Original Article

DOI: 10.5582/bst.2021.01064

Combination of albumin-bilirubin grade and clinically significant portal hypertension predicts the prognosis of patients with hepatocellular carcinoma after liver resection

Li Qin[1,2], Chuan Li[1,*], Fei Xie[3], Zhenxia Wang[4], Tianfu Wen[1]

[1] Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan, China;
[2] West China School of Nursing, Sichuan University, Chengdu, Sichuan, China;
[3] Department of Hepato-pancreato-biliary Surgery, First People's Hospital of Neijiang, Neijiang, Sichuan, China;
[4] Department of Hepato-pancreato-biliary Surgery, Chengdu Second People's Hospital, Chengdu, Sichuan, China.

SUMMARY There is little information concerning whether incorporating clinically significant portal hypertension (CSPH) into albumin-bilirubin (ALBI) grading could improve its predictive capacity. In this study, we investigated the predictive ability of ALBI grade plus CSPH (ALBI-P score) for patients with hepatocellular carcinoma (HCC) after liver resection. Data from 1,679 patients were retrospectively reviewed. The ALBI-P score was calculated from the ALBI grade and a point for CSPH (0 for absence of CSPH and 1 for presence of CSPH). Independent risk factors for recurrence-free survival (RFS) and overall survival (OS) were analyzed. Multivariate analysis suggested that the ALBI-P score was an independent risk factor for both postoperative recurrence (HR = 1.441, 95% CI = 1.328-1.563, $P < 0.001$) and mortality (HR = 1.332, 95% CI = 1.156-1.535, $P < 0.001$). Both the RFS and OS of patients with an ALBI-P score of 1 were significantly better than those of patients with ALBI-P scores of 2 and 3 (5-year RFS of 38.9%, 26.1%, and 14.7%, respectively, $P < 0.001$; 5-year OS of 52.7%, 42.6%, and 29.3%, $P < 0.001$). When the ALBI-P score and BCLC stage were combined, the ALBI-P-BCLC score showed the highest area under the receiver operating characteristic curve to predict both postoperative recurrence and mortality compared with BCLC stage alone, BCLC stage combined with ALBI grade, or platelet-albumin-bilirubin grade. These results suggested incorporating CSPH into the ALBI grade could strengthen its prognostic power. The ALBI-P score may serve as a surrogate marker to predict HCC patient outcomes after liver resection.

Keywords hepatocellular carcinoma, albumin-bilirubin grade, clinically significant portal hypertension

1. Introduction

Hepatocellular carcinoma (HCC) is a heavy public health burden and is a leading cause of cancer-related mortality in many parts of the world, ranking as the fifth most common malignancy and third most frequent cause of cancer-related death worldwide (*1*). Chronic hepatitis virus infections, including chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, are the most important causes of HCC. Every year, approximately 1-8% of patients with cirrhosis from chronic HBV and HCV infections will develop HCC (*2*). Previous investigations revealed that chronic hepatitis infections may contribute to approximately 80% of HCC cases globally (*1*). Since many patients with HCC suffer from chronic hepatitis virus infections, many HCC patients also have cirrhosis and even portal hypertension.

In contrast to other kinds of cancers, liver function greatly impacts the prognosis of HCC following many treatments, such as liver resection, radiofrequency ablation, and transarterial chemoembolization (*2,3*). Currently, the Child-Pugh score is the most commonly used tool to assess liver function. However, the accuracy of the Child-Pugh score varies due to subjective variables, including hepatic encephalopathy and ascites. In 2015, Johnson *et al.* (*4*) developed the albumin-bilirubin (ALBI) grade, which only includes total bilirubin and albumin as two objective parameters, to evaluate a patient's liver function. Subsequently, a number of studies confirmed that ALBI was better than the Child-Pugh score in predicting the prognosis of patients with HCC after many management strategies. For example, Na *et al.* (*5*) suggested that ALBI provided better prognostic performance in survival analysis and a more accurate distribution of grades than the Child-Pugh score for HCC patients. Moreover, portal hypertension

is also often detected in cirrhosis and could adversely influence the outcomes of patients with HCC after liver resection. The Barcelona Clinic Liver Cancer (BCLC) system does not recommend liver resection for HCC patients with portal hypertension (2). In our clinical practice, portal hypertension occurs not only in patients with poor liver function but also in those with compensated liver function. However, neither the Child-Pugh score nor the ALBI grade involved variables that could assess portal hypertension. Accordingly, we suspected that the combination of liver function assessed by ALBI grade and clinical portal hypertension could more exactly predict the prognosis of patients with HCC following liver resection.

2. Patients and Methods

The records of patients with HCC who had undergone liver resection between 2012 and 2020 at West China Hospital of Sichuan University were retrospectively analyzed. Patients who underwent re-resection, had ruptured HCC, received preoperative antitumor treatment, had a positive surgical margin, or had other types of tumors were excluded. All HCC cases were confirmed by postoperative pathology. This study was approved by the ethics committee of West China Hospital. In our center, Clinically significant portal hypertension (CSPH) is not a contraindication of liver resection for patients with HCC. Liver function of patients who underwent liver resection should be in Child-Pugh A grade. For patients with cirrhosis, if the indocyanine green retention rate at 15 minutes < 10%, the future liver remnant should be at least 40%. If the indocyanine green retention rate at 15 minutes is between 10% and 20%, the future liver remnant should be at least 50%. Additionally, for patients with liver fibrosis, the future liver remnant volume should be greater than 30%, and for patients without an underlying liver disease, the future liver remnant volume should be greater than 20% (*6*). Simultaneous splenectomy will be performed on patients with a preoperative platelet count of less than 50 $\times 10^9$/L.

2.1. Follow-up

All preoperative blood tests were performed 1 week before the operation. After liver resection, the patients were regularly followed up every 3 months. Before and after the operation, antiviral drugs (entecavir, lamivudine or tenofovir) were conventionally administered to patients with a positive HBV-DNA load. The routine follow-up included blood cell tests, liver function tests, serum alpha-fetoprotein (AFP) measurement, HBV-DNA tests, visceral ultrasonography, computed tomography or magnetic resonance imaging and chest radiography. Bone scintigraphy was performed whenever HCC recurrence was suspected. Postoperative recurrence was defined as positive imaging findings compared with the preoperative examination values or as confirmed by biopsy or resection (*7*).

2.2. Definitions

High alpha-fetoprotein (AFP) was defined as > 400 ng/mL (*7*). The neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the lymphocyte count (*8*). An NLR greater than 3 was defined as being high (*8*). The prognostic nutrition index (PNI) was the sum of serum albumin (g/L) and 5× lymphocyte count (10^9/L) (*9*). The cut-off value of PNI was 45, as reported in the literature (*9*). ALBI grade was calculated according to the following formula: ALBI = ($\log_{10}$ bilirubin (μmol/L) × 0.66) + (albumin (g/L) × -0.085) (*4*). ALBI values were divided into 3 grades as follows: grade 1 (less than -2.60), grade 2 (between -2.60 and -1.39) and grade 3 (above -1.39) (*4*). Platelet-albumin-bilirubin (PALBI) was calculated based on the following equation: $2.02 \times \log_{10}$ bilirubin (μmol/L) - $0.37 \times (\log_{10}$ bilirubin (μmol/L))^2 - $0.04 \times$ albumin (g/L) - $348 \times \log_{10}$ platelets (1,000/μL) + $1.01 \times (\log_{10}$ platelets (1,000/μL))^2 (*10*). PALBI was divided into 3 grades as follows: grade 1 (≤ -2.53), grade 2 (> -2.53 and ≤-2.09), and grade 3 (>-2.09) (*10*). Clinically significant portal hypertension (CSPH) was defined by the presence of esophagogastric varices and/or a platelet count < 100 × 10^9/L in association with splenomegaly (*11*). The ALBI-portal hypertension (ALBI-P) score was defined as the summary of the ALBI grade and status of CSPH: (1 for the presence of CSPH and 0 for the absence of CSPH). For example, if a patient with ALBI grade 1 (score of 1) and CSPH (score of 1), the ALBI-P score of this patient is 2. If a patient with ALBI grade 2 (score 2), but without CSPH (score 0), the ALBI-P score of this patient is also 2. We also analyzed the predictive ability of the combination of BCLC stage and ALBI grade, PALBI grade, or ALBI-P score, where we allocated 0 to BCLC stage 0, 1 to BCLC stage A, 2 to BCLC stage B and 3 to BCLC stage C. The ALBI-BCLC score was defined as the summary of the ALBI grade and BCLC score. The PALBI-BCLC score was defined as the summary of the PALBI grade and BCLC score. The ALBI-P-BCLC score was defined as the summary of the ALBI-P score and BCLC score.

2.3. Statistical analysis

All statistical analyses were performed by SPSS 26.0 (SPSS Company, Chicago, IL) for Windows. All continuous variables were analyzed using one-way analysis of variance. The χ^2 test or Fisher's exact test was used to compare the categorical variables. The Kaplan-Meier method was applied to determine recurrence-free survival (RFS) and overall survival, and the log-rank test was performed to test the survival differences.

Multivariable analysis was carried out using Cox regression analysis to identify independent risk factors for OS and RFS. All variables with a *P* value < 0.1 in the univariate analysis were included in the multivariate analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was used to estimate the predictive accuracy. MedCalc software version 11.2 was used to compare the ROC curves. A *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 1,679 patients were enrolled in this study. The mean age of the patients was 51.3 ± 12.1 years. According to the ALBI grade, 1,156 patients were ALBI grade 1, and 523 patients were ALBI grade 2. There were no patients with ALBI grade 3. According to the PALBI grade, 1,173 patients were PALBI grade 1, 445 patients were PALBI grade 2, and 61 patients were PALBI grade 3. CSPH was detected in 597 patients. According to the definition of the ALBI-P score, 791 patients were classified as ALBI-P score 1, 655 as ALBI-P score 2, and 233 as ALBI-P score 3. The mean tumor size was 6.7 ± 3.6 cm in this study. Multiple tumors were found in 362 patients. High preoperative AFP levels were observed in 690 patients. A total of 757 patients had positive preoperative HBV DNA. Microvascular invasion (MVI) was detected in 871 patients. Satellite lesions were found in 249 patients. Thirty-six patients were in BCLC stage 0, 849 patients were in BCLC stage A, 167 patients were in BCLC stage B, and 627 patients were in BCLC stage C.

During a median 39.8 months of follow-up, 1,128 patients experienced recurrence, and 825 patients died. The 1-, 3-, and 5-year RFS rates of the whole cohort were 72.8%, 41.2% and 30.2%, respectively (Figure 1A), whereas the 1-, 3-, and 5-year OS rates were 91.5%, 62.1%, and 45.1% (Figure 1B).

3.2. Prognostic factors for RFS

The prognostic factors for RFS according to the univariate and multivariate analyses are listed in Table 1. The potential risk factors for RFS detected by univariate analysis were tumor size > 5 cm, multiple tumors, tumor differentiation, AFP > 400 ng/mL, presence of microvascular invasion (MVI), satellite lesions, cirrhosis, Milan criteria, platelet count < 100 (10^9/L), NLR > 3, PNI < 45, ALBI grade, PALBI grade, ALBI-P score and BCLC stage. In the multivariate analysis, the independent risk factors for RFS were only tumor size > 5 cm (HR = 1.737, 95% CI = 1.459-2.068, *P* < 0.001), MVI (HR = 1.574, 95% CI = 1.321-1.877, *P* < 0.001), satellite lesions (HR = 1.435, 95% CI = 1.229-1.676, *P* < 0.001), ALBI-P score (HR = 1.441, 95% CI = 1.328-

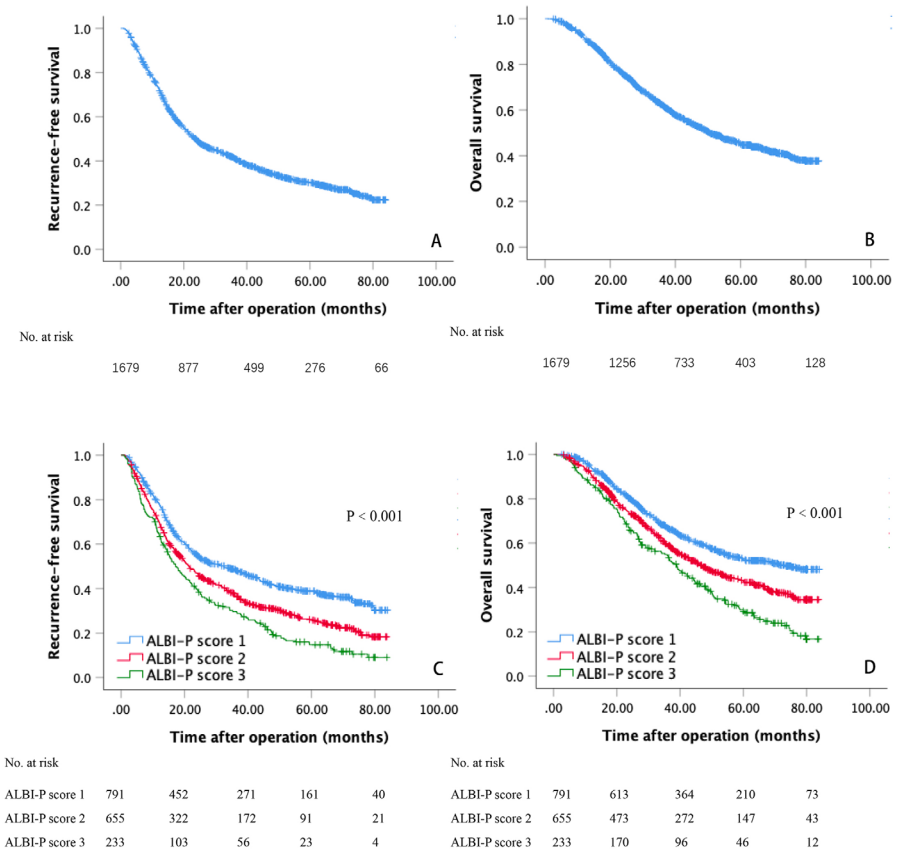

Figure 1. Recurrence-free (A) and overall (B) survival in all patients. Recurrence-free (C) and overall (D) survival comparison of patients with different ALBI-P scores. Patients with a high ALBI-P score had a high risk of postoperative recurrence and death.

1.563, $P < 0.001$), and BCLC stage (HR = 1.125, 95% CI = 1.018-1.242, $P = 0.020$).

3.3. Prognostic factors for OS

As shown in Table 2, tumor size > 5 cm, multiple tumors, tumor differentiation, AFP > 400 ng/mL, presence of microvascular invasion (MVI), satellite lesions, cirrhosis, Milan criteria, platelet count < 100 (10^9/L), NLR >3, PNI <45, ALBI grade, PALBI grade, ALBI-P score and BCLC stage were associated with poor OS in the univariate analysis. In multivariate analysis, only tumor size > 5 cm (HR = 1.647, 95% CI = 1.317-2.059, $P < 0.001$), platelet count < 100 (10^9/L) (HR = 1.282, 95% CI = 1.037-1.585, $P = 0.022$), MVI (HR = 1.549, 95% CI = 1.238-1.937, $P < 0.001$), satellite lesions (HR = 1.295, 95% CI = 1.080-1.552, $P = 0.005$), ALBI-P score (HR = 1.332, 95% CI = 1.156-1.535, $P < 0.001$), and BCLC stage (HR = 1.589, 95% CI = 1.404-1.799, $P < 0.001$) were independent prognostic factors of poor OS.

3.4. Comparison of the clinicopathological data of patients according to different ALBI-P scores

As presented in Table 3, a higher proportion of patients with older age, multiple tumors, poor tumor

Table 1. Variables associated with recurrence-free survival according to the Cox proportional hazards model

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age > 60 years	0.981	0.856-1.123	0.776			
Male	1.023	0.870-1.203	0.781			
Tumor size > 5 cm	2.542	2.224-2.907	< 0.001	1.737	1.459-2.068	< 0.001
Multiple tumors	1.528	1.330-1.756	< 0.001			
Differentiation	1.183	1.075-1.302	0.001			
AFP > 400 ng/mL	1.269	1.128-1.427	< 0.001			
High positive HBV DNA	1.034	0.920-1.163	0.575			
MVI	2.424	2.145-2.740	< 0.001	1.574	1.321-1.877	< 0.001
Satellite lesion	1.580	1.353-1.846	< 0.001	1.435	1.229-1.676	< 0.001
Fulfill Milan criteria	0.407	0.357-0.465	< 0.001			
Cirrhosis	1.220	1.027-1.449	0.023			
Platelet < 100 (10^9/L)	1.357	1.205-1.528	< 0.001			
NLR > 3	1.347	1.182-1.536	< 0.001			
PNI < 45	1.337	1.167-1.532	< 0.001			
ALBI grade	1.463	1.295-1.653	< 0.001			
ALBI-P score	1.353	1.249-1.466	< 0.001	1.441	1.328-1.563	< 0.001
PALBI grade	1.216	1.094-1.352	< 0.001			
BCLC stage	1.366	1.309-1.426	< 0.001	1.125	1.018-1.242	0.020

Table 2. Variables associated with overall survival according to the Cox proportional hazards model

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age > 60 years	1.114	0.917-1.353	0.276			
Male	0.944	0.805-1.107	0.479			
Tumor size > 5 cm	3.499	2.961-4.134	< 0.001	1.647	1.317-2.059	< 0.001
Multiple tumors	1.646	1.403-1.931	< 0.001			
Differentiation	1.338	1.194-1.500	< 0.001			
AFP >400 ng/mL	1.377	1.201-1.579	< 0.001			
High positive HBV DNA	0.919	0.801-1.055	0.231			
MVI	3.561	3.065-4.137	< 0.001	1.549	1.238-1.937	< 0.001
Satellite lesion	1.448	1.209-1.733	< 0.001	1.295	1.080-1.552	0.005
Fulfill Milan criteria	0.304	0.258-0.358	< 0.001			
Cirrhosis	1.344	1.090-1.657	0.006			
Platelet < 100 (10^9/L)	1.371	1.195-1.573	< 0.001	1.282	1.037-1.585	0.022
NLR > 3	1.419	1.220-1.650	< 0.001			
PNI < 45	1.391	1.190-1.625	< 0.001			
ALBI grade	1.549	1.346-1.782	< 0.001			
ALBI-P score	1.391	1.269-1.525	< 0.001	1.332	1.156-1.535	< 0.001
PALBI grade	1.309	1.161-1.476	< 0.001			
BCLC stage	1.668	1.584-1.757	< 0.001	1.589	1.404-1.799	< 0.001

Table 3. Comparison of the clinicopathological characteristics of patients with different ALBI-P scores

Characteristics	ALBI-P score 1	ALBI-P score 2	ALBI-P score 3	*P* values
Age > 60 years (yes/no)	172/619	152/503	76/157	0.003
Sex (female/male)	129/662	104/551	28/205	0.270
Multiple tumors (yes/no)	156/635	140/515	66/167	0.019
Tumor size > 5 cm	520/271	421/234	137/96	0.151
Cirrhosis	625/166	583/72	220/13	< 0.001
Satellite lesion	128/662	91/564	30/203	0.331
MVI	402/389	361/294	108/125	0.051
Differentiation	130/483/178	130/377/148	26/138/69	0.012
AFP > 400 ng/mL	327/464	274/381	89/144	0.614
Positive HBV DNA	423/476	319/336	114/119	0.006
NLR > 3	172/619	170/485	68/165	0.034
PNI < 45	39/752	191/464	134/99	< 0.001
BCLC stage (0/A *vs.* B/C)	427/364	331/423	127/106	0.357

differentiation, positive HBV DNA, cirrhosis, high NLR, and low PNI were observed in patients with a high ALBI-P score. The 1-, 3-, and 5-year RFS rates were 78.0%, 48.7%, and 38.9% for patients with an ALBI-P score of 1; 69.7%, 36.6% and 26.1% for patients with an ALBI-P score of 2; and 63.9%, 29.7% and 14.7% for patients with an ALBI-P score of 3 respectively. Statistically significant differences were observed ($P < 0.001$, Figure 1C). The 1-, 3-, and 5-year OS rates were 93.8%, 66.6%, and 52.7% for patients with an ALBI-P score of 1; 90.6%, 59.5% and 42.6% for patients with an ALBI-P score of 2; and 86.2%, 54.4% and 29.3% for patients with an ALBI-P score of 3 respectively ($P < 0.001$, Figure 1D).

3.5. Comparison of the RFS and OS of HCC patients with different ALBI-P scores when stratified by BCLC stage

We performed a subgroup analysis stratified by BCLC stage. Because there were few patients in BCLC stage 0, we combined BCLC stage 0 and BCLC stage A for analysis. As shown in Figure 2, significant differences were observed among patients with different ALBI-P scores, regardless of whether they were BCLC stage 0/A, B or C, for both RFS and OS. In each BCLC stage, patients with a high ALBI-P score had a high incidence of postoperative recurrence and mortality.

3.6. Comparison of predictive capacity when integrating ALBI-P score and BCLC stage

We also compared the prognostic ability of the combination of the ALBI-P score and BCLC stage. As shown in Figure 3A, for predicting postoperative recurrence, the ALBI-P-BCLC score showed the highest AUC (0.681), with a sensitivity of 60.1% and a specificity of 69.7%, followed by the ALBI-BCLC score (0.653, $P_{\text{ALBI-P-BCLC } vs. \text{ ALBI-BCLC}} = 0.002$), PALBI-BCLC score (0.633, $P_{\text{ALBI-P-BCLC } vs. \text{ PALBI-BCLC}} < 0.001$), and BCLC stage (0.632, $P_{\text{ALBI-P-BCLC } vs. \text{ BCLC}} < 0.001$). For predicting postoperative mortality (Figure 3B), the ALBI-P-BCLC score also had the highest AUC (0.723), with a sensitivity of 69.5% and a specificity of 68.2%, followed by the ALBI-BCLC score (0.705, $P_{\text{ALBI-P-BCLC } vs. \text{ ALBI-BCLC}} = 0.003$), BCLC stage (0.683, $P_{\text{ALBI-P-BCLC } vs. \text{ BCLC}} < 0.001$), and PALBI-BCLC score (0.680, $P_{\text{ALBI-P-BCLC } vs. \text{ PALBI-BCLC}} < 0.001$).

4. Discussion

Cirrhosis is often observed in patients with HCC and could also cause poor liver function and CSPH. In the past, investigations have suggested that both liver function and CSPH could adversely influence both short-term and long-term outcomes of patients with HCC following liver resection (*12,13*). Although some studies suggested liver transplantation provided better prognosis than liver resection for HCC patients with CSPH (*14,15*). However, due to the scarcity of liver grafts, many HCC patients with CSPH received liver resection in many centers (*11,15*). In our clinical practice, some HCC patients had poor liver function only or CSPH only. However, some HCC patients may suffer from both poor liver function and CSPH. Unfortunately, there is little information regarding whether incorporating CSPH into ALBI could strengthen its predictive ability. In the current study, we clarified this issue. Patients with both poor liver function and CSPH had a poorer prognosis than those with only one or none of the above-mentioned risk factors.

Johnson and his colleagues introduced the ALBI grade to assess liver function (*4*). Many studies have confirmed that the ALBI grade is better than the Child-Pugh score to assess patients' liver function (*16,17*). The ALBI grade is calculated with total bilirubin and serum albumin, two objective variables that could be easily obtained from laboratory tests. In contrast, the Child-Pugh score uses ascites and hepatic encephalopathy, two subjective parameters that could negatively affect its accuracy. Many studies have also suggested that ALBI grade could predict the outcomes of patients with

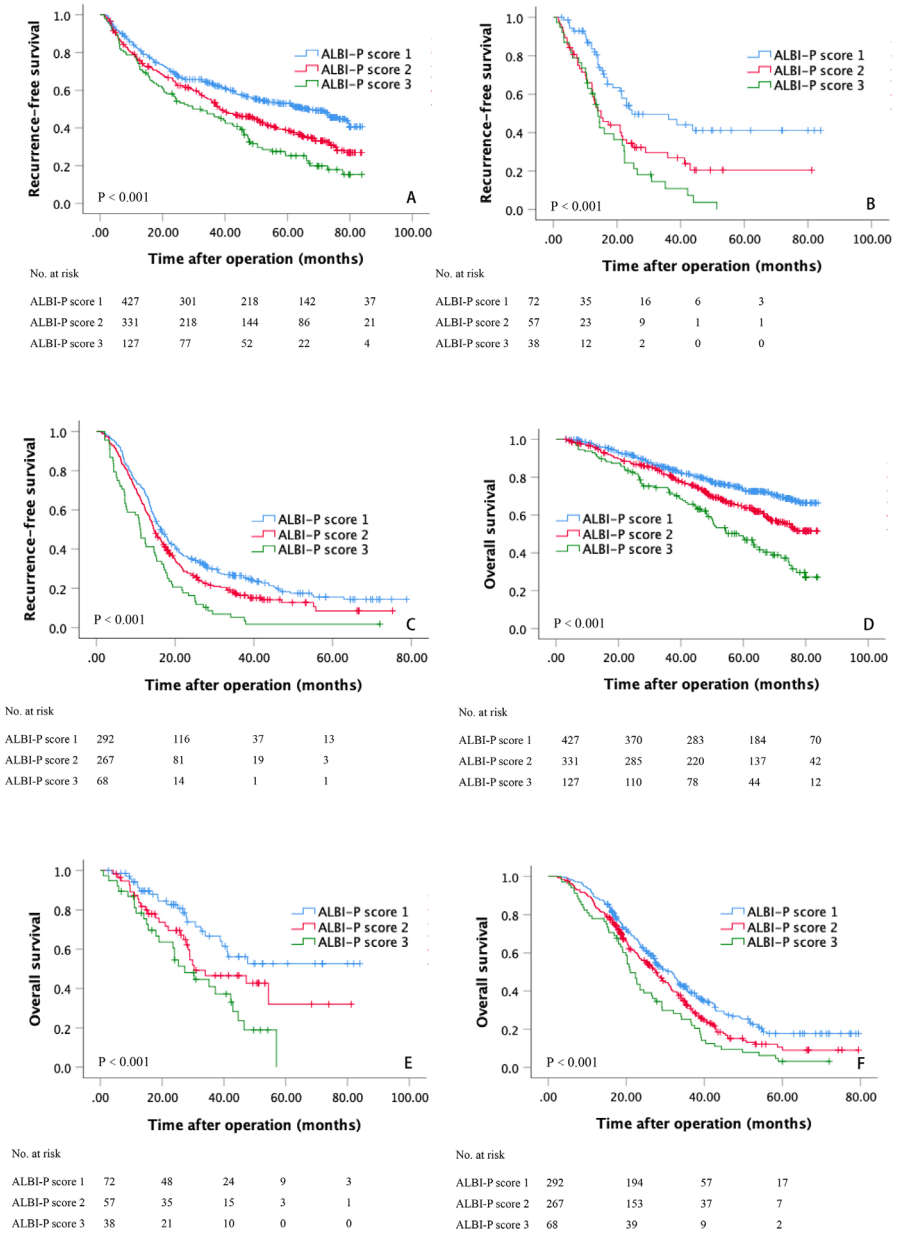

Figure 2. Kaplan-Meier survival plots comparing recurrence-free survival (RFS) and overall survival (OS) in Barcelona Clinic Liver Cancer (BCLC) stage 0/A (A for RFS and D for OS), BCLC stage B (B for RFS and E for OS) and BCLC stage C (C for RFS and F for OS) patients. Patients with high ALBI-P scores showed both poor RFS and OS regardless of BCLC stage.

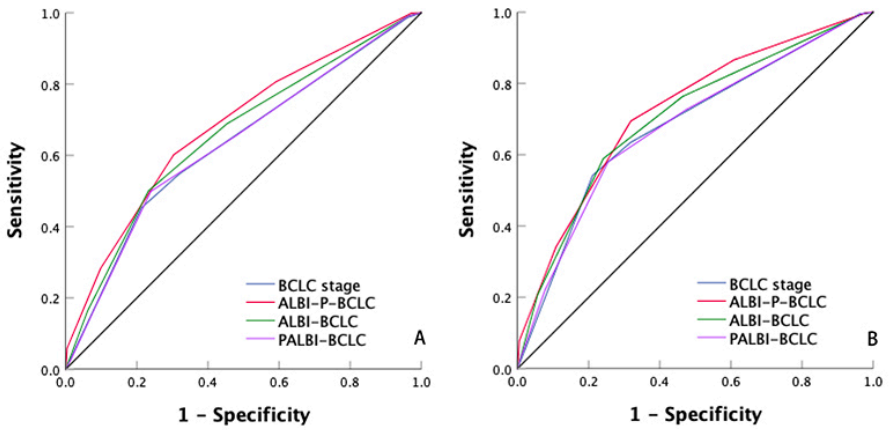

Figure 3. Comparison of the area under the receiver operating characteristic curves of the ALBI-P-BCLC score, ALBI-BCLC score, PALBI-BCLC score and BCLC stage in predicting postoperative recurrence (A) and survival (B).

HCC after liver resection (*12,18,19*). Toyoda *et al.* (*20*) suggested that for post liver resection HCC patients, the overall survival (OS) of those with ALBI grade 1 was approximately two times longer than that of patients with ALBI grade 2, although all patients were in Child-Pugh grade A. Ho *et al.* (*21*) also suggested that ALBI is a surrogate marker for predicting the postoperative recurrence of HCC patients who underwent liver resection. However, CSPH may also be observed in patients with very good liver function. Some authors suggested that failure to incorporate portal hypertension may be a potential weakness of the ALBI grade (*10,22*). Some investigations suggested that PALBI, which integrates platelets, albumin, and bilirubin, could also assess patient liver function and predict the outcomes of HCC patients (*10*). However, in our study, PALBI was not an independent risk factor for RFS or OS, although it showed significance in the univariate analysis. This result suggested that perhaps using scores including CSPH may be better than using a model incorporating platelets to predict HCC patient outcomes.

According to the treatment guidelines for HCC proposed by both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, liver resection is not recommended for HCC patients with CSPH, even though the liver function of these patients may be Child-Pugh class A (*2,23*). Previous studies have confirmed that low preoperative platelet counts contribute to a high incidence of postoperative complications and poor long-term survival (*24,25*). Some investigators argued that liver resection may be safely performed in selected HCC patients with portal hypertension (*11,26-28*). However, several meta-analyses confirmed that CSPH could negatively impact the prognosis of HCC patients following liver resection (*29-32*). For instance, Liu *et al.* suggested that compared to those without CSPH, patients with CSPH had a higher incidence of morbidity and 5-year mortality (*30*). A meta-analysis performed by Berzigotti *et al.* (*29*) confirmed that CSPH could increase 3-year and 5-year mortality and clinical decompensation after surgery regardless of the evaluation methods for CSPH. In fact, CSPH can also occur in patients with relatively healthy liver function, such as those in Child-Pugh class A. ALBI can subdivide Child-Pugh grade A liver function. However, previous investigations did not consider the impact of relatively poor liver function on the outcomes of patients with CSPH although they were in Child-Pugh grade A. In this study, our results suggested that the combination of CSPH and high ALBI grade could further adversely affect HCC patient prognosis after liver resection.

Our study also revealed that many unfavorable clinicopathological variables were observed in patients with high ALBI-P scores, such as high NLR and low PNI. Portal hypertension could cause splenomegaly and even hypersplenism, which could result in not only low platelet counts but also low lymphocyte counts. This may be why more patients with high NLR and low PNI were observed in those with high ALBI-P scores. The patient's anticancer response mainly depends on lymphocytes. Accordingly, the anticancer response was impaired in patients with low lymphocyte counts. Moreover, the NLR and PNI were also considered two markers that mirror a patient's systemic inflammatory response (*8*). Many studies have indicated that high NLR and low PNI are associated with a poor systemic inflammatory response and poor prognosis after liver resection (*9,33-35*).

Interestingly, the ALBI-P-BCLC score showed better prognostic ability than the ALBI-BCLC score and BCLC stage. The BCLC staging system is recommended by many associations for staging HCC, including the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (*2,23*). The BCLC staging system considers liver function to influence the choice of treatments and uses the Child-Pugh score to evaluate liver function. Pinato *et al.* (*18*) confirmed that the ALBI grade offered exact hepatic reserve evaluation across each BCLC stage of HCC. Chan *et al.* (*19*) even suggested that integrating ALBI into the BCLC system could achieve a similar prognostic performance to that of the Child-Pugh score-based BCLC system. However, neither the ALBI-based BCLC nor the Child-Pugh score-based BCLC consider the influence of portal hypertension. For example, if an HCC patient had multiple extrahepatic metastases, Child-Pugh class A liver function and a healthy physical status, he or she would be classified as BCLC stage C. According to the BCLC staging system, oral targeted drugs may be the first choice for this patient. However, if the platelet count of this patient was very low, *e.g.*, 20×10^9/L, it would not be suitable to administer oral targeted drugs to him or her. Accordingly, portal hypertension could also influence the management and prognosis of HCC patients. This may be one potential explanation why integrating the ALBI-P score into the BCLC stage achieved better predictive capacity.

There are also some limitations in this study. This is a single center retrospective study. Therefore, the prognostic performance of the ALBI-P score lacks external validation. Moreover, the ALBI-P score's suitability to predict the prognosis of HCC patients who receive other treatments needs further study. Additionally, in the current study, CSPH as defined used only clinical parameters, rather than using duplexsonography or measurement of hepatic venous pressure gradient. We acknowledge that the current standard for assessing the severity of portal hypertension is the measurement of hepatic venous pressure gradient. However, this is an invasive procedure which is not conventionally used in our clinical practice.

In conclusion, our study suggested that incorporating CSPH into ALBI strengthened its prognostic ability.

The ALBI-P score may serve as a surrogate marker for predicting HCC patient prognosis after liver resection in different BCLC stages. A high ALBI-P score was associated with a high incidence of postoperative recurrence and poor long-term survival.

Funding: This study was supported by grants from the State Key Scientific and Technological Research Programs (2017ZX10203207-003-0020), the National Natural Science Foundation of China (81900576), and the Science and Technological Supports Project of Sichuan Province (2019YJ0149).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019; 16:589-604.
2. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69:182-236.
3. Sayiner M, Golabi P, Younossi ZM. Disease Burden of Hepatocellular Carcinoma: A Global Perspective. Dig Dis Sci. 2019; 64:910-917.
4. Johnson PJ, Berhane S, Kagebayashi C, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015; 33:550-558.
5. Na SK, Yim SY, Suh SJ, Jung YK, Kim JH, Seo YS, Yim HJ, Yeon JE, Byun KS, Um SH. ALBI versus Child-Pugh grading systems for liver function in patients with hepatocellular carcinoma. J Surg Oncol. 2018; 117:912-921.
6. Wen T, Jin C, Facciorusso A, *et al.* Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. Hepatobiliary Surg Nutr. 2018; 7:353-371.
7. Li C, Shen JY, Zhang XY, Peng W, Wen TF, Yang JY, Yan LN. Predictors of Futile Liver Resection for Patients with Barcelona Clinic Liver Cancer Stage B/C Hepatocellular Carcinoma. J Gastrointest Surg. 2018; 22:496-502.
8. Yamamura K, Sugimoto H, Kanda M, Yamada S, Nomoto S, Nakayama G, Fujii T, Koike M, Fujiwara M, Kodera Y. Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci. 2014; 21:682-688.
9. Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, Chan HL, To KF. Prognostic Nutritional Index (PNI) Predicts Tumor Recurrence of Very Early/Early Stage Hepatocellular Carcinoma After Surgical Resection. Ann Surg Oncol. 2015; 22:4138-4148.
10. Liu PH, Hsu CY, Hsia CY, Lee YH, Chiou YY, Huang YH, Lee FY, Lin HC, Hou MC, Huo TI. ALBI and PALBI grade predict survival for HCC across treatment modalities and BCLC stages in the MELD Era. Journal of gastroenterology and hepatology. 2017; 32:879-886.
11. Takemura N, Aoki T, Hasegawa K, Kaneko J, Arita J, Akamatsu N, Makuuchi M, Kokudo N. Hepatectomy for hepatocellular carcinoma after perioperative management of portal hypertension. Br J Surg. 2019; 106:1066-1074.
12. Ho SY, Hsu CY, Liu PH, Hsia CY, Lei HJ, Huang YH, Ko CC, Su CW, Lee RC, Hou MC, Huo TI. Albumin-bilirubin grade-based nomogram of the BCLC system for personalized prognostic prediction in hepatocellular carcinoma. Liver Int. 2020; 40:205-214.
13. Choi GH, Park JY, Hwang HK, Kim DH, Kang CM, Choi JS, Park YN, Kim DY, Ahn SH, Han KH, Chon CY, Lee WJ. Predictive factors for long-term survival in patients with clinically significant portal hypertension following resection of hepatocellular carcinoma. Liver Int. 2011; 31:485-493.
14. Li Y, Ruan DY, Jia CC, Zhao H, Wang GY, Yang Y, Jiang N. Surgical resection versus liver transplantation for hepatocellular carcinoma within the Hangzhou criteria: a preoperative nomogram-guided treatment strategy. Hepatobiliary Pancreat Dis Int. 2017; 16:480-486.
15. Lee WC, Lee CF, Cheng CH, Wu TJ, Chou HS, Wu TH, Soong RS, Chan KM, Yu MC, Chen MF. Outcomes of liver resection for hepatocellular carcinoma in liver transplantation era. Eur J Surg Oncol. 2015; 41:1144-1152.
16. Zou H, Yang X, Li QL, Zhou QX, Xiong L, Wen Y. A Comparative Study of Albumin-Bilirubin Score with Child-Pugh Score, Model for End-Stage Liver Disease Score and Indocyanine Green R15 in Predicting Posthepatectomy Liver Failure for Hepatocellular Carcinoma Patients. Dig Dis. 2018; 36:236-243.
17. Wang YY, Zhong JH, Su ZY, Huang JF, Lu SD, Xiang BD, Ma L, Qi LN, Ou BN, Li LQ. Albumin-bilirubin versus Child-Pugh score as a predictor of outcome after liver resection for hepatocellular carcinoma. Br J Surg. 2016; 103:725-734.
18. Pinato DJ, Sharma R, Allara E, *et al.* The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2017; 66:338-346.
19. Chan AW, Kumada T, Toyoda H, Tada T, Chong CC, Mo FK, Yeo W, Johnson PJ, Lai PB, Chan AT, To KF, Chan SL. Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. J Gastroenterol Hepatol. 2016; 31:1300-1306.
20. Toyoda H, Lai PB, O'Beirne J, *et al.* Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. Br J Cancer. 2016; 114:744-750.
21. Ho SY, Hsu CY, Liu PH, Hsia CY, Su CW, Huang YH, Hou MC, Huo TI. Albumin-bilirubin (ALBI) grade-based nomogram to predict tumor recurrence in patients with hepatocellular carcinoma. Eur J Surg Oncol. 2019; 45:776-781.
22. Huo TI. ALBI grade as a new player in hepatocellular carcinoma. J Chin Med Assoc. 2019; 82:1.
23. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67:358-380.
24. Tomimaru Y, Eguchi H, Gotoh K, Kawamoto K, Wada H, Asaoka T, Noda T, Yamada D, Ogawa H, Umeshita K,

Nagano H, Doki Y, Mori M. Platelet count is more useful for predicting posthepatectomy liver failure at surgery for hepatocellular carcinoma than indocyanine green clearance test. J Surg Oncol. 2016; 113:565-569.
25. Maithel SK, Kneuertz PJ, Kooby DA, Scoggins CR, Weber SM, Martin RC, 2nd, McMasters KM, Cho CS, Winslow ER, Wood WC, Staley CA, 3rd. Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: a multi-institutional analysis. J Am Coll Surg. 2011; 212:638-648; discussion 648-650.
26. Jang CW, Kwon HJ, Kong H, Ha H, Han YS, Chun JM, Kim SG, Hwang YJ. Impact of clinically significant portal hypertension on surgical outcomes for hepatocellular carcinoma in patients with compensated liver cirrhosis: a propensity score matching analysis. Ann Hepatobiliary Pancreat Surg. 2016; 20:159-166.
27. Ohkubo T, Midorikawa Y, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Higaki T, Takayama T. Liver resection of hepatocellular carcinoma in patients with portal hypertension and multiple tumors. Hepatol Res. 2018; 48:433-441.
28. Lim C, Osseis M, Lahat E, Doussot A, Sotirov D, Hemery F, Lanteri-Minet M, Feray C, Salloum C, Azoulay D. Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study. Surg Endosc. 2019; 33:811-820.
29. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology. 2015; 61:526-536.
30. Liu J, Zhang H, Xia Y, Yang T, Gao Y, Li J, Wu Y, Shen F. Impact of clinically significant portal hypertension on outcomes after partial hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. HPB (Oxford). 2019; 21:1-13.
31. Choi SB, Kim HJ, Song TJ, Ahn HS, Choi SY. Influence of clinically significant portal hypertension on surgical outcomes and survival following hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. J Hepatobiliary Pancreat Sci. 2014; 21:639-647.
32. Tang YH, Zhu WJ, Wen TF. Influence of clinically significant portal hypertension on hepatectomy for hepatocellular carcinoma: a meta-analysis. Asian Pac J Cancer Prev. 2014; 15:1649-1654.
33. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer. 2012; 106:1439-1445.
34. Shiraki T, Ishizuka M, Kubota K, Kato M, Matsumoto T, Mori S, Shimizu T, Aoki T. An elevated neutrophil-to-lymphocyte ratio predicts a poor postoperative survival in primary hepatocellular carcinoma patients with a normal preoperative serum level of alpha-fetoprotein. Surg Today. 2019; 49:661-669.
35. Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, Xu MQ. Postoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio predicts the outcomes of hepatocellular carcinoma. J Surg Res. 2015; 198:73-79.

Received February 8, 2021; Revised February 20, 2021; Accepted February 22, 2021.

*Address correspondence to:
Chuan Li, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China.
E-mail: lichuan@scu.edu.cn

Released online in J-STAGE as advance publication February 24, 2021.