transpeptidase, GPR = γ-glutamyl transpeptidase to platelet ratio, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio, OS = overall survival, PVTT = portal vein tumor thrombus, RFA = radiofrequency ablation.

Keywords: γ-glutamyl transpeptidase to platelet ratio, GPR, HCC, hepatocellular carcinoma, prognosis

1. Introduction

Hepatocellular carcinoma (HCC), one of the most common malignancies, is ranked the second most frequent cause of death from cancer and the fifth common cancer from global cancer statistics.[1] China alone accounts for about 50% of the total number of new liver cancer cases and deaths.[1] Most of the cases are associated with liver cirrhosis on account of chronic hepatitis B virus (HBV) infection, particularly in China.[2] Patients with HCC can achieve a 5-year survival rate approximately 70% by liver transplantation, radiofrequency ablation (RFA), or curative hepatic resection in early tumor stage; nevertheless, patients with advanced HCC have median survival time <1 year.[3,4] Long-term survival remains far from satisfactory owing to the high cancer recurrence.[5]

Curative hepatic resection is considered to be the most powerful curative therapy for patients with HCC when liver transplantation is not immediately accessible or not an option.[3] After resection of HCC, prognosis is dependent on factors such as tumor size and differentiation, vascular invasion, and resection margin status.[5] Most of these factors are determined only after surgery. Therefore, the widespread research for a potential effective hematological prognostic indicator that would be available before surgery and improved prognosis by allowing earlier intervention.[6,7] Inflammation-based prognostic scores have been formed to predict cancer survival. Subsets of peripheral blood, including lymphocytes, monocytes, platelets (PLT), and neutrophil to lymphocyte ratio, have been found to be associated with prognosis of different cancers.[8–10] Anti-PLT therapy has

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been found in the prevention of HBV-related HCC.[11] Studies concerning PLT status and HCC diagnosis with postoperative complication and survival have been extensively described.

To date, α-fetoprotein (AFP) is an immensely studied tumor biomarker for HCC prognosis.[7] A meta-analysis shows that the most powerful predictors of death in patients with cirrhosis and HCC are liver related and/or tumor related; especially, AFP was among the most robust predictors.[12] To date, many tumor markers including AFP-L3, glypican-3, γ-glutamyl transferase (GGT), DCP, GP73, and osteopontin have also been evaluated as substitutes or complements for AFP in the diagnosis and prognosis of HCC.[4,6,7,13] Moreover, AFP concentration rose in 11% to 47% of patients with liver cirrhosis and in 15% to 58% of patients with chronic hepatitis. Thus, reevaluating tumor biomarkers to find potential candidates to be included in the surveillance of HCC prognosis might be of great importance in clinical practice.

Liver function is associated with HCC treatment selection and treatment response.[14] Liver function parameters could be transiently deteriorated in patients after hepatectomy, transcatheter arterial chemoembolization, or RFA.[14,15] Kuroda et al evaluated the liver function parameter changes after percutaneous RFA and concluded that a Child–Pugh score of ≥9 represents a main risk factor for the aggravation of liver function through a retrospective study.[15] Previous study presented preoperative aspartate aminotransferase to platelet ratio as an independent prognostic factor for HBV-induced HCC after curative hepatic resection.[16] What is noteworthy is that a recent study reports that the γ-glutamyl transpeptidase to platelet ratio (GPR) has the power to predict liver cirrhosis and fibrosis in chronic HBV-infected patients in West Africa.[17] Therefore, as the most common tests in clinics, the roles of liver function parameters in HCC prognosis should be evaluated.

Considering all the aforementioned concerns, the aim of this study was to reevaluate the prognostic value of liver function parameters, clinicopathological characteristics, and treatment regimen in HCC overall survival (OS) after hepatic resection.

2. Patients and methods

2.1. Patients

The medical records of all patients with HCC who were admitted to the First Affiliated Hospital, Health Science Center, Xi'an Jiaotong University, during 2006 to 2013 were retrospectively reviewed to confirm the relevant clinicopathological parameters. HCC diagnosis was based on radiologic criteria according to European Association for the Study of the Liver and was finally verified pathologically after surgery.[18] All experiments in this study were approved by the Ethics Committee of Health Science Center of Xi'an Jiaotong University and informed consent was signed. All patients, after hepatectomy, were monitored for a period of 7.1 to 106.3 months with a median length of 62.6 months till the end of 2014 by ultrasonography and enhanced CT or MRI every 3 to 6 months. The study included only patients with HBV-related HCC who underwent curative hepatic resection, and the cases without death in the perioperative period. Patients who are younger than 18 years old, with non–HBV-induced HCC, underwent noncurative hepatic resection, died in the perioperative period, or received sorafenib treatment before the recurrence of HCC were excluded from the study.

2.2. Study design and methods

This is a retrospective, single-center study. The demographics, diagnoses, preoperative condition, tumor markers, blood routine

test, liver function parameters, surgical procedures, and postoperative outcomes of patients were extracted. We derived patients' follow-up data from a review of inpatient and outpatient medical records and from direct follow-up visits. Following data were recorded for further analysis: sex, age, etiology, date of HCC diagnosis, date of recurrence, date of death or last information, presence of cirrhosis, HBV DNA, ascites, main serological parameters (PLT, aspartate aminotransferase, alanine aminotransferase, total bilirubin [TBIL], direct bilirubin, albumin, alkaline phosphatase, γ-glutamyl transpeptidase [GGT], prothrombin time [PT], AFP, etc.), tumor characteristics (number of lesions, location of lesions, diameter of largest lesion, portal vein invasion, organ invasion, nodes status), and surgical procedures.

OS was defined as the time from HCC diagnosis to the death due to any cause. Disease-free survival (DFS) denotes the chances of staying free of disease after hepatic resection for patients with HCC. Tumor differentiation was graded according to Edmonson–Steiner stage. Child–Pugh score (sometimes the Child–Turcotte–Pugh score) was calculated based on the severity of hepatic encephalopathy, ascites, TBIL, albumin, and PT. Tumor characteristics and liver histology status including cirrhosis, tumor size, multicentric tumor, portal vein invasion, and organ invasion were diagnosed by imaging studies such as enhanced CT/MRI.

2.3. Statistical analysis

Statistical analysis was performed with SPSS software (version 19.0; SPSS Inc, Chicago, IL) for analysis. Fisher's exact test (in cases of low frequency) and univariate χ^2 were implemented to discriminate discrete variables. And nonparametric statistical analyses were used for non-normally distributed data. Differences between groups with continuous variables were tested by Mann–Whitney U tests and categorical variables were detected by χ^2 analysis. OS between different groups was compared by the Kaplan–Meier method and the log-rank test was used to estimate the difference in survival. Factors independently related to survival were tested by a Cox regression model adjusted for a propensity score. Only covariates significantly associated with outcomes at univariate analysis (2-sided $P < 0.05$) were included in the multivariate analysis model. Results were reported as hazard ratio (HR) adjusted for the propensity score in 4 strata with 95% confidence intervals (CIs). $P < 0.05$ was considered significant.

2.4. Propensity score analysis

As patients with HBV-related HCC were grouped based on GPR cutoff value without any randomized study design, in order to control the group selection bias, a propensity score, as an adjustment variable, was built. A logistic regression model was developed to estimate the individual propensity score for the 357 patients. The model included covariates that may have influences on both the grouping and the survival (Table 1). The model showed 68.2% of correctly classified patients. Based on the estimated propensity score, patients were allocated to 4 strata, with each stratum having 25% of the patients. A multivariate analysis of the entire population was adjusted for the propensity score in 4 strata.[16]

3. Results

3.1. Demographics and perioperative details

A total of 357 patients with HBV-related HCC who underwent curative hepatic resection were included in this study. There were

Table 1

Baseline comparison between patients with GPR ≥0.84 and <0.84.

Variable	GPR <0.84 (n=217)	GPR ≥0.84 (n=140)	P
Sex, male/female	173/44	121/19	0.105
Age, y (mean±SD)	52.10±11.95	50.83±11.53	0.322
HBV DNA, 10^3 copies/mL (mean±SD)	1.18±0.23	1.26±0.29	0.204
AFP, ng/mL, <200/≥200	134/83	102/38	0.030
Differentiation, I–II/III–IV*	167/50	96/44	0.079
Tumor size, cm	5.94±3.40	6.74±3.77	0.039
Surgical margin, <1/≥1cm	70/147	44/96	0.870
Liver cirrhosis, no/yes	40/177	10/130	0.003
PVTT, no/yes	148/69	73/67	0.002
Number of tumors, 1/≥2	189/28	120/20	0.709
Vascular invasion, no/yes	172/45	110/30	0.876
Child–Pugh score	5.2±0.71	5.7±0.69	0.002
ASA grading, <3/≥3	116/43	958/73	0.027
TBIL, μmol/L (mean±SD)	16.49±8.79	35.26±66.29	0.001
Albumin, g/L (mean±SD)	40.48±5.61	37.88±5.90	<0.001
ALT, U/L (mean±SD)	32.20±17.25	74.83±73.25	<0.001
AST, U/L (mean±SD)	30.40±10.75	73.29±69.31	<0.001
PT, S (mean±SD)	13.31±1.20	13.76±1.53	0.007
APTT, S (mean±SD)	36.9±7.58	38.47±7.10	0.084
INR (mean±SD)	1.06±0.11	1.12±0.13	<0.001
RBC, 10^{12}/L (mean±SD)	4.30±0.56	4.09±0.64	0.004
HB, g/dL (mean±SD)	132.70±21.63	128.30±19.16	0.075
WBC, 10^9/L (mean±SD)	5.90±2.36	4.65±2.37	<0.001
PLT, 10^9/L (mean±SD)	165.09±72.61	87.14±37.361	<0.001
Blood loss, mL (mean±SD)	570.27±587.90	882.46±1041.00	0.003
Operation time, min (mean±SD)	200.73±71.40	212.31±75.80	0.192

AFP = α-fetoprotein, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, ASA = American Society of Anesthesiology, AST = aspartate aminotransferase, GPR = γ-glutamyl transpeptidase to platelet ratio, HB = hemoglobin B, HBV = hepatitis B virus, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, PVTT = portal vein tumor thrombus, RBC = red blood count, SD = standard deviation, TBIL = total bilirubin, WBC = white blood cell.
* Edmondson–Steiner stage.

294 male patients (82.4%) and 63 female patients (17.6%). Recurrence occurred in a total of 220 patients (61.6%), whereas 170 patients (47.6%) died during follow-up. Hepatitis B surface antigen was positive in all patients, with 307 (86.0%) patients having underlying cirrhosis. Increased AFP (≥200 ng/mL) was found in 121 cases (33.9%), and 48 patients (13.4%) had multiple tumors. With regard to tumor differentiation according to Edmondson–Steiner stage, there were 263 (73.7%) stages I to II and 94 (26.3%) stages III to IV. Details of these features are shown in Table 1.

3.2. ROC curves of GPR for HCC overall survival

To evaluate the predictive accuracy of serum GPR for HCC OS, we performed receiver operating characteristic (ROC) curve analyses indicating that elevated GPR could significantly more accurately predict HCC OS. An optimal cutoff value of 0.84 corresponded to the maximum joint sensitivity and specificity on the ROC plot for GPR (area under ROC=0.653, 95% CI=0.596–0.710, P<0.001; Fig. 1), with sensitivity of 64.2% and specificity of 61.2% in the prediction of death.

3.3. Risk factors for prognosis of HCC after hepatectomy

Univariate analysis showed that AFP, Edmondson–Steiner stage, tumor size, surgical margin, portal vein tumor thrombus (PVTT), vascular invasion, GPR, blood loss, and blood transfusion were all factors related to the OS in patients with HCC (all P<0.05).
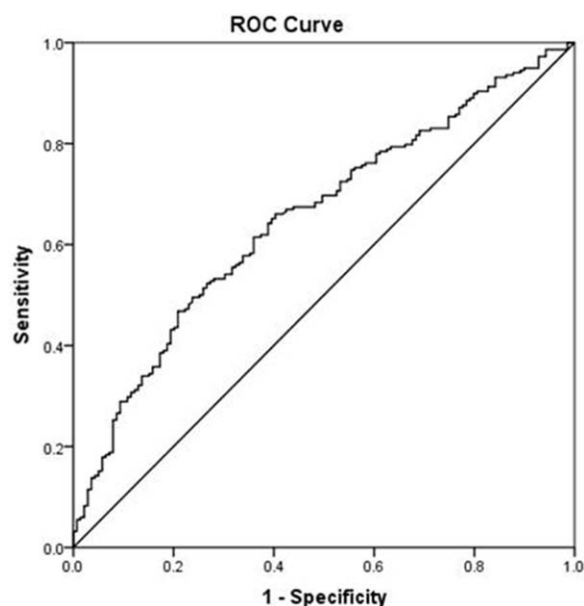

Figure 1. ROC curves for GPR in relation to death. AUROC curves were 0.653 (95% confidence interval, 0.596–0.710, P<0.001) for GPR. The calculated cutoff value for GPR was 0.84, with sensitivity of 64.2% and specificity of 61.2%. AUROC = area under ROC curve, GPR = γ-glutamyl transpeptidase to platelet ratio, ROC = receiver operating characteristic.

When these factors were evaluated by a multivariate model using forward selection, AFP, PVTT, GPR, tumor size, and blood transfusion were significantly associated with HCC OS (HR = 1.991, 95% CI=1.179–3.178, P=0.002; HR=2.173, 95% CI= 1.471–3.198, P<0.001; HR=2.734, 95% CI=1.681–3.832, P<0.001; HR=1.785, 95% CI=1.178–3.426, P=0.039; and HR=1.734, 95% CI=1.041–3.829, P=0.015, respectively) (Table 2).

Univariate analysis identified AFP, tumor size, Edmondson–Steiner stage, surgical margin, PVTT, vascular invasion, GPR, blood loss, and blood transfusion as elements that have strong association with the DFS after patients' hepatectomy. Based on the multivariate analysis, surgical margin, vascular invasion, GPR, and blood transfusion are also independent variables linked to lower DFS rates (Table 3).

As shown in Fig. 2, we performed a Kaplan–Meier event analysis. We grouped the GPR levels with abnormal cutoff values into normal group and elevated group. This revealed that the higher the levels of GPR, the greater is the risk of worse prognosis (all log rank P<0.001). OS was higher in patients with a GPR <0.84 versus ≥0.84 (5-year survival rates 58.6% vs. 38.5%; P< 0.001). DFS was also worse in patients with a GPR ≥0.84 than in those with GPR <0.84 (5-year recurrence rates 42.8% vs. 22.8%; P<0.001).

3.4. Relationship between clinicopathological features and GPR status

Clinicopathological features of patients with different GPR status are summarized in Table 1. AFP, tumor size, liver cirrhosis, PVTT, number of tumors, Child–Pugh score, American Society of Anesthesiology grading, TBIL, albumin, alanine aminotransferase, aspartate aminotransferase, PT, international normalized ratio, red blood cell, PLT, white blood cell, and blood loss were significantly different between the 2 groups (P<0.05).

Table 2

Univariate and multivariate analyses of OS after propensity score adjustment.

Categories	Subcategories	Univariate analysis P value	Multivariate analysis HRa (95% CI)	P value
Sex	Male	0.398		
	Female			
Age, y	<60	0.412		
	≥60			
Child–Pugh class	A	0.653		
	B			
HBV DNA, copies/mL	<10^3	0.236		
	≥10^3			
AFP, ng/mL	<200	0.008	1.532 (1.013–2.654)	0.042
	≥200			
Differentiation*	I–II	0.021	1.720 (1.236–3.953)	0.035
	III–IV			
Tumor size, cm	<5	0.048	1.785 (1.178–3.426)	0.039
	≥5			
Surgical margin, cm	<1	0.014	1.873 (1.221–3.081)	<0.001
	≥1			
PVTT	Absent	<0.001	2.173 (1.471–3.198)	<0.001
	Present			
Capsulation	Capsulated	0.335		
	Noncapsulated			
Tumor number	Single	0.149		
	Multiple			
Vascular invasion	Absent	0.001	1.781 (1.153–2.931)	0.032
	Present			
GPR	<0.84	<0.001	2.734 (1.681–3.832)	<0.001
	≥0.84			
Blood loss	<600	0.007	2.283 (1.136–4.332)	0.023
	≥600			
Blood transfusion	No	0.003	1.734 (1.041–3.829)	0.015
	Yes			

AFP = α-fetoprotein, CI = confidence interval, GPR = γ-glutamyl transpeptidase to platelet ratio, HBV = hepatitis B virus, HRa = hazard ratio adjusted for the propensity score in 4 strata, OS = overall survival, PVTT = portal vein tumor thrombus.
* Edmondson–Steiner stage.

Table 3

Univariate and multivariate analyses of DFS after propensity score adjustment.

Categories	Subcategories	Univariate analysis P value	Multivariate analysis HRa (95% CI)	P value
Sex	Male	0.178		
	Female			
Age, y	<60	0.382		
	≥60			
HBV DNA, copies/mL	<10^3	0.327		
	≥10^3			
Child–Pugh class	A	0.512		
	B			
AFP, ng/mL	<200	0.013	2.342 (1.134–3.541)	0.035
	≥200			
Differentiation*	I–II	0.032	1.124 (1.027–1.320)	0.012
	III–IV			
Tumor size, cm	<5	0.008	1.956 (1.478–2.823)	0.019
	≥5			
Surgical margin, cm	<1	0.001	1.178 (1.089–1.289)	<0.001
	≥1			
PVTT	Absent	<0.001	2.147 (1.246–3.467)	0.004
	Present			
Capsulation	Capsulated	0.435		
	Noncapsulated			
Tumor number	Single	0.079		
	Multiple			
Vascular invasion	Absent	0.048	1.241 (1.021–2.348)	0.013
	Present			
GPR	<0.84	<0.001	2.241 (1.911–3.741)	<0.001
	≥0.84			
Blood loss	<600	0.003	2.045 (1.156–3.332)	0.001
	≥600			
Blood transfusion	No	<0.001	1.513 (1.093–2.870)	0.012
	Yes			

AFP = α-fetoprotein, CI = confidence interval, DFS = disease-free survival, GPR = γ-glutamyl transpeptidase to platelet ratio, HBV = hepatitis B virus, HRa = hazard ratio adjusted for the propensity score in 4 strata, PVTT = portal vein tumor thrombus.
* Edmondson–Steiner stage.

4. Discussion

HCC is one of the major health burdens in the world. To date, many tumor markers have been proposed in the early detection, diagnosis, and prognosis of HCC. Unfortunately, few tumor markers have been externally validated in HCC survival prediction. AFP is still the most widely studied and robust predictor of biomarker for HCC prognostication. Our previous studies have confirmed that AFP-L3% and osteopontin have significant prognostic value in patients with HCC.[6,7] Furthermore, p53, glypican-3, GGT, DCP, and GP73 are also being evaluated as a complement or substitute for AFP in the diagnosis and prognosis of HCC, especially with low AFP concentration.[4,19] In most cases, especially in Asia, it is associated with concomitant liver cirrhosis due to chronic HBV infection.[1,20] Therefore, reevaluation of tumor biomarkers based on liver function tests and other clinicopathological features to find potential candidates to be included in the surveillance of HCC prognosis is of great importance in clinical practice.

Child–Pugh class based on liver function is one of the significant factors influencing the prognosis of patients with HCC.[14,15] But the percentage of patients diagnosed with initial HCC with good liver function continues to increase, owing to improved surveillance methods and effective anti-HBV drug treatment. Child–Pugh class A liver function was found in the majority of patients with HCC who had curative hepatic resection. Hence, discriminating the prognosis of patients with HCC treated with curative hepatectomy regarding Child–Pugh class based on liver function is ineffective. Thrombocytopenia is a cirrhosis surrogate that is associated with HCC development.[21] It has been found that anti-PLT therapy is effective in the prevention of HBV-induced HCC.[11] Recently, a study reported a noteworthy finding that GPR has the power to predict liver cirrhosis and fibrosis in chronic HBV-infected patients in West Africa.[17] In this study, we tried to associate PLT with liver function as a predictive variable, using a hematological parameter, the GGT to PLT ratio, or GPR for short, for the outcome of patients with HBV-related HCC who underwent curative hepatic resection. We found that levels of AFP, GPR, blood loss, and blood transfusion were statistically higher in patients with death outcome according to the baseline characteristics analysis of patients with HCC with different outcomes and more patients suffered from liver cirrhosis, PVTT, and vascular invasion in HCC death group. Because PVTT, portal vein invasion, and advanced Barcelona Clinic Liver Cancer staging have been considered to be associated with poor prognosis of patients with HCC,[22,23] we assume that liver function parameters associated with PLT could be potential biomarkers for the
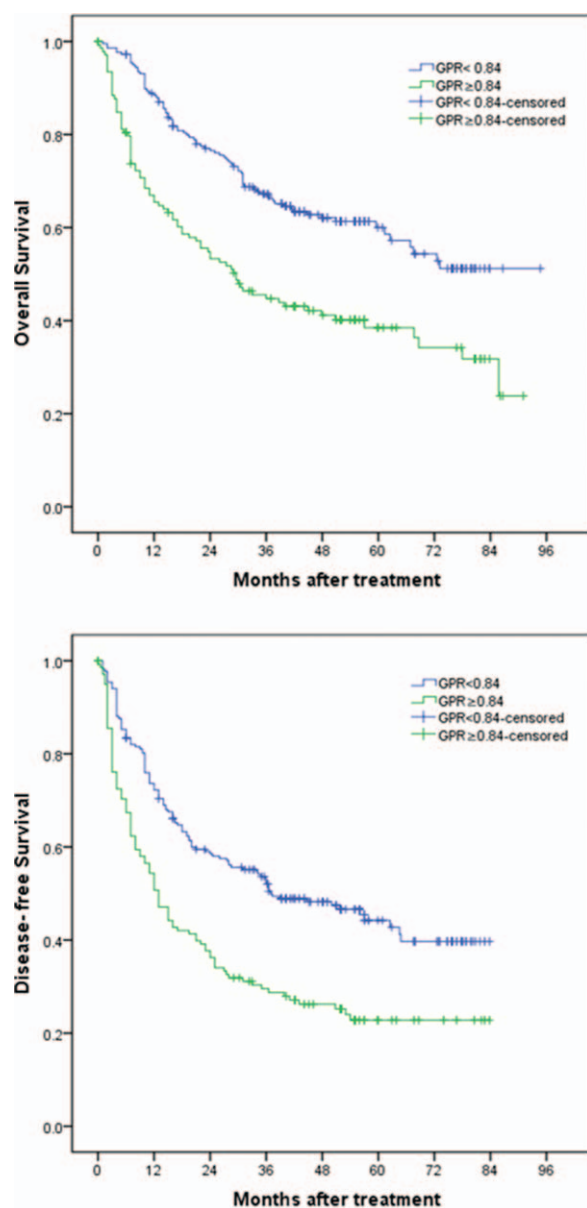
Figure 2. Kaplan–Meier survival plots comparing OS and DFS for patients stratified as low and high GPR groups. (A) OS of patients with GPR ≥0.84 was lower than in those with GPR <0.84 ($P < 0.001$, log-rank test); (B) DFS of patients with GPR ≥0.84 was worse than in those with GPR <0.84 ($P < 0.001$, log-rank test). DFS = disease-free survival, GPR = γ-glutamyl transpeptidase to platelet ratio, OS = overall survival.

prediction of HCC prognosis. In this study, we implemented further analysis of the relationship between these factors and HCC OS.

GGT has been regarded as a significant diagnostic marker for liver diseases.[24] Hepatocarcinogenesis models showed that GGT expression was related to tumor formation and progression.[24] Additionally, the GGT level was significantly higher in patients with HCC with larger tumors.[21] Previous studies have pointed out that patients with elevated GGT level have a worse prognosis than those with low GGT level; therefore, GGT may be a potential tumor prognosis marker in HCC, especially in low-AFP cohort.[25,26] A study carried out by Ruhl and Everhart has shown that elevated GGT was associated with mortality from all causes, diabetes, liver disease, and cancers.[27] Another report from Ma et al showed that serum GGT is a convenient prognostic biomarker related to OS and DFS in patients with HCC treated by RFA.[28] In addition to this, a study from Song et al also suggested that high levels of GGT and indocyanine green retention rate at 15 minutes (ICG-R15) can be preoperative predictor factor when evaluating postoperative tumor recurrence.[29] In patients with chronic HBV infection, GGT has been previously considered as an independent variable for significant fibrosis[30,31] and GPR can predict severe liver cirrhosis and fibrosis in chronic HBV-infected patients in West Africa.[17] In most Asian cases, it is related to concomitant liver cirrhosis due to chronic HBV infection.[2] Consistently with the previous studies, we performed ROC curve analyses of GPR for HCC OS and demonstrated that the GPR score of ≥0.84 represents a major risk factor for the adverse prognosis after hepatic resection. OS was higher in patients with a GPR <0.84 versus ≥0.84 (5-year survival rates 58.6% vs. 38.5%; $P < 0.001$). DFS was also worse in patients with a GPR ≥0.84 than in those with GPR <0.84 (5-year recurrence rates 42.8% vs. 22.8%; $P < 0.001$). The present study demonstrated that GPR can be an independent predictive factor for HBV-related HCC OS.

Although we can draw a conclusion that GPR served as an independent predictive factor for HBV-related HCC OS, there are several limitations in this study. First, this was a retrospective single-center study. Second, all patients with HCC were ethnically Chinese. Third, HBV infection was the only cause of liver fibrosis in all the patients. In order to extend our findings for general cases, multicenter clinical studies are needed, and patients of other ethnicities with various etiologies of liver fibrosis should be also evaluated.

5. Conclusions

In conclusion, serum GGT, among liver function tests, together with PLT should be a potential predictive factor for HCC OS. GPR score of ≥0.84 represents a major risk factor for the poor prognosis for HBV-related HCC after curative hepatic resection, and GPR served as an independent predictive factor for HBV-related HCC OS.

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