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Platelet-albumin-bilirubin versus albumin–bilirubin as a predictor of long-term survival for hepatitis B-Induced hepatocellular carcinoma after hepatic resection

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Abstract

Background The Child–Pugh (CP) score is widely used to evaluate the severity of liver dysfunction in patients with hepatocellular carcinoma (HCC). Recently, both the albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI) grade have been raised to be objective measurement indexes of liver function which can sufficiently stratify HCC patient survival. In this study, we aim to compare the ability of albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI) grade to predict outcomes in hepatitis B-Induced HCC after liver resection with curative intent.

Methods Between April 2013 and April 2023, 1005 consecutive hepatitis B-Induced HCC patients who underwent liver resection were included in this study. The performance of PALBI and ALBI score in predicting long-term survival was evaluated.

Results The area under the ROC curve (AUC) of the PALBI(AUC:0.618) for predicting long-term survival was greater than that of the ALBI(AUC:0.522). In the multivariate analysis for OS, both the ALBI (HR: 1.246 95%CI: 1.029–1.508 $P=0.024$) and PALBI (HR: 1.207 95%CI: 1.049–1.388 $P=0.009$) scores were identified as independent predictors of OS in HCC patients. In the univariate analysis for DFS, the PALBI grade was also significantly associated with poor DFS ($P=0.041$). In contrast, the ALBI grade was not found to be significantly associated with poor DFS ($P=0.414$). Subgroup analysis also showed, among patients across each BCLC stage, the group with ALBI grade 1 had DFS similar to that of the group with ALBI grade 2 (both $P>0.05$). However, the PALBI grade can differentiate each BCLC stages into three prognostic groups (all $P<0.05$).

Conclusion Compared to ALBI grade, the PALBI grade is more clinically feasible and has better prognostic ability regardless of the grade of BCLC stage.

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Keywords PALBI, ALBI, Hepatocellular carcinoma, Liver function, Prognosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the leading cause of tumor-related death in the world [1]. Hepatectomy is a potentially curative treatments for HCC patients with early- and advanced-stage disease [2–4]. The prognosis of HCC is influenced not only by the tumor burden itself, but also by the patient's liver reserve [3]. Therefore, assessing liver functional reserve is an essential component in the management of HCC.

The Child–Pugh (CP) score system, which includes serum albumin, coagulation profile, serum bilirubin, hepatic encephalopathy, and ascites, is widely used to assess liver function. However, numerous limitations of this classification system have been increasingly recognized [5]. The prognostic ability of the Child–Pugh (CP) score system is limited by the use of inter-correlated and subjective variables, such as albumin and ascites, as well as encephalopathy and ascites. Moreover, the CP score system was originally designed for patients with cirrhosis, which may not fully address the specific needs of those with hepatocellular carcinoma (HCC). In 2015, Johnson et al. introduced the albumin-bilirubin (ALBI) grade as an alternative tool to assess liver function specifically in patients with HCC [6]. The ALBI grade was calculated based on two objective variables: serum albumin and bilirubin levels. This evidence-based model has been validated in several studies [7–12]. However, the ALBI grade does not include portal hypertension. To address this limitation, platelet count was introduced as a surrogate marker for portal hypertension, leading to the development of the platelet-bilirubin-albumin (PALBI) grade [13, 14].

Although both ALBI and PALBI grade are raised to be objective measurement indexes of liver function which can sufficiently stratify HCC patient survival, there is a lack of data regarding their use in hepatitis B-Induced HCC after hepatic resection and their utility in this population has not been well evaluated. In this study, we sought to compare the ability of ALBI and PALBI grades in predicting outcomes in hepatitis B-Induced HCC after liver resection with curative intent.

Materials and methods

This research was approved by the Ethics Committee of Changde Hospital (The First People's Hospital of Changde), Xiangya School of Medicine, Central South University and Guangxi Medical University Cancer Hospital, and was performed in compliance with the Helsinki Declaration. Written informed consent was obtained from patients prior to surgery.

Patients

Between April 2013 and April 2023, All HCC patients underwent liver resection with curative intent at the First People's Hospital of Changde City and Guangxi Medical University Cancer Hospital were considered for our study. The inclusion criteria were: no other simultaneous malignancies; initial liver resection with curative intent performed at the authors' center; no treatment for HCC before liver resection; no coexistent hematologic disorders so that the preoperative platelet count reflected normal baseline values; and no cerebral, renal, or cardiopulmonary dysfunction before liver resection.

Diagnosis and definitions

Diagnose of HCC was based on the results of postoperative pathology. Hepatectomy with curative intent is defined as complete resection of all visible tumor and there is no remaining tumor cells at the surgical margin [15].

The ALBI and PALBI score were calculated using the following formulas [11, 14]: ALBIscore=($\log_{10}$T-bilirubin[μmol/L]×0.66)+(albumin[g/L]×-0.085);PALBI core=(2.02×$\log_{10}$T-bilirubin)+(-0.37×[$\log_{10}$T-bilirubin]^2)+(-0.04×albumin)+(-3.48×$\log_{10}$ platelets)+(1.01×[$\log_{10}$ platelets]^2). The HCC patients were categorized into three groups based on ALBI scores(grade 1: ≤−2.60, grade 2:−1.39 to −2.60, and grade 3: >−1.39) and PALBI scores(grade1:≤−2.53, grade 2: −2.09 to −2.53, and grade 3:>−2.09).

Follow-up visits

All HCC patients were inspected one month after liver resection, every 3 months for the rest of the first year and then every 3–6 months in subsequent years, as appropriate. At each follow-up, serum AFP assay, serum biochemistry, ultrasound, chest X-ray and abdominal CT or MRI were performed.

Statistical analysis

Statistical analysis was performed with SPSS 19.0 (IBM, USA). Continuous data with normal distribution are expressed as mean (s.d.) and the value with non-normal distribution are expressed as median (range). Survival analysis was conducted to compare the over survival(OS) and disease free survival(DFS) rates using Kaplan-Meier survival curves with log-rank tests and Cox proportional hazard regression analyses, and $p<0.05$ was considered statistically significant.

Results

Baseline characteristics of all patients

Of 1436 HCC patients who underwent hepatectomy with curative intent from April 2013 to April 2023 inclusive, 120 patients (8.4%) were not hepatitis B-induced hepatocellular carcinoma; 220 patients (15.3%) experienced other treatments before hepatic resection; 38 patients (2.6%) had coexistent hematologic disorders; 30 patients (2.1%) had other malignant tumors simultaneously; and 23 patients (1.6%) had cerebral, cardiopulmonary or renal dysfunction before hepatic resection. After exclusion, 1005 patients (70%) were enrolled in our research.

Table 1 Baseline characteristics of HCC patients treated by resection

Variables	No. of patients (*n*=1005)
Age (years)	
≥60	126(12.5%)
<60	879(87.5%)
Sex ratio (M: F)	882:123
Liver cirrhosis	
Yes	855(85.1%)
No	150(14.9%)
AFP, ng/mL	
<400	645(64.2%)
≥400	360(35.8%)
BCLC stage	
0 or A	368(36.6%)
B	445(44.3%)
C	192(19.1%)
Child-Pugh class	
A	950(94.5%)
B	55(5.5%)
Tumor size, cm	7.1 ± 3.2
Tumor capsule	
Complete	416(41.4%)
Incomplete	589(58.6%)
Edmonson grade	
I-II	592(58.9%)
III–IV	413(41.1%)
Albumin, g/L	39.93±4.52
Platelet count,10^9/L	179±75.70
AST, U/L	45.0(34.0–65.0)
ALT, U/L	42.0(31.0–59.0)
Tumor number	
≥3	300(29.9%)
<3	705(70.1%)
Total bilirubin, μmol/L	13.3(9.4–17.5)
ALBI grade	
1	739(73.5%)
2	264(26.3%)
3	2(0.2%)
PALBI grade	
1	518(51.5%)
2	412(41.0%)
3	75(7.5%)

Data are mean ± standard deviation or median (25th–75th interquartile range) unless otherwise indicated

Abbreviations: HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCC, Hepatocellular Carcinoma

The baseline characteristics of the 1005 HCC patients are shown in Table 1. According to the ALBI grade, a total of 739(73.5%) HCC patients were classified as ALBI grade 1, 264(26.3%) as ALBI grade 2 and 2(0.2%) as ALBI grade 3; According to the PALBI grade, A total of 518(51.5%) HCC patients were classified as PALBI grade 1, 412(41.0%) as PALBI grade 2 and 75(7.5%) as PALBI grade 3.

The area under the ROC curve (AUC) of the PALBI(AUC:0.618) for predicting long-term survival was greater than that of the ALBI(AUC:0.522)(Fig. 1).

Performances of ALBI and PALBI grade in the univariate and multivariate analyzes for long-term survival

Univariate analysis and cox proportional hazards regression were used to identify factors associated with OS and DFS. OS and DFS were not analysed for ALBI grade 3 because only two patients fell into this category. For multivariate analysis, the ALBI and PALBI grade were entered in two different logistic regression models to avoid collinearity and the detailed results were shown in Tables 2 and 3.

Factors associated with poor OS($P<0.05$) in univariate analysis included: ALBI grade, PALBI grade, AFP ≥ 400 ng/mL, tumor number, tumor size ≥ 5 cm, tumor capsule, albumin ≥ 35 g/L and AST ≥ 80U/L. In the univariate analysis for DFS, the PALBI grade was also significantly associated with poor DFS ($P=0.041$). In contrast, the ALBI grade was not found to be significantly associated with poor DFS ($P=0.414$). In addition, AFP ≥ 400 ng/mL, tumor number, tumor size ≥ 5 cm, tumor capsule and platelet count ≥ 100×10^9/L were also significantly associated with poor DFS(all $P<0.05$, Tables 2 and 3).

In the multivariate analysis for OS, both the ALBI (HR: 1.246 95%CI: 1.029–1.508 $P=0.024$) and PALBI (HR: 1.207 95%CI: 1.049–1.388 $P=0.009$) scores were identified as independent predictors of OS in HCC patients. In addition, AFP ≥ 400 ng/mL, tumor number, tumor size ≥ 5 cm and tumor capsule were found to be independent predictors of OS in both multivariable logistic regression models (all $P<0.05$ Table 2). And in the multivariate analysis for DFS, patients with higher PALBI grade had a trend ($P=0.060$) to have poor DFS (Table 2).

Performances of ALBI and PALBI grade among Barcelona Clínic liver cancer stages

We performed subgroup analysis by stratifying them according to BCLC stage, and the prognostic capabilities of ALBI and PALBI grade within BCLC stages were

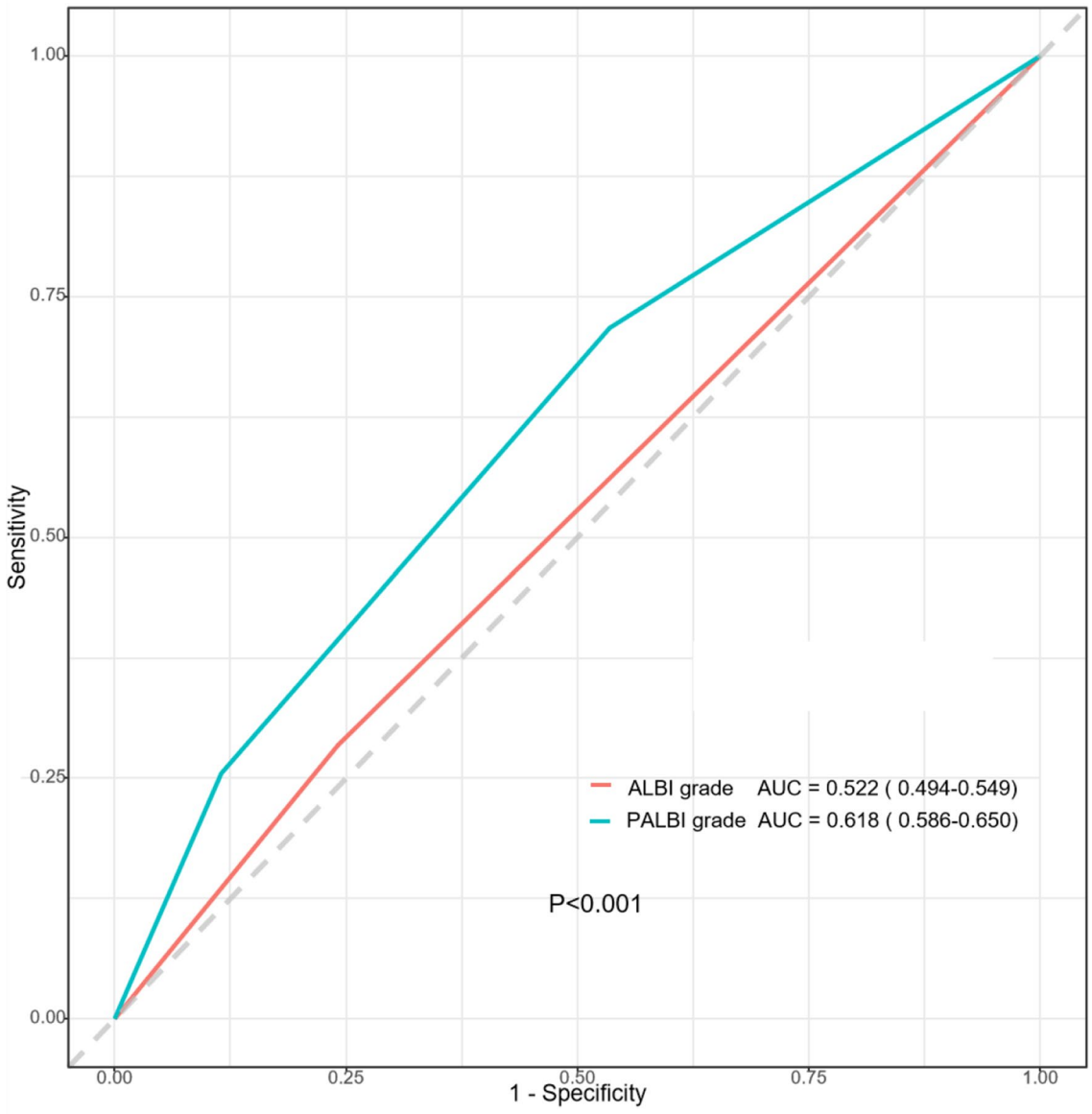

Fig. 1 Receiver operating curve (ROC) for the preoperative ALBI and PALBI in predicting long-term survival

investigated. Among patients across each BCLC stage, the group with ALBI grade 1 had DFS similar to that of the group with ALBI grade 2 (both $P > 0.05$) (Figs. 2D and 3D), however, the PALBI grade can differentiate each BCLC stages into three prognostic groups (all $P < 0.05$, Fig. 2AC and Fig. 3AC).

Discussion

In this research, we analyze a relatively large cohort of hepatitis B-Induced HCC patients to evaluate the performance of the ALBI and PALBI grade. We confirm that both ALBI and PALBI grading systems serve as valuable prognostic tools for predicting long-term outcomes in patients with hepatitis B-Induced HCC undergoing curative hepatic resection. However, Our findings robustly demonstrate that the PALBI grade exhibits superior prognostic discrimination and enhanced clinical utility compared to the ALBI grade in this cohort, particularly in stratifying DFS outcomes across the entire HCC population and within distinct BCLC subgroups.

Long-term infections with hepatitis B virus (HBV) account for about 80% of HCC cases in the Asia, especially in China and are the main etiologies of this malignant tumor [1, 3]. Liver functional reserve is an important factor affecting the survival of HCC patients and is frequently used as a preoperative assessment of the safety of liver resection [4]. It is critical to assess preoperative liver functional reserve in predicting the prognosis of HCC. Usually, the CP score classification system is used as an alternative indicators for the liver functional reserve in

Table 2 Univariable and multivariable analyses to identify predictors of overall survival in HCC patients treated by resection

Univariable				Multivariable					
				ALBI model			PALBI model		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Male	0.949	0.743-1.211	0.672						
Age (≥60 years)	1.172	0.921-1.492	0.196						
PALBI grade	1.265	1.103-1.452	<0.001				1.207	1.049-1.388	**0.009**
ALBI grade	1.243	1.031-1.498	0.023	1.246	1.029-1.508	**0.024**			
Liver cirrhosis	1.257	0.984-1.606	0.067						
AFP≥400 ng/mL	1.637	1.380-1.942	<0.001	1.289	1.079-1.539	**0.005**	1.286	1.077-1.535	**0.005**
Edmonson grade III–IV	1.243	0.768-2.179	0.243						
Child-Pugh class B	**1.172**	0.810-1.697	0.400						
Tumor number	1.908	1.603-2.271	<0.001	1.401	1.160-1.693	**<0.001**	1.419	1.174-1.716	**<0.001**
Tumor size≥5 cm	2.435	2.001-2.963	<0.001	1.790	1.431-2.239	**<0.001**	1.772	1.417-2.217	**<0.001**
Tumor capsule	1.969	1.644-2.357	<0.001	1.570	1.298-1.900	**<0.001**	1.531	1.264-1.853	**<0.001**
Albumin≥35 g/L	1.388	1.059-1.819	0.018						
Plateletcount≥100 × 10^9/L	1.057	0.824-1.357	0.662						
AST≥80U/L	1.429	1.149-1.778	0.001	1.169	0.933-1.463	0.174	1.164	0.930-1.457	0.185
ALT≥80U/L	0.998	0.767-1.297	0.986						
Total bilirubin ≥17.1μmol/L	1.065	0.878-1.291	0.524						

Abbreviations: HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; ALT, alanineaminotransferase; HR = hazard ratio; CI = confience interval

Table 3 Univariable and multivariable analyses to identify predictors of disease free survival in HCC patients treated by resection

Univariable				Multivariable					
				ALBI model			PALBI model		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Male	1.022	0.802-1.303	0.859						
Age (≥60 years)	1.038	0.813-1.324	0.766						
PALBI grade	1.145	1.023-1.310	0.041				1.140	0.994-1.307	**0.060**
ALBI grade	1.081	0.897-1.302	0.414						
Liver cirrhosis	1.165	0.929-1.461	0.186						
AFP≥400 ng/mL	1.660	1.408-1.958	<0.001				1.479	1.245-1.756	**<0.001**
Edmonson grade III–IV	1.325	0.843-1.856	0.352						
Child-Pugh B class	0.895	0.606-1.323	0.579						
Tumor number	1.910	1.611-2.263	<0.001				1.586	1.300-1.890	**<0.001**
Tumor size≥5 cm	2.022	1.690-2.419	<0.001				1.289	1.048-1.585	**0.016**
Tumor capsule	1.656	1.398-1.961	<0.001				1.225	1.023-1.467	**0.027**
Albumin≥35 g/L	0.983	0.725-1.333	0.912						
Plateletcount≥100 × 10^9/L	1.439	1.108-1.869	0.006						
AST≥80U/L	1.306	0.856-1.625	0.417						
ALT≥80U/L	0.962	0.746-1.241	0.768						
Total bilirubin ≥17.1μmol/L	0.957	0.797-1.151	0.643						

Abbreviations: HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; ALT, alanineaminotransferase; HR = hazard ratio; CI = confience interval

HCC patients [16–20]. However, the CP score system has some limitations [21, 22], including subjective evaluation of hepatic encephalopathy and ascites and interrelationships between variables. The ALBI and PALBI grade system, which are objective and simple in assessing liver functional reserve, are recently introduced.

In our study, multivariable analysis showed that both the ALBI and PALBI scores system were independent indicators of OS (both $P<0.05$). However, the PALBI score system provided greater discriminatory power for predicting DFS than ALBI score system, because we found that the PALBI grade was significantly associated with poor DFS ($P=0.041$) in the univariate analysis, in contrast, the ALBI grade was not found to be significantly associated with poor DFS ($P=0.414$) in the univariate analysis.

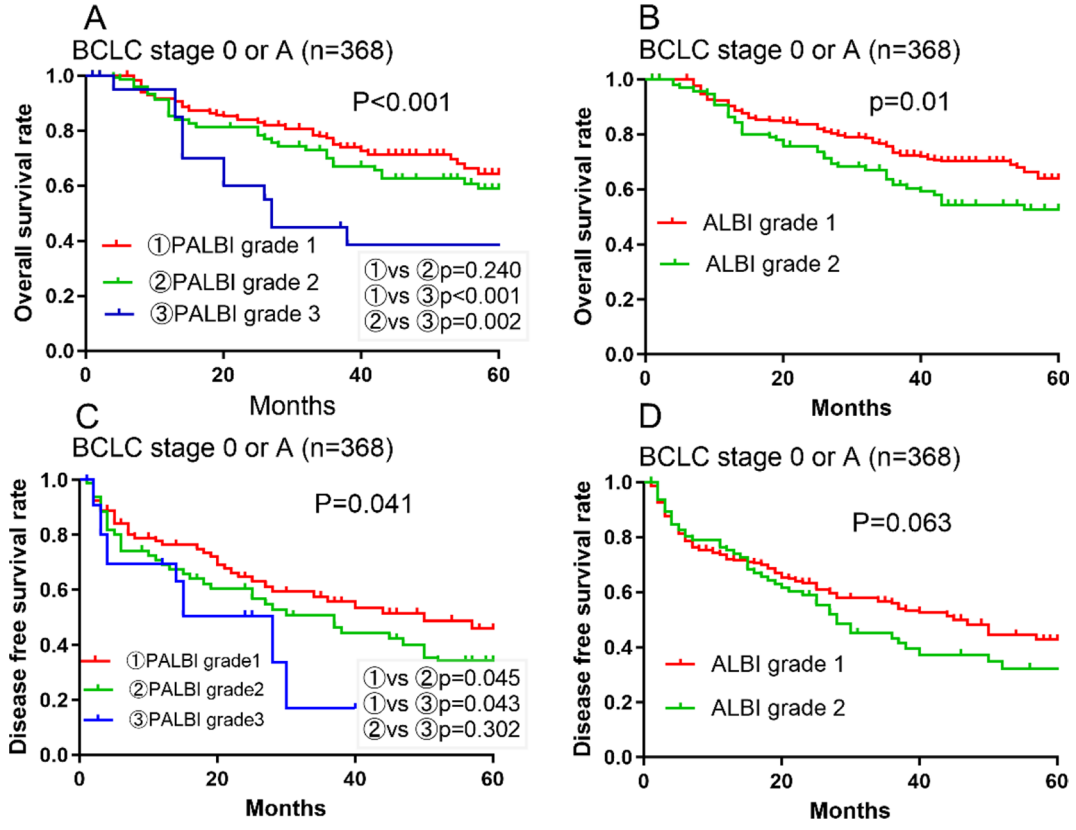

Fig. 2 Kaplan–Meier curves illustrating overall survival and disease free survival according to albumin–bilirubin (ALBI, **B**, **D**) in the BCLC stage 0 or A cohort and platelet-bilirubin-albumin (PALBI, **A**, **C**) grade in the BCLC stage 0 or A cohort

It is generally believed that survival of HCC patients depends not only on potential liver function but also on tumor staging [23]. At present, the BCLC stage is the most widely used HCC staging system and provides the advantage of integrating prediction of survival results and treatment options [24]. In clinical diagnosis and treatment, patients with BCLC stage 0 or A are usually classified as early stage patients with a lower tumor burden and better prognosis than patients with BCLC stage B or C usually classified as advanced stage patients [25, 26]. However, the survival of HCC patients with the same BCLC stage is also very different, and almost half of patients with early-stage disease and those receiving recommended treatment according to BCLC stage always died within 5 years after therapy [24, 27, 28]. Therefore, the identification of high-risk groups for early-stage and advanced stage HCC has become a top priority. In the present study, the PALBI grade can differentiate each BCLC stages into three prognostic groups, while the ALBI grade cannot differentiate.

Both the ALBI and PALBI grade show promising predictive ability for HCC. In the present study, we show that the PALBI grade had greater discriminatory power than ALBI grade based on several reasons. First, the PALBI grade combines with blood platelet count as an indicator of severity of portal hypertension, which can provide more information regarding prognosis compared to ALBI grade. Second, In terms of long-term survival, the ALBI can only differentiate the HCC patients into two groups, However, the PALBI grade is capable of stratifying the HCC patients into three groups with distinct prognoses, which demonstrated a more adequate and clinical meaningful stratifying potential than that of the ALBI grade. Third, We also find that the PALBI grade could be more accurate as compared with the ALBI grade system in discriminating DFS for all hepatitis B-Induced HCC patients as well as patients with different BCLC stages.

Although offering some new findings, the present study has several limitations that need to be addressed. First, This study's retrospective design has inherent limitations, including potential biases. Future prospective studies and external validation are needed. Second, the study exclusively comprised Chinese patients, with hepatitis B virus (HBV) infection, limiting the generalizability of our findings to HCC cases with different etiologies, particularly those associated with hepatitis C virus infection or alcohol-related liver disease. Third, Adjuvant therapies (e.g., TACE) or post-recurrence interventions were not analyzed. Future studies should adjust for these factors. The last, our study lack direct comparison between

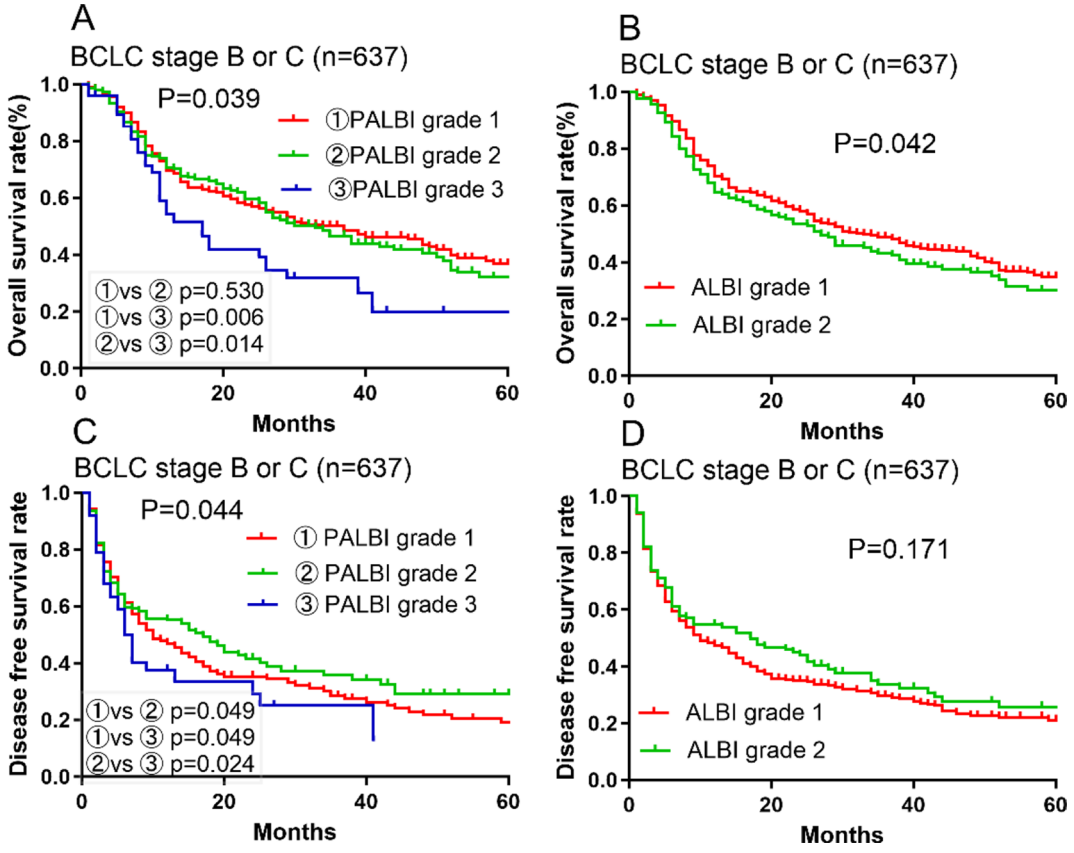

Fig. 3 Kaplan–Meier curves illustrating overall survival(OS) and disease free survival(DFS) according to albumin–bilirubin (ALBI, **B**, **D**) in the BCLC stage B or C cohort and platelet-bilirubin-albumin (PALBI, **A**, **C**) grade in the BCLC stage B or C cohort

PALBI and other established scoring systems such as MELD-Na and FIB-4. This omission means that we cannot definitively conclude whether PALBI outperforms these other models in predicting survival outcomes for HCC patients.

In conclusion, both the PALBI and ALBI grade are discriminatory, objective, and statistical evidence-based methods to evaluate liver dysfunction. The PALBI grade is more clinically feasible and it has superior prognostic ability regardless of the grade of BCLC stage.

Author contributions

HJY and SS contributed equally to this work. YTY, HPZ and BDX contributed to the study design and conception. HJY and SS collected the relative data. HJY and SS analyzed and interpreted the data. HJY and BDX contributed to editing of the article. YTY, HPZ and BDX contributed to quality control and review of the data and article.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Consent for publication

Not applicable.

Informed consent

All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Data sharing statement

Technical appendix, statistical code, and dataset are available from yhj643607891@163.com. Participants gave informed consent for data sharing.

Institutional review board statement

The study was reviewed and approved by Guangxi Medical University Cancer Hospital and Changde Hospital (The First People's Hospital of Changde), Xiangya School of Medicine, Central South University.

Competing interests

The authors declare no competing interests.

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