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Albumin-bilirubin and platelet-albumin-bilirubin grades for hepatitis B-associated hepatocellular carcinoma in Child–Pugh A patients treated with radical surgery

A retrospective observational study

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Abstract

Child–Pugh (CP) grade A patients with early stage hepatocellular carcinoma (HCC) are candidates for curative surgery, while some patients still have a poor outcome. The aim of this study was to investigate the prognostic values of 2 new evaluation models for liver function, named albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI) grades, in CP grade A patients with HCC.

In this retrospective cohort study, we reviewed 134 cases of CP grade A patients with hepatitis B-associated HCC who underwent radical surgery. ALBI and PALBI grades were calculated based on preoperative serologic examinations. Overall survival (OS) and recurrence-free survival (RFS) were estimated by Kaplan–Meier curve and Cox regression. The prognostic performances of the models were estimated by using the concordance index (C-index).

During a median follow-up time of 27 months, 27.6% (37/134) of patients died and 26.1% (35/134) experienced recurrence. Kaplan–Meier analyses showed that ALBI and PALBI grades were significantly associated with OS and RFS. Multivariate analyses further revealed that both ALBI and PALBI grades were independent predictors for survival. Furthermore, the prognostic values of the combination of tumor size with ALBI (C-index = 0.754, 95% confidence interval [CI]: 0.675–0.849) or with PALBI (C-index = 0.762, 95% CI: 0.664–0.844) may be comparable with both Barcelona Clinic Liver Cancer and Cancer of Liver Italian Program staging systems.

The ALBI and PALBI grades, in particular the combination with tumor size, are effective models for discriminating survival in CP grade A patients with HCC.

Abbreviations: AFP = alpha-fetoprotein, ALB = albumin, ALBI = albumin-bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of Liver Italian Program, CP = Child–Pugh, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, OS = overall survival, PALBI = platelet-albumin-bilirubin, PLT = platelet count, PT-INR = prothrombin time-international normalized ratio, RFS = recurrence-free survival, TBIL = total bilirubin.

Keywords: albumin-bilirubin, Child–Pugh, hepatocellular carcinoma, platelet-albumin-bilirubin, survival

1. Introduction

Worldwide, hepatocellular carcinoma (HCC) is the 4th leading cause of cancer death, with approximately 841,000 new cases and 782,000 deaths annually.[1] Chronic infections with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), chronic alcohol abuse, and nonalcoholic steatohepatitis are the major risk factors for HCC.[2,3] In high risk areas for HCC, such as China and Sub-Saharan Africa, HBV is the main pathogenic factor.

Surgical resection is the crucial curative treatment option for patients with early stage HCC, with 5-year survival rate up to 70%.[4,5] As HCC mainly develops in the background of chronic liver diseases and cirrhosis, hepatic dysfunction is relatively

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common at the time of diagnosis. Previous studies have suggested that in addition to tumor burden, liver function determines treatment options and prognosis of HCC.[5] For decades, the Child–Pugh (CP) grade is widely used as the standard method for assessing liver function. In the HCC guidelines of American and European, CP grade has been adopted in tumor stage and treatment selection.[4,6] According to the guidelines, radical surgery is recommended in CP grade A patients with early stage HCC; however, some of the patients may still have a poor prognosis.[7] Therefore, the prognostic assessment according to CP grade remains unsatisfactory in HCC.

The classic model for end-stage liver disease (MELD) score has also been recognized as a good mortality predictor in HCC.[8] Recently, a novel and simple evaluation model for liver function, called albumin-bilirubin (ALBI) grade, has been established by Johnson et al.[9] The new grade model has been demonstrated to be superior to conventional CP grade in evaluating liver function, posthepatectomy liver failure, and survival of patients with HCC.[10,11] Another new model for liver function, named platelet-albumin-bilirubin (PALBI), has also been validated as a better method of assessing liver function and prognosis than CP grade.[12,13] However, to our knowledge, the prognosis values of ALBI and PALBI grades have rarely been investigated in CP grade A patients with HCC. In this study, we firstly compared the prognostic performance of the 2 grades with MELD and classic prognostic models for HCC, including the Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program (CLIP) staging systems.

2. Methods

2.1. Study population

The medical records of patients with HCC who undergone radical resection in our department between January 2014 and June 2018 were retrospectively analyzed. The inclusion criteria were: HCC with histologic confirmation; positive hepatitis B surface antigen; received radical hepatectomy (complete resection of the tumor with negative margin) for the 1st time; and CP grade A. Exclusion criteria were: surgery-related mortality; rehepatectomy; coinfection with HCV; mixed hepatocellular cholangiocarcinoma; extrahepatic metastasis; incomplete information on the calculation of ALBI and PALBI; and coexistent hematologic disorders, malnutrition, or other serious diseases that significantly influence scores of ALBI and PALBI. The present report was in compliance with the guideline of Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD).[14] Our study was in accordance with the Declaration of Helsinki[15] and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Written informed consent was given by patients.

2.2. Data collection

We extracted the following baseline information by using the electronic medical records: age, gender, tumor characteristics (number, diameter of the largest lesion, and vascular invasion), presence of ascites, presence of liver cirrhosis, pathologic results, and preoperative serologic tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum bilirubin (TBIL), albumin (ALB), platelet count (PLT), prothrombin time-international normalized ratio (PT-INR), creatinine (Cr), and alpha-fetoprotein (AFP). TBIL and ALB were detected by automatic biochemistry analyser (Cobas C8000; Roche Inc, Basel, Switzerland) and PLT was detected by automatic hematology analyzer (XE-5000; Sysmex Inc, Kobe, Japan). Preoperative clinical data were used to calculate ALBI, PALBI, and MELD scores according to the following formula:

1. ALBI score: $0.66 \times \log_{10}$ TBIL (μmol/L) – $0.085 \times$ ALB (g/L). ALBI grade was defined as: grade 1: ≤–2.60; grade 2: –1.39 to –2.60; grade 3: >–1.39.[9]
2. PALBI score: $2.02 \times \log_{10}$TBIL (μmol/L) $- 0.37 \times (\log_{10}$TBIL$)^2 - 0.04 \times$ ALB (g/L) $- 3.48 \times \log_{10}$PLT (10^9/L) $+ 1.01 \times (\log_{10}$PLT$)^2$. PALBI grade was defined as: grade 1: ≤–2.53; grade 2: –2.09 to –2.53; grade 3: >–2.09.[12]
3. MELD score: $9.57 \times \log_e$ (Cr mg/dL) $+ 3.78 \times \log_e$ (TBIL mg/dL) $+ 11.2 \times \log_e$ (INR) + 6.43. Patients were stratified into 3 risk groups: MELD < 10, MELD 10–14, and MELD > 14.[16]

2.3. Follow-up

After discharge from the hospital, patients were regularly followed-up (every 2 months for the 1st year, every 3 months for the 2nd year, and every 6 months thereafter) until December 2018 or until death. The follow-up contents mainly included CT/MRI, abdominal ultrasound, and serologic tests. Postoperative recurrence and death were recorded. Recurrent patients received salvage treatments, including re-resection, ablation, or transcatheter arterial chemoembolization, as appropriate.

2.4. Statistical analysis

We used SPSS version 18.0 for data collection and analysis. Continuous variables with normal distribution (Kolmogorov–Smirnov test, $P > .05$) were expressed as mean value ± standard deviation (SD). Or else, median (interquartile range) was used. Comparisons between groups were performed by using the *t*, Wilcoxon, or χ^2 test, as appropriate.

The primary outcomes were overall survival (OS) and recurrence-free survival (RFS), which were estimated by Kaplan–Meier curve and log-rank test. All variables that were found to be statistically or nearly significant ($P < .10$) entered into the multivariate Cox regression model. The prognostic values were compared between different models by using concordance index (C-index), a value reflects the prognostic discrimination ability: the higher the C-index, the more accurate the prognostic prediction is (C-index, low accuracy: 0.50–0.70; medium accuracy: 0.70–0.90; high accuracy: >0.90).[17] A *P*-value < .05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

A total of 134 CP grade A patients with HCC were included in this study. It consisted of 102 men and 32 women, with a mean age of 51.8 ± 11.1 years. Based on ALBI grade, patients could be divided into 2 groups: ALBI grade 1 (n = 86, 64.2%) and grade 2 (n = 48, 35.8%). According to the PALBI grade, there were 83 (61.9%) patients with grade 1, 44 (32.8%) patients with grade 2, and 7 (5.2%) patients with grade 3. During a median follow-up time of 27 months, 35 (26.1%) experienced postoperative recurrence, and 37 (27.6%) patients died (29 died from recurrence and tumor progression, 3 from distant metastasis, 3 from hepatic failure, and 2 from gastrointestinal hemorrhage).

Table 1

Basic characteristics of patients with hepatocellular carcinoma stratified according to level of the ALBI and PALBI.

Variables	Overall (n = 134)	ALBI grade			PALBI grade		
		1 (n = 86)	2 (n = 48)	*P*	1 (n = 83)	2/3 (n = 51)	*P*
Sex, male/female	102/32	66/20	36/12	.820	67/16	35/16	.111
Age, yr	51.8 ± 11.1	51.5 ± 10.9	52.3 ± 11.5	.935	51.5 ± 10.5	52.2 ± 12.0	.668
ALT, IU/L	34.3 (24.4–59.8)	30.7 (20.0–47.9)	38.7 (26.9–91.3)	**.027**	33.0 (23.2–47.5)	36.0 (25.5–82.1)	.349
AST, IU/L	34.7 (25.4–52.2)	32.5 (25.4–45.2)	39.3 (25.6–76.3)	.146	32.4 (24.4–44.6)	42.0 (27.8–79.7)	**.017**
TBIL, μmol/L	13.8 (10.4–18.4)	13.1 (10.0–16.1)	15.7 (11.6–20.3)	**.020**	11.8 (9.6–14.3)	18.5 (14.9–24.3)	**<.001**
ALB, g/L	40.6 (36.9–43.4)	42.2 (40.7–45.2)	36.2 (34.0–37.2)	**<.001**	41.7 (39.0–44.4)	38.1 (35.9–41.7)	**<.001**
PT-INR	1.07 (1.03–1.14)	1.06 (1.03–1.12)	1.09 (1.02–1.19)	.238	1.06 (1.02–1.13)	1.09 (1.03–1.18)	.239
PLT, 10^9/L	142 (104–186)	146 (111–190)	120 (95–183)	.097	130 (96–169)	173 (105–235)	**.003**
AFP: ≥400/<400 ng/mL	40/82	28/50	12/32	.330	26/48	14/34	.493
Ascites: yes/no	18/116	10/76	8/40	.412	10/73	8/43	.549
Tumor size, cm	5.0 (3.0–8.0)	4.5 (3.0–8.0)	6.5 (4.0–10.0)	**.023**	4.0 (3.0–6.5)	8.0 (4.4–10.0)	**<.001**
Tumor number: multiple/single	11/123	6/80	5/43	.713	6/77	5/46	.839
Vascular invasion: yes/no	19/115	14/72	5/43	.351	15/68	4/47	.099
Cirrhosis: yes/no	75/59	46/40	29/19	.439	48/35	27/24	.580
BCLC: A/B + C	109/25	69/17	40/8	.659	66/17	43/8	.489
CLIP: 0/1–4	63/59	40/38	23/21	.916	38/36	25/23	.937
MELD score	2.8 (1.4–5.2)	3.0 (1.4–5.1)	2.5 (1.3–5.8)	.954	2.5 (1.2–4.8)	4.0 (1.6–5.8)	.062
ALBI grade (1/2)	86/48	–	–	–	67/16	19/32	**<.001**
PALBI grade (1/2–3)	83/51	67/19	16/32	**<.001**	–	–	–

Data were expressed as median (interquartile range), mean ± standard deviation, or no.

Statistically significant values are given in bold.

AFP = alpha-fetoprotein, ALB = albumin, ALBI = albumin-bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of the Liver Italian Program, MELD = model for end-stage liver disease, PALBI = platelet-albumin-bilirubin, PLT = platelet count, PT-INR = prothrombin time-international normalized ratio, RFA = radiofrequency ablation, TBIL = total bilirubin.

3.2. Associations between the ALBI, PALBI grades, and clinicopathologic feature

Table 1 shows the demographic data, serologic tests, tumor characteristics, and stages of patients stratified according to preoperative ALBI and PALBI grades. Clinical characteristics were comparable between ALBI grade 1 and grade 2 except for ALT, TBIL, ALB, tumor size, and PALBI grade. In contrast, patients with elevated grades (2 and 3) of PALBI had significantly higher levels of AST, TBIL, PLT, larger tumor size, lower ALB, and higher ALBI grade. The scatter plot further revealed the strong correlation between ALBI score and PALBI score (Fig. 1, Pearson $r = 0.6804$, $P < .0001$).

3.3. Prognosis of the entire cohort

Figure 2A, B showed the Kaplan–Meier cumulative OS and RFS curves of the entire cohort. The 1-, 2-, and 3-year OS rates were 83.5%, 72.9%, and 66.4%, respectively, and the 1-, 2-, and 3-year RFS rates were 78.4%, 65.4%, and 62.1%, respectively.

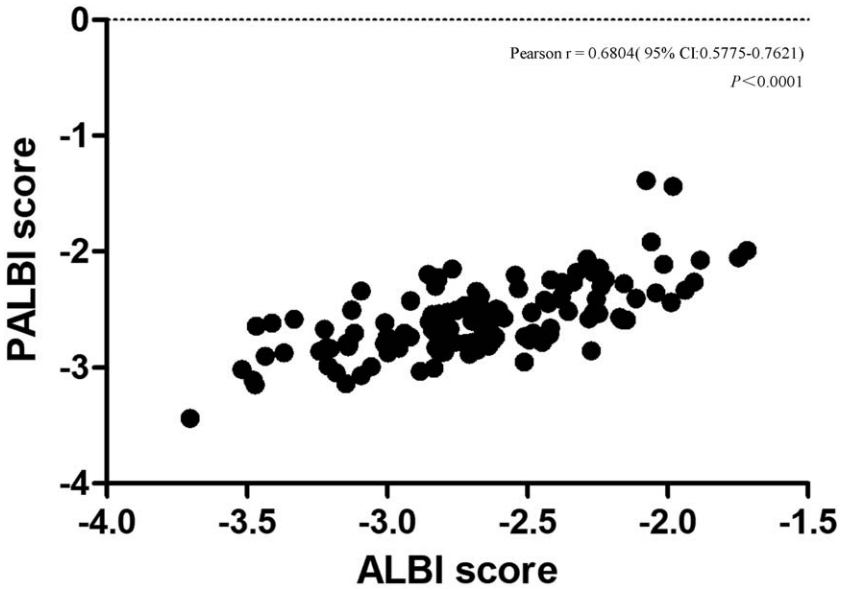


Figure 1. The scatter plot of the relationship between albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI).

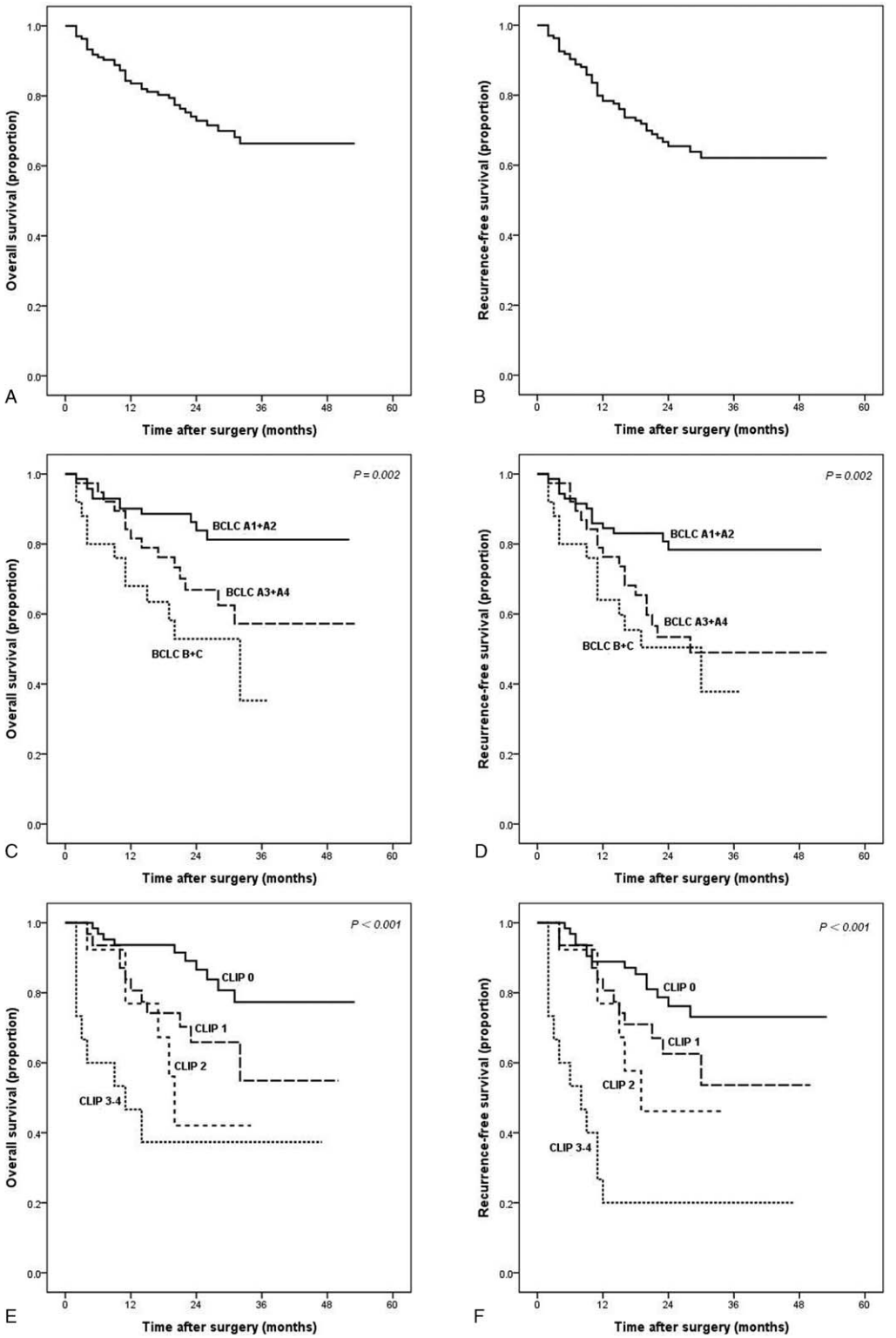


Figure 2. Kaplan–Meier cumulative overall survival (A) and recurrence-free survival (B) curves of the study population, and overall survival and recurrence-free survival curves of patients stratified according to Barcelona Clinic Liver Cancer (BCLC) (C, D) and Cancer of the Liver Italian Program (CLIP) (E, F) staging systems.

Moreover, Figure 2C–F showed the Kaplan–Meier curves of patients stratified according to BCLC stage and CLIP stage. The log-rank tests demonstrated that OS and RFS varied significantly with different BCLC stage (Fig. 2C, D, both $P < .05$) and CLIP stage (Fig. 2E, F, both $P < .05$).

3.4. Predictors of OS and RFS

Kaplan–Meier analyses with log-rank tests showed that ALBI (Fig. 3A, B, both $P < .05$) and PALBI (Fig. 3C, D, both $P < .05$) were both significantly associated with OS and RFS. Univariate analyses revealed that AST, AFP, tumor size, tumor number,

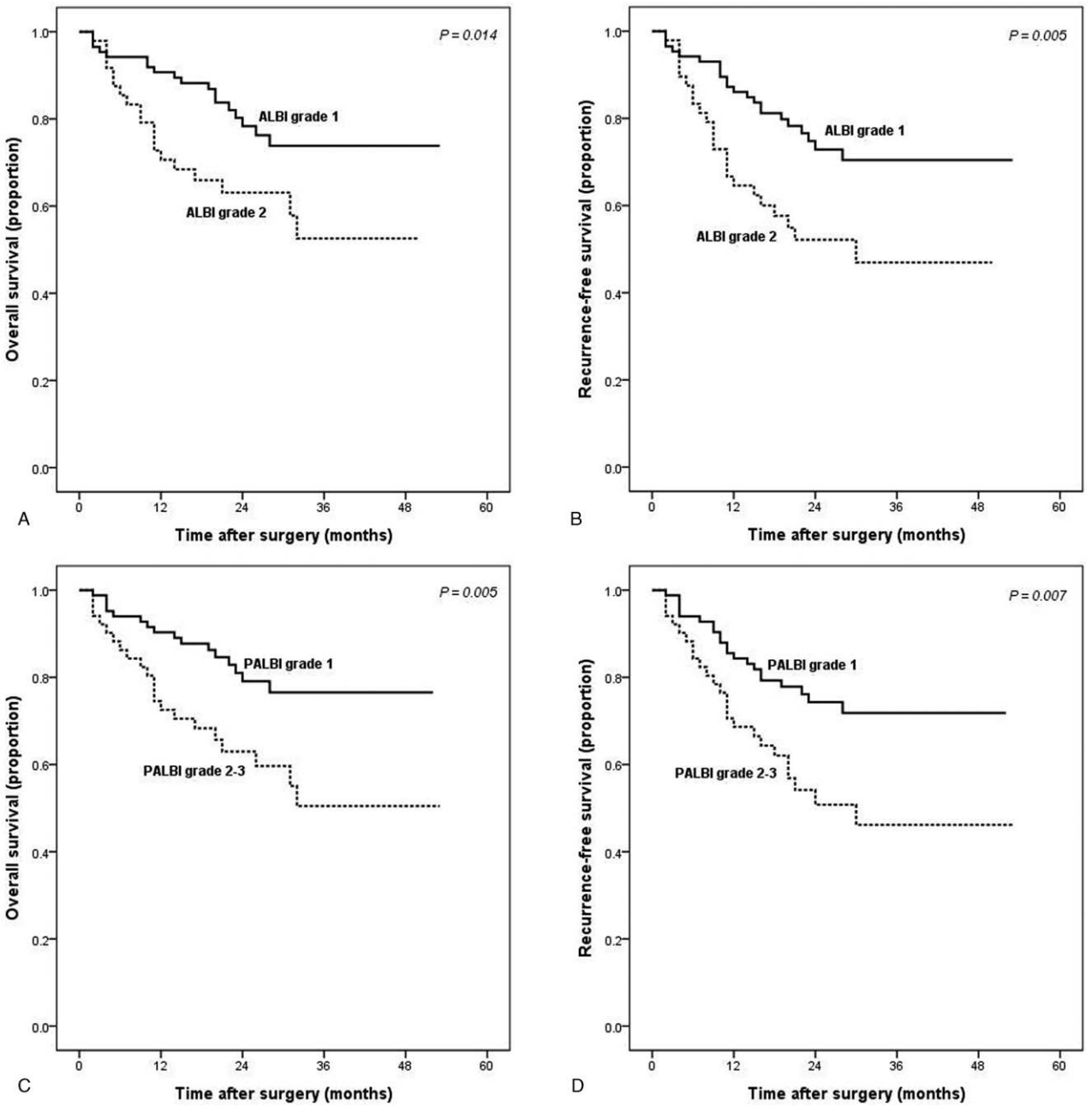


Figure 3. Kaplan–Meier cumulative overall survival and recurrence-free survival curves of patients stratified according to albumin-bilirubin (ALBI) (A, B) and platelet-albumin-bilirubin (PALBI) (C, D).

BCLC, CLIP, ALBI, and PALBI were significantly associated with OS. In addition to the above factors, TBIL and status of cirrhosis were also found to be significantly associated with RFS (Table 2). Surprisingly, vascular invasion was not a significant prognostic factor in our study, which was consistent with several previous reports.[18,19]

Furthermore, multivariate analyses were performed and the results were presented in the forest plots (Fig. 4). AFP, tumor size, tumor number, CLIP, ALBI, and PALBI grades were independent predictors for OS and RFS. However, BCLC stage was not independently associated RFS.

3.5. Comparison of predictive accuracy for survival between the ALBI, PALBI grades, and BCLC, CLIP staging systems

Based on C-index, the order of the models in discriminating survival was as follows: CLIP, PALBI, ALBI, BCLC, and MELD. As all patients in our study were ALBI grades 1 and 2 and no patients belonged to BCLC stage 0, the integration of ALBI grade into original BCLC stage (BCLC-ALBI) had the same value of C-index as BCLC stage. In addition, the integration of ALBI grade into original CLIP stage (CLIP-ALBI) provided higher

Table 2

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

	OS		RFS	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex (male/female)	0.600 (0.301–1.195)	.146	0.651 (0.346–1.223)	.182
Age (>60/≤60 yrs)	1.025 (0.468–2.243)	.951	0.792 (0.369–1.701)	.549
ALT (>60/≤60 IU/L)	1.104 (0.533–2.288)	.790	1.246 (0.653–2.380)	.505
AST (>45/≤45 IU/L)	1.967 (1.025–3.773)	**.042**	1.961 (1.084–3.548)	**.026**
TBIL (>17/≤17 μmol/L)	1.455 (0.749–2.829)	.269	1.826 (1.010–3.301)	**.046**
ALB (<35/≥35 g/L)	1.360 (0.529–3.496)	.523	1.605 (0.716–3.598)	.250
PT-INR (per 1 unit increase)	2.249 (0.095–53.461)	.616	3.033 (0.182–50.529)	.439
PLT (<100/≥100 × 10^9/L)	1.005 (0.474–2.131)	.990	1.276 (0.669–2.432)	.459
AFP (≥400/<400 ng/mL)	3.187 (1.650–60156)	**.001**	3.193 (1.760–5.791)	**<.001**
Ascites (yes/no)	1.520 (0.667–3.463)	.319	1.496 (0.697–3.215)	.302
Tumor size (>5/≤5 cm)	6.158 (2.699–14.047)	**<.001**	5.426 (2.678–10.991)	**<.001**
Tumor number (multiple/single)	3.078 (1.351–7.014)	**.007**	2.432 (1.085–5.451)	**.031**
Vascular invasion (yes/no)	1.829 (0.799–4.189)	.153	1.552 (0.721–3.338)	.261
Cirrhosis (yes/no)	1.978 (0.977–4.005)	.058	2.056 (1.079–3.919)	**.029**
BCLC (B + C/A)	2.749 (1.375–5.493)	**.004**	2.181 (1.143–4.162)	**.018**
CLIP (1–4/0)	3.638 (1.748–7.571)	**.001**	2.928 (1.549–5.534)	**.001**
ALBI grade (2/1)	2.197 (1.152–4.191)	**.017**	2.261 (1.258–4.062)	**.006**
PALBI grade (2 and 3/1)	2.452 (1.279–4.702)	**.007**	2.194 (1.220–3.945)	**.009**
MELD score (≥10/<10)	1.684 (0.404–7.016)	.474	2.192 (0.526–9.140)	.281

Statistically significant values are given in bold.

AFP = alpha-fetoprotein, ALB = albumin, ALBI = albumin-bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, HR = hazard ratio, MELD = model for end-stage liver disease, OS = overall survival, PALBI = platelet-albumin-bilirubin, PLT = platelet count, PT-INR = prothrombin time-international normalized ratio, RFA = radiofrequency ablation, RFS = recurrence-free survival, TBIL = total bilirubin.

accuracy in predicting survival compared with CLIP stage. In our study, tumor size was a crucial prognostic factor of HCC, which was consistent with previous reports.[4,20] When combined with tumor size, prognostic values of both ALBI (C-index = 0.754, 95% confidence interval [CI]: 0.675–0.849) and PALBI (C-index = 0.762, 95% CI: 0.664–0.844) may be not inferior to BCLC, BCLC-ALBI, CLIP, as well as CLIP-ALBI staging systems (Table 3). In particular, PALBI was more useful than ALBI regardless of the combination with tumor size.

3.6. Stratification of patients according to the combination of tumor size with ALBI or with PALBI

The simple combination of tumor size with ALBI or with PALBI presented medium accuracy (the value of C-index more than 0.70) in predicting survival. Based on ALBI and tumor size, we stratified patients as stage I (ALBI grade 1 and tumor size ≤5 cm), stage II (ALBI grade 1 and tumor size >5 cm, or ALBI grade 2 and tumor size ≤5 cm), and stage III (ALBI grade 2 and tumor size >5 cm). The 1-, 2-, and 3-year OS rates were 100.0%, 92.9%, and 92.9% vs 82.7%, 68.2%, and 57.9% vs 55.6%, 47.3%, and 35.5% for patients with stages I, II, and III, respectively (Fig. 5A, $P < .001$). In addition, compared with stages II and III, patients in stage I had significantly better RFS (Fig. 5B, $P < .001$).

Furthermore, based on PALBI and tumor size, we stratified patients as stage I (PALBI grade 1 and tumor size ≤5 cm), stage II (PALBI grade 1 and tumor size >5 cm, or PALBI grades 2 and 3 and tumor size ≤5 cm), and stage III (PALBI grades 2 and 3 and tumor size >5 cm). Similarly, patients in stage I had significantly better OS and RFS (Fig. 5C, D, $P < .001$).

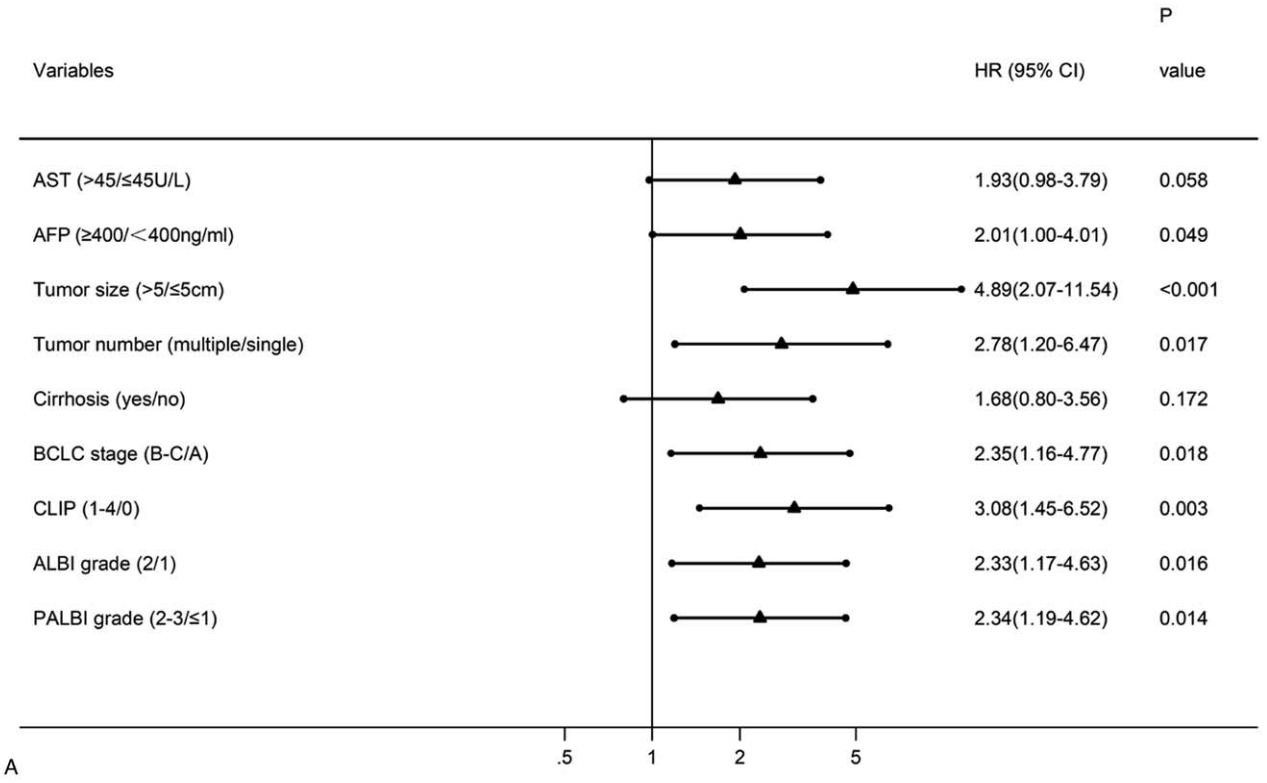
4. Discussion

As most cases originate from damaged liver tissue, prognosis of HCC depends on not only tumor burthen but also liver functional reserve.[5] Worldwide, classic CP grade is used as a standard for assessing the degree of liver function injury, selecting treatment, and evaluating prognosis in HCC.[4,6,21] Moreover, several HCC staging systems that consider CP grade, such as CLIP[22] and BCLC,[23] have been widely proposed as effective tools for predicting survival in HCC. However, flaws of the CP grade have recently been proposed.[24,25]

According to HCC clinical guidelines, CP grade A is the requirement for hepatectomy,[4,6] while some patients still have a poor prognosis.[7] Therefore, derived from a cohort of 1313 patients with HCC, Johnson et al recently established the new ALBI grade system.[9] The ALBI grade only contains serum TBIL and ALB, and has been demonstrated to have superior prognostic value than the CP grade.[10,11,26–28] ALBI grade has also been recommended as a substitute for CP grade in BCLC stage, CLIP stage and as the addition of tumor-lymph node-metastasis stage for HCC.[29–31] In addition, the PALBI grade offers better performance of evaluating hepatic functional reserve and prognosis than the CP grade.[12,13,32]

According to the ALBI grade, CP grade A patients with HCC could be divided into 2 groups with clearly different prognoses.[9] In the present study, patients with CP grade A were divided into ALBI grade 1 (64.2%) and 2 (35.8%) groups, and PALBI grade 1 (61.9%) and PALBI grades 2 and 3 (38.1%) groups. In line with previous reports,[9,33] we found that patients with ALBI grade 2 had significantly worse survival than patients with ALBI grade 1. Our findings also indicated that PALBI grade could be used as a predictor of survival in CP grade A patients with HCC.

The comparisons of prognostic ability between ALBI, PALBI, MELD, and classic HCC stages have rarely been performed. In the present study, the combination of tumor size with ALBI, particularly with PALBI, showed higher performance for survival prediction than MELD, BCLC, and CLIP staging systems. Patients with lower grade of ALBI (or PALBI) and smaller tumor size had significantly better outcomes. Chan et al recently



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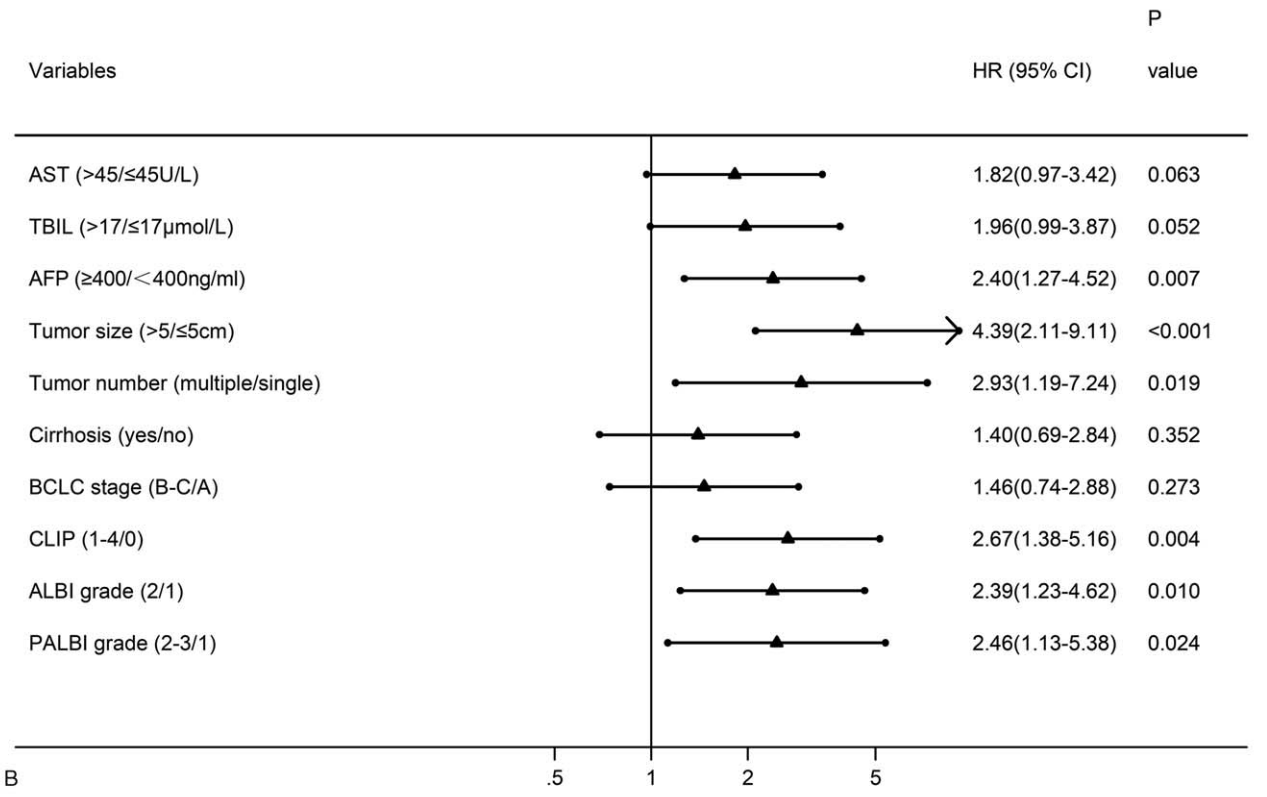

B

Figure 4. Forest plots based the results of multivariate analysis for overall survival (A) and recurrence-free survival (B).

Table 3

Ranking of discriminatory ability of the prognostic systems on the basis of the C-index.

Rank	System	C-index	95% CI
1	PALBI + tumor size	0.762	0.675–0.849
2	ALBI + tumor size	0.754	0.664–0.844
3	CLIP-ALBI	0.727	0.626–0.828
4	CLIP stage	0.699	0.594–0.804
5	PALBI	0.671	0.565–0.776
6	BCLC-ALBI	0.670	0.565–0.775
7	BCLC stage	0.670	0.565–0.775
8	ALBI	0.650	0.542–0.758
9	MELD	0.477	0.366–0.588

ALBI = albumin-bilirubin, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, MELD = model for end-stage liver disease, PALBI = platelet-albumin-bilirubin.

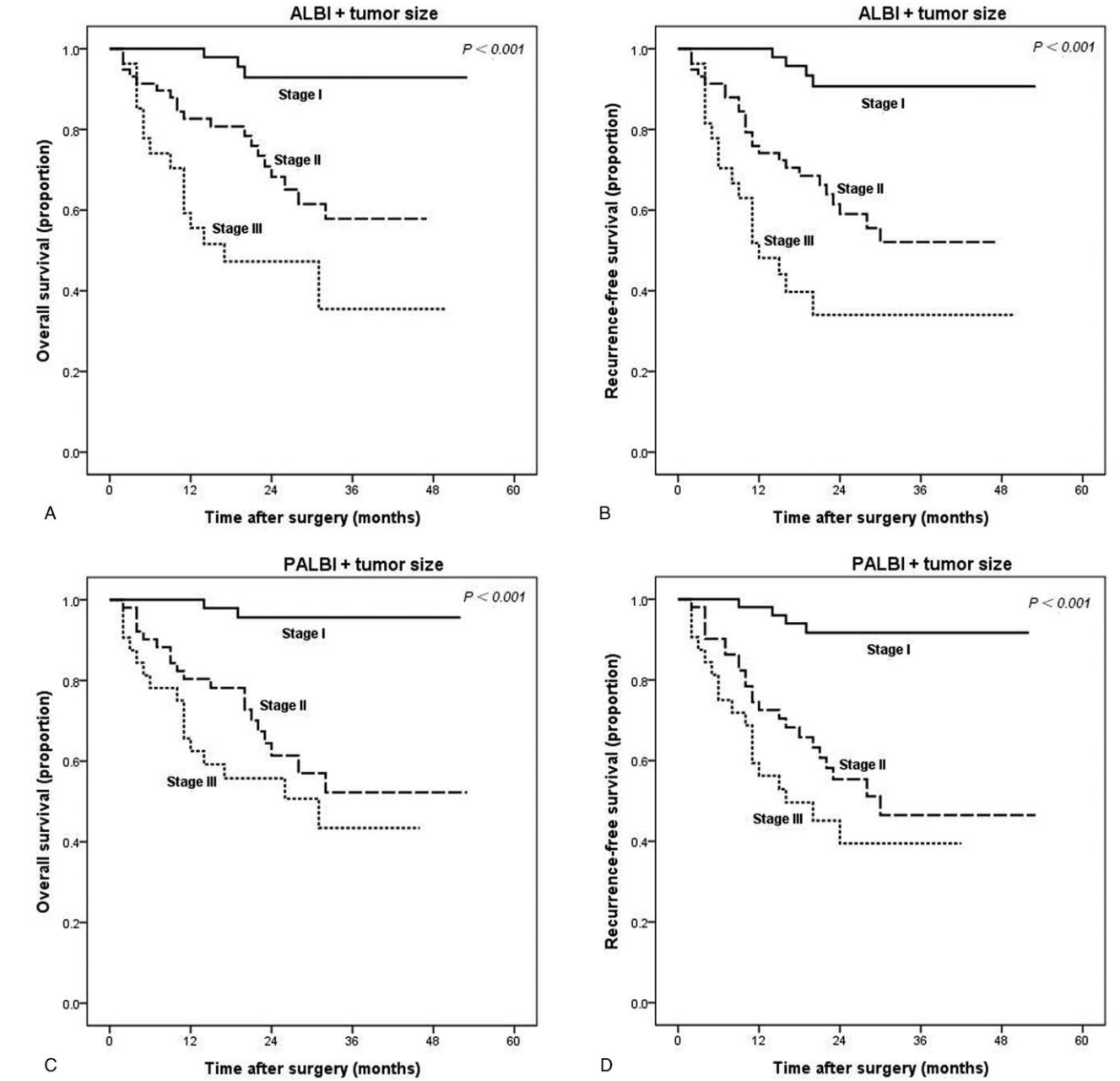

Figure 5. Cumulative overall survival and recurrence-free survival curves of patients stratified according to the albumin-bilirubin (ALBI) and tumor size (A, B, stage I: ALBI grade 1 and tumor size ≤5 cm; stage II: ALBI grade 1 and tumor size >5 cm, or ALBI grade 2 and tumor size ≤5 cm; stage III: ALBI grade 2 and tumor size >5 cm), platelet-albumin-bilirubin (PALBI), and tumor size (C, D: stage I: PALBI grade 1 and tumor size ≤5 cm; stage II: PALBI grade 1 and tumor size >5 cm, or PALBI grades 2 and 3 and tumor size ≤5 cm; stage III: PALBI grades 2 and 3 and tumor size >5 cm).

recruited 1973 patients with HCC regardless of CP grade and showed that the integrations of ALBI grade into original BCLC and CLIP staging systems provided high accuracy in predicting survival, with the C-indices 0.760 and 0.789, respectively.[31] Other studies have also suggested that the modification of BCLC and CLIP systems with ALBI grade can improve prognosis prediction for HCC.[29,34] However, substituting CP grade by ALBI grade in the 2 staging systems has never been investigated in CP grade A patients. In our study, the simple combinations of tumor size with ALBI and with PALBI showed comparable C-indices when compared to BCLC-ALBI and CLIP-ALBI, indicating that both of them can be recommended to assess the prognosis of CP grade A patients with HCC.

The underlying mechanisms enable higher grades of ALBI and PALBI to indicate worse OS and RFS in HCC are not well established. All the components in the 2 grades, including ALB, TBIL, and platelets, may contribute to the development and prognosis of HCC. In vitro study showed that direct addition of exogenous ALB could inhabit tumor growth in HCC cell lines via the modulation of α-fetoprotein and growth-controlling kinases.[35] Hypoalbuminemia has widely been demonstrated to be associated with the progress, survival, and recurrence of several types of tumors, including HCC.[36–38] Elevated serum TBIL is a sensitive reflection of liver injury due to an injurious effect on hepatocytes. A systematic review summarized the prognostic indicators of liver function and identified serum ALB and TBIL as the 2 most prominent prognostic factors.[39] Platelets are known to stimulate HCC tumor growth via producing several stimulants, including vascular endothelial growth factor, platelet-derived growth factor, serotonin, and so forth.[40–43] Platelets can also accelerate angiogenesis and metastasis of HCC via releasing platelet-derived mediators.[43,44] PLT, used for PALBI, might affect survival by the presence of portal hypertension. Numerous studies have shown that PLT is significantly associated with OS and RFS of HCC.[45–47] In addition, PLT is positively correlated with tumor size in patients with HCC and platelets promote tumor growth while ALB inhabits tumor growth in vitro.[35,41,43] Therefore, PALBI and ALBI may be significant factors related to tumor size.

There are several limitations in the present study. Firstly, this is a single-center retrospective study with relatively small sample size, thus external validation from larger multicenter prospective studies is still needed. Secondly, the results are based on patients with HCC who underwent radical resection and who were CP grade A. Less than 20% of patients with HCC were BCLC stages B and C. Therefore, further study is needed to validate the prognostic accuracy of ALBI and PALBI grades in patients with HCC with different treatment modalities and to compare with BCLC and CLIP in patients regardless of CP grade. Thirdly, it has been recently reported that postoperative grade of ALBI may be more valuable than preoperative grade in predicting outcome of HCC.[48] However, as the retrospective design, the majority of patients in the cohort had missing data of dynamic measures. Lastly, the ALB replacement therapy, methods for measuring serum ALB, and the presence of constitutional jaundice may affect the role of ALBI and PALBI.

In conclusion, ALBI and PALBI grades, in particular the combination with tumor size, are effective models for discriminating survival in HBV-associated patients with HCC with CP grade A. Future studies should explore whether the survival of HCC can be prolonged by improving ALBI and PALBI grades.

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