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ORIGINAL ARTICLE

Retrospective Cohort Study

Albumin–bilirubin grade as a predictor of survival in hepatocellular carcinoma patients with thrombocytopenia

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Abstract

BACKGROUND

The models for assessing liver function, mainly the Child–Pugh (CP), albumin-bilirubin (ALBI), and platelet–ALBI (PALBI) classifications, have been validated for use in estimating the prognosis of hepatocellular carcinoma (HCC) patients. However, thrombocytopenia is a common finding and may influence the prognostic value of the three models in HCC.

AIM

To investigate and compare the prognostic performance of the above three models in thrombocytopenic HCC patients.

METHODS

A total of 135 patients with thrombocytopenic HCC who underwent radical surgery were retrospectively analyzed. Preoperative scores on the CP, ALBI and PALBI classifications were estimated accordingly. Kaplan–Meier curves with log-rank tests and Cox regression models were used to explore the significant factors associated with overall survival (OS) and recurrence-free survival (RFS).

RESULTS

The preoperative platelet counts were significantly different among the CP, ALBI and PALBI groups. After a median follow-up of 28 mo, 39.3% (53/135) of the patients experienced postoperative recurrence, and 36.3% (49/135) died. Univariate analysis suggested that α-fetoprotein levels, tumor size, vascular invasion, and ALBI grade were significant predictors of OS and RFS. According to the multivariate Cox regression model, ALBI was identified as an independent prognostic factor. However, CP and PALBI grades were not statistically signi-

ficant prognostic indicators.

CONCLUSION
The ALBI grade, rather than CP or PALBI grade, is a significant prognostic indicator for thrombocytopenic HCC patients.

Key Words: Hepatocellular carcinoma; Thrombocytopenia; Child-Pugh; Albumin-bilirubin; Platelet-albumin-bilirubin

Core Tip: Thrombocytopenia is a common finding in hepatocellular carcinoma (HCC) and may influence the prognostic value of the Child–Pugh (CP), albumin–bilirubin (ALBI), and platelet–ALBI (PALBI) grade. We showed that the preoperative platelet count was significantly different among the different CP, ALBI and PALBI groups of thrombocytopenic HCC patients. The statistically significant prognostic model was verified to be ALBI, rather than CP or PALBI. Therefore, ALBI grade is a significant prognostic indicator for thrombocytopenic HCC patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents 85%–90% of all liver cancer cases and is an essential health problem with a growing incidence worldwide[1,2]. HCC could be due to various causes, mainly chronic hepatitis B or C, alcoholic or nonalcoholic fatty liver, and cirrhosis[3,4]. To date, hepatectomy is the preferred radical therapy for HCC patients in the early and middle stages, and the postoperative 5-year survival rate is approximately 70%[5,6].

Most cases of HCC occur in patients with a background of chronic hepatic diseases. Therefore, perioperative liver dysfunction is one of the common reasons for postoperative morbidity and mortality in patients with HCC. Abnormal liver function is also one of the crucial factors for treatment options and long-term outcomes in HCC patients[7]. Previously, several noninvasive tools have been proposed to estimate liver function, tumor stage, treatment choice, and outcome in HCC patients. The Child–Pugh (CP) grade is among the most commonly used models[8,9]. The CP grade is widely used in cirrhotic patients, but it is not suitable for assessing tumor patients. In the CP classification, ascites and encephalopathy are subjective variables, and the levels of albumin (ALB) and ascites are inter-related elements. Therefore, the clinical application of the CP grade in treating HCC is limited and unsatisfactory. In terms of this situation, recently, the ALB–bilirubin (ALBI) and platelet–ALBI (PALBI) combinations have been established in sequence to evaluate the preoperative liver function and prognosis of HCC patients[10,11]. It has been demonstrated that the two emerging models are superior to the classical CP grade in the assessment of preoperative liver function, posthepatectomy liver failure, and outcomes in HCC patients following various treatment modalities[12-15].

Thrombocytopenia is a known noninvasive factor associated with the severity of liver disease. However, platelets have dual effects on liver tumorigenesis and progression. On the one hand, platelets promote tumor growth and angiogenesis by releasing numerous growth factors, such as α-granules and dense granules[16,17]. Thrombocytosis is associated with adverse outcomes in several solid tumors, including HCC[18]. On the other hand, thrombocytopenia is a usual manifestation of HCC and has been reported to be a valuable predictive factor of poor survival and postoperative recurrence[19]. Recently, the platelet count (PLT) was shown to be significantly correlated with hepatic function indices total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), *etc*., as well as the CP, ALBI and PALBI grades in HCC[18,20]. Therefore, PLT influences the prognostic value of the three models in HCC. The present study first explored and compared the prognostic significance of the three models in thrombocytopenic HCC patients.

MATERIALS AND METHODS

Study population

A retrospective cohort study of thrombocytopenic HCC patients who underwent radical surgery at the First Affiliated Hospital of Bengbu Medical College between January 2015 and December 2019 was conducted. The inclusion criteria for patients were as follows: (1) Diagnosed pathologically with HCC; (2) underwent radical surgery for the first time; (3) not receiving preoperative antitumor treatment modalities, including targeted treatment and interventional therapy; and (4) preoperative thrombocytopenia (PLT < 100×10^9/L). The exclusion criteria for patients were as follows: (1) Perioperative mortality; (2) repeat hepatectomy; (3) tumor lesions at other sites; (4) incomplete calculations of the CP, ALBI or PALBI

grade; and (5) malnutrition or hematological disorders; prophylactic platelet transfusions; antiplatelet drugs; *etc*. The study conformed with transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines[21] and the Declaration of Helsinki[22]. The Institutional Review Boards of Bengbu Medical College approved this study, No. 2019-055. All the included patients signed informed consent for the operation.

Data collection

The following baseline information was extracted: age; sex; etiology (hepatitis B virus (HBV) or other); size and number of tumors; presence of vascular invasion; presence of ascites; cirrhosis; and hematological indicators, including preoperative α-fetoprotein (AFP), PLT, TBIL, ALT, AST and ALB levels; and the prothrombin time–international normalized ratio. Preoperative scores and grades of ALBI[10] and PALBI[11] were calculated and evaluated according to the corresponding formulas.

Follow-up

All patients were regularly followed up until December 2021. The follow-up interval, treatment course and salvage treatment were consistent with previous studies[18].

Statistical analysis

All the statistical analyses were carried out with SPSS version 22.0. The dichotomous variables were compared using the χ^2 test. The Wilcoxon test or t test was used to compare the continuous variables. Kaplan–Meier curves were plotted to analyze overall survival (OS) and recurrence-free survival (RFS) rates, and differences were estimated using the log-rank test. Cox regression models were further constructed to explore the independent prognostic factors. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Patients' basic information

A total of 135 HCC patients with thrombocytopenia were recruited in the current cohort, and the basic information is shown in Table 1. The cohort was composed of 113 men and 22 women, and the mean age was 53.7 ± 9.8 years. There were 113 (83.7%) patients with grade A CP and 22 (16.3%) with grade B CP. According to the ALBI classification, patients were divided into grade 1 (n = 59, 43.7%) and grade 2/3 (n = 76, 56.3%) groups. In terms of the PALBI grade, 89 (65.9%) patients had a grade 1 lesion, and 46 (34.1%) had a grade 2/3 lesion. After a median follow-up of 28 mo, 53 (39.3%) patients experienced postoperative recurrence, and 50 (37.0%) patients died (37 from recurrent and progressive tumors, 6 from metastasis, 4 from liver failure, and 3 from upper gastrointestinal hemorrhage). There were significant differences in the PLT among the different groups (CP, ALBI and PALBI) (Figure 1).

Table 1 Basic characteristics of hepatocellular carcinoma patients

Variables	Overall
Etiology: HBV/others	118/17
Sex: Male/female	113/22
Age (yr)	53.7 ± 9.8
Age: ≥ 60/< 60 yr	37/98
ALT (U/L)	38.0 (26.0-63.2)
AST (U/L)	40.0 (29.4-63.0)
TBIL (μmol/L)	14.8 (11.8-20.1)
ALB (g/L)	38.9 (34.1-42.0)
PLT (10^9/L)	80 (62-90)
AFP: ≥ 400/< 400 ng/mL	43/92
Ascites: Yes/no	29/106
Tumor size: > 5/≤ 5 cm	64/71
Tumor number: Multiple/single	20/115
Vascular invasion: Yes/no	15/120
Cirrhosis: Yes/no	89/46

CP grade (A/B)	113/22
ALBI score	-2.53 (-2.76 to -2.15)
ALBI grade (1/2-3)	59/76
PALBI score	-2.65 (-2.82 to -2.44)
PALBI grade (1/2-3)	89/46

Data were expressed as median (interquartile range), mean ± SD, or No. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; ALB: Albumin; PLT: Platelet count; AFP: α-fetoprotein; CP: Child–Pugh; ALBI: Albumin–bilirubin; PALBI: Platelet–albumin–bilirubin; HBV: Hepatitis B virus.

Prognosis of the whole population

Figure 2 shows the Kaplan–Meier survival curves of the whole population. The OS rates at 1, 2 and 3 years were 87.1%, 68.1% and 55.9%, respectively, and the RFS rates at 1, 2 and 3 years were 75.7%, 53.4% and 45.0%, respectively.

Predictors of OS and RFS

Kaplan–Meier survival curves and log-rank analyses demonstrated that the CP and PALBI grades ($P > 0.05$; Figure 3A–D) were not significant predictors of OS and RFS. However, ALBI grade (Figure 3E and F; $P < 0.05$) was found to be a significant predictor of OS and RFS. Univariate Cox regression identified AFP, tumor size, vascular invasion and ALBI grade as valuable predictors of OS and RFS. Ascites was also a significant predictor of worse RFS.

Cox multivariate analyses were conducted, and the results are shown in the forest plot (Figure 4). The AFP level [hazard ratio (HR) 1.98, 95%CI 1.10–3.56] ($P = 0.023$), vascular invasion (HR 2.71, 95%CI: 1.33–5.54) ($P = 0.006$), and ALBI grade (HR 2.78, 95%CI: 1.49–5.19) ($P = 0.001$) were found to be independent predictors of OS. In contrast, tumor size (HR 1.75, 95%CI: 1.03–2.96) ($P = 0.037$), vascular invasion (HR 2.26, 95%CI: 1.15–4.45) ($P = 0.019$), and ALBI grade (HR 1.78, 95%CI: 1.08–2.96) ($P = 0.025$) were found to be independent predictors of RFS (Table 2).

Table 2 Univariate analysis of factors associated with overall survival and recurrence-free survival of hepatocellular carcinoma patients

Variables	OS		RFS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Etiology (HBV/others)	1.908 (0.755-4.824)	0.172	1.449 (0.687-3.058)	0.330
Sex (male/female)	1.510 (0.728-3.129)	0.268	1.245 (0.649-2.389)	0.509
Age (> 60/≤ 60 years)	0.598 (0.297-1.204)	0.150	0.553 (0.292-1.050)	0.070
ALT (> 40/≤ 40 U/L)	1.250 (0.710-2.198)	0.441	1.272 (0.778-2.083)	0.786
AST (> 40/≤ 40 U/L)	1.027 (0.585-1.802)	0.927	1.092 (0.672-1.770)	0.916
TBIL (> 17/≤ 17 μmol/L)	1.411 (0.800-2.487)	0.234	1.156 (0.527-1.418)	0.566
ALB (< 35/≥ 35 g/L)	1.029 (0.566-1.871)	0.924	1.074 (0.635-1.818)	0.789
AFP (≥ 400/< 400 ng/mL)	1.881 (1.054-3.357)	0.032[a]	1.863 (1.128-3.077)	0.015[a]
Ascites (yes/no)	1.692 (0.908-3.152)	0.098	1.788 (1.054-3.033)	0.031[a]
Tumor size (> 5/≤ 5 cm)	1.919 (1.080-3.411)	0.026[a]	2.189 (1.330-3.602)	0.002[a]
Tumor number (multiple/single)	1.265 (0.645-2.481)	0.494	1.161 (0.620-2.175)	0.641
Vascular invasion (yes/no)	2.384 (1.181-4.812)	0.015[a]	2.509 (1.306-4.820)	0.006[a]
Cirrhosis (yes/no)	1.006 (0.563-1.796)	0.984	1.127 (0.668-1.899)	0.654
CP grade (B/A)	1.279 (0.654-2.504)	0.472	0.998 (0.533-1.868)	0.994
ALBI grade (2/1)	2.704 (1.448-5.047)	0.002[a]	1.768 (1.066-2.932)	0.027[a]
PALBI grade (2-3/1)	1.666 (0.945-2.940)	0.078	1.250 (0.758-2.060)	0.382

[a]$P < 0.05$: Statistically significant values.

OS: Overall survival; RFS: Recurrence-free survival; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; ALB: Albumin; PLT: Platelet count; AFP: α-fetoprotein; CP: Child–Pugh; ALBI: Albumin–bilirubin; PALBI: Platelet–albumin–bilirubin; HR: Hazard ratio; HBV: Hepatitis B virus.

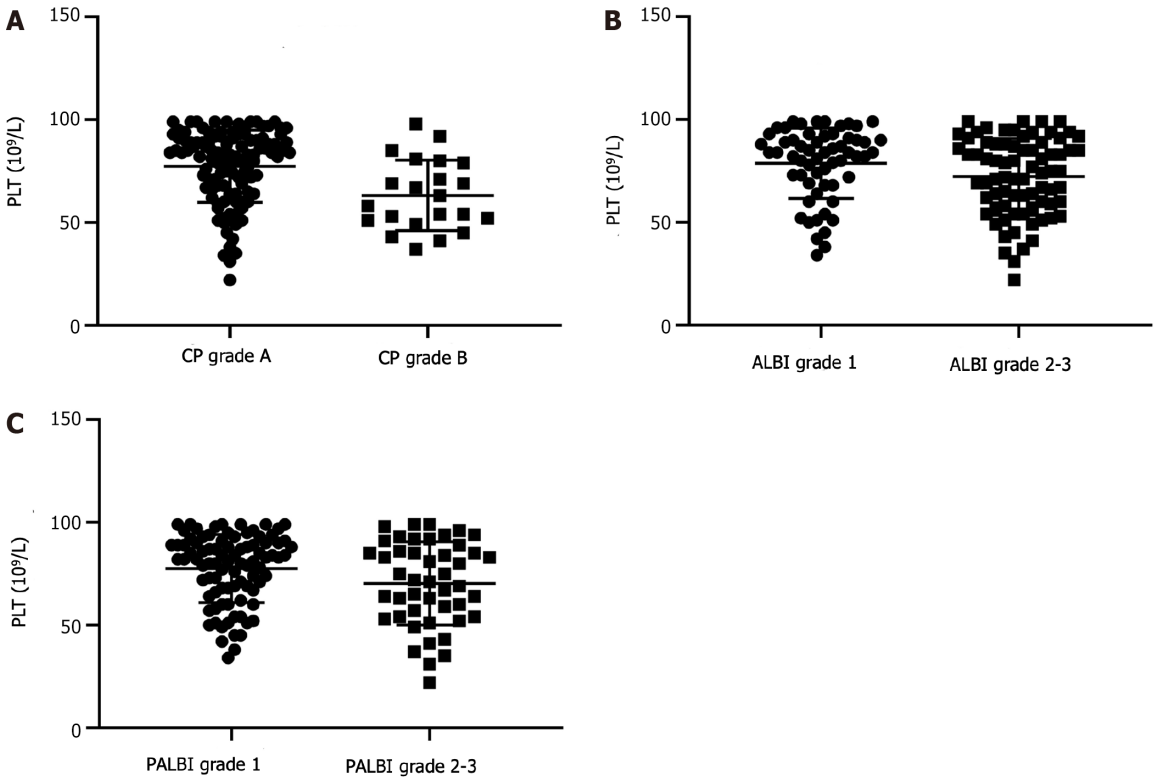

Figure 1 Platelet count in hepatocellular carcinoma patients stratified according to Child–Pugh, albumin–bilirubin and platelet–albumin–bilirubin grades. A: Stratified according to Child–Pugh; B: Stratified according to albumin–bilirubin; C: Stratified according to platelet–albumin–bilirubin. ALBI: Albumin–bilirubin; PALBI: Platelet–albumin–bilirubin; CP: Child–Pugh; PLT: Platelet count.

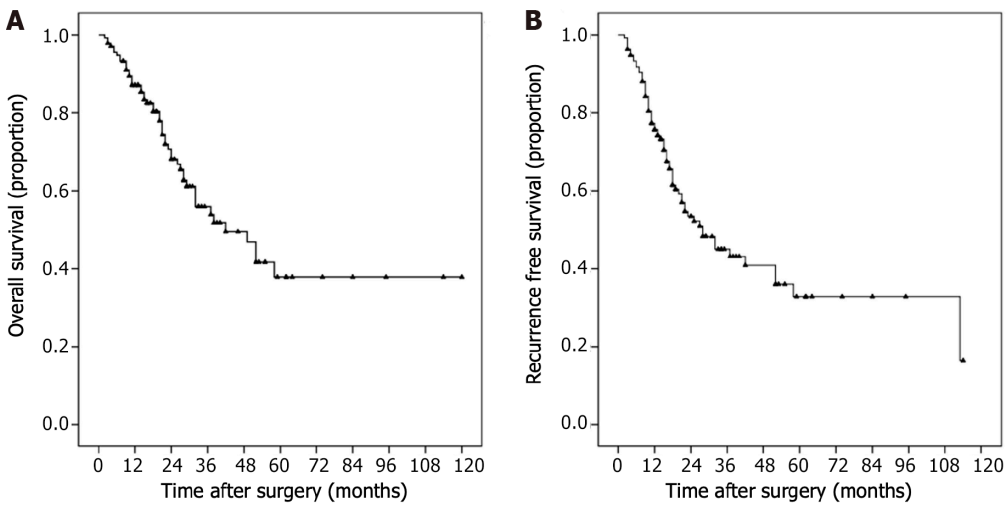

Figure 2 Kaplan–Meier cumulative overall survival and recurrence-free survival curves of the included population. A: Kaplan–Meier cumulative overall survival curve; B: Kaplan–Meier cumulative recurrence-free survival curve.

DISCUSSION

When accompanied by chronic injury or cirrhosis, HCC outcome is associated not only with tumor characteristics but also with hepatic function[7]. Previously, the CP classification has been widely applied to estimate hepatic reserve function, determine treatment, and evaluate the outcome of HCC[8,9,23]. In recent years, it has been shown that CP grade is not satisfactory[24]. In terms of a large HCC cohort, Johnson *et al*[10] recently established the ALBI classification for HCC[10]. Subsequent research has shown that ALBI grade is superior to CP for prediction of HCC outcomes[13,14,25]. In the HCC staging systems, which include the Barcelona Clinic Liver Cancer and the Cancer of Liver Italian Program stages, the ALBI classification was proposed as a replacement for the CP grade, and in the HCC tumor–node–metastasis staging system, the ALBI grade was added as an external supplement[26,27]. PALBI classification is also a more accurate prognostic tool than the CP in HCC patients[15,28].

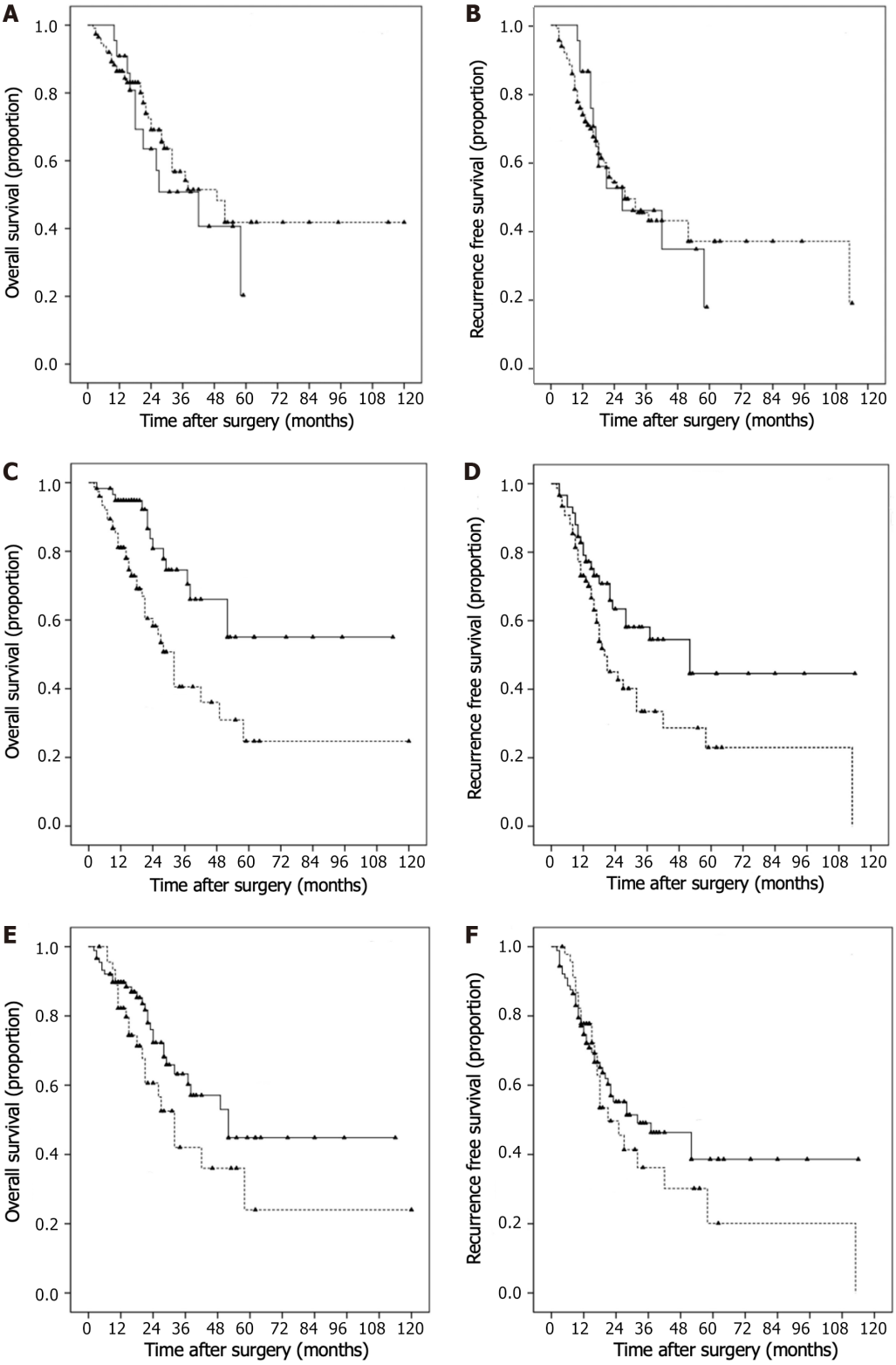

Figure 3 Kaplan–Meier cumulative overall survival and recurrence-free survival curves of the included patients stratified according to Child–Pugh, albumin–bilirubin and platelet–albumin–bilirubin. A: Overall survival (OS) curves stratified according to Child–Pugh (CP) classification; B: Recurrence-free survival (RFS) curves stratified according to CP; C: OS curves stratified according to albumin–bilirubin (ALBI); D: RFS curves stratified according to ALBI; E: OS curves stratified according to Platelet ALBI; F: RFS curves stratified according to PALBI. OS: Overall survival; RFS: Recurrence-free survival; CP: Child–Pugh; ALBI: Albumin–bilirubin; PALBI: Platelet–albumin–bilirubin.

Platelets are associated with the aggressive biological behavior of several types of cancer. However, in liver tumors, platelets have dual regulatory effects. On the one hand, platelets have been proven to accelerate hepatic fibrosis and tumor progression by releasing growth factors normally stored within platelet granules, including platelet-derived growth factor and serotonin[29,30]. Platelets also facilitate angiogenesis, aggressiveness and metastasis of liver tumors *via* these stimulants[31-33]. In contrast, platelets inhibit HCC growth through P2Y12-dependent CD40L release[34].

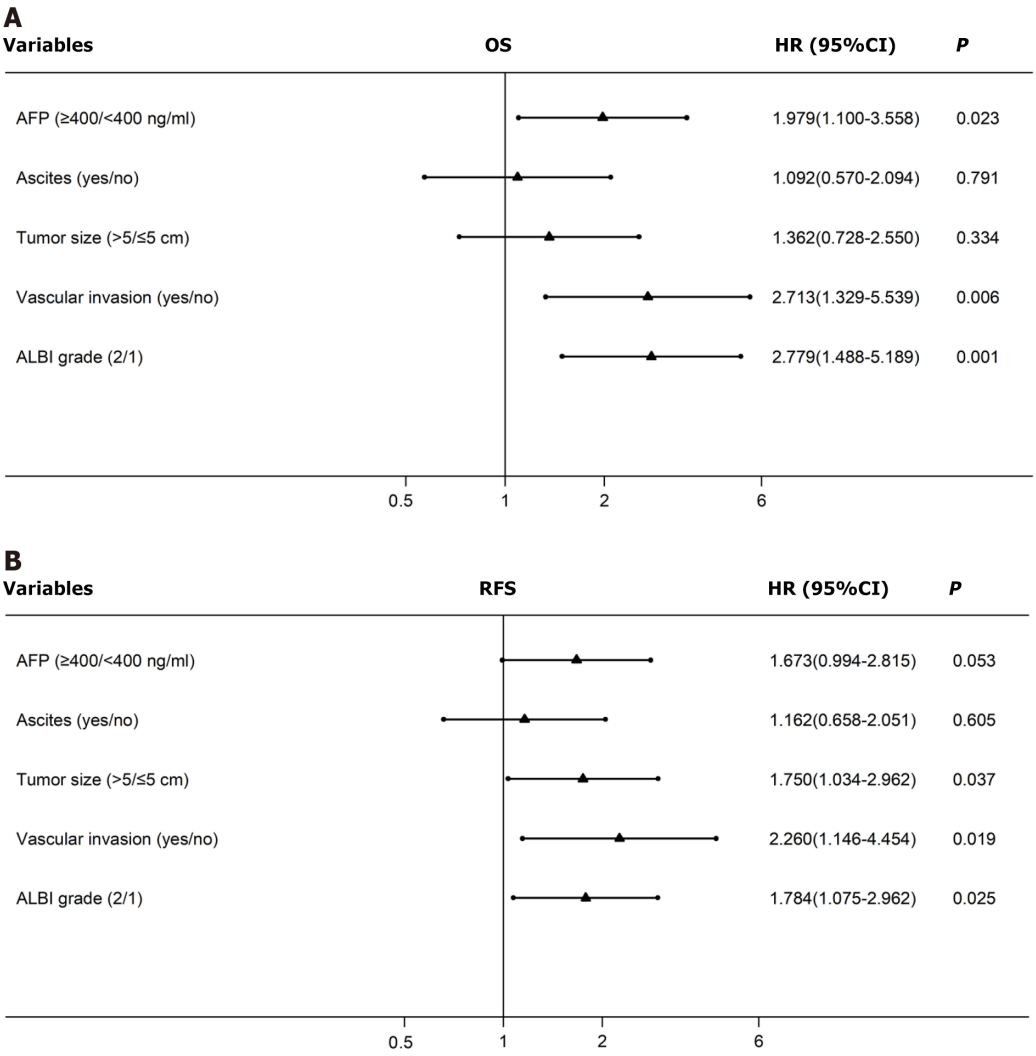

Figure 4 Forest plots based the multivariate analyses results for overall survival and recurrence-free survival. A: Forest plot for overall survival; B: Forest plot for recurrence-free survival. HR: Hazard ratio; AFP: α-fetoprotein; RFS: Recurrence-free survival; OS: Overall survival.

Consistent with these findings, we recently showed that, compared with those with normal PLTs, both high and low PLTs were significantly related to worse survival in patients with HCC[18].

Patients with hepatic cirrhosis and tumors, such as thrombocytopenia and functional changes in platelets, have profound alterations in primary hemostasis[35,36], which makes the assessment of platelets more challenging. PLTs are significantly correlated with liver function and CP, ALBI and PALBI grades[18,20]. Therefore, the PLT influences the prognostic performance of the three models. Recently, we showed that PALBI grade was closely related to OS and RFS in HCC patients, excluding those with thrombocytopenia, and that the order of the models used for identifying survival was as follows: PALBI, ALBI and CP grade[18]. However, in HCC patients with thrombocytopenia, the PALBI grade had a low predictive value[18]. The prognostic abilities of these three models for thrombocytopenic HCC have never been investigated previously. In this study, we found that a higher ALBI grade was significantly associated with worse OS and RFS in thrombocytopenic HCC patients. However, the CP and PALBI grades were not significant prognostic models. Multivariate analyses further identified ALBI grade as a prognostic factor independent of tumor size, AFP level, vascular invasion, and ascites. The underlying reasons that enable ALBI rather than CP or PALBI grade to determine outcome in patients with HCC and thrombocytopenia have not been well established. As the ALBI grade is an index of liver function irrespective of the presence and severity of underlying liver cirrhosis, thrombocytopenia may have less impact on ALBI grade than on CP and PALBI grades.

In previous research, the importance of the ALBI in treating HCC has been emphasized. We recently summarized 12 studies involving > 20 000 HCC patients and demonstrated that a higher preoperative ALBI grade was related to a greater incidence of posthepatectomy liver failure and mortality[37]. Wong *et al*[38] indicated that ALBI grade was a better predictor of severe hepatic failure and 30-d mortality than was the PALBI grade in patients with HCC[38]. The ALBI grade had superior discriminatory potential compared with the CP grade for differentiating outcomes among HCC patients receiving drug-eluting embolic transarterial chemoembolization (TACE)[39], TACE combined with cryoablation or sorafenib[40,41], and thermal ablation[42].

There were several limitations to our study. First, this was a retrospective study with a small sample size and single-center design. Second, only HCC patients who underwent radical hepatectomy were included. However, the superior

performance of the ALBI grade in thrombocytopenic HCC patients receiving other treatments has not been validated. Third, the majority of the included patients had HBV infection. Therefore, comparisons among the three models in patients with other causes, such as hepatitis C virus, require further study. Fourth, other therapies for HCC after recurrence may influence patient outcomes. However, therapeutic information for most patients was missing after recurrence.

CONCLUSION

The ALBI grade, rather than CP or PALBI grade, is an effective prognostic indicator for thrombocytopenic HCC patients. Future research should focus on whether the outcome of thrombocytopenic HCC could be improved by decreasing the ALBI grade.

FOOTNOTES

Co-corresponding authors: Qing Pang and Bin-Quan Wu.

Author contributions: Man ZR and Gong XK contributed to the manuscript preparation; Qu KL helped to perform the statistical analysis and the literature research; Man ZR and Gong XK contributed to data collection and analysis. Both Pang Q and Wu BQ have played important and indispensable roles in the study design, data analysis and manuscript preparation as the co-corresponding authors. Pang Q conceptualized, designed, and supervised the whole process of the research. Wu BQ was responsible for data re-analysis, figures and tables plotting, literature search, and preparation of the final version of the manuscript. This collaboration between Pang Q and Wu BQ is crucial for the publication of this manuscript.

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