Original Article

Postoperative albumin-bilirubin grade and albumin-bilirubin change predict the outcomes of hepatocellular carcinoma after hepatectomy

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Background: The albumin-bilirubin (ALBI) grade is an index that could objectively evaluate liver function. The purpose of this study was to evaluate the prognostic value of postoperative ALBI (post-ALBI) grade and ALBI changes (△ALBI) after hepatectomy in patients with hepatocellular carcinoma (HCC).

Methods: The clinical and pathological data of 300 patients with HCC who underwent hepatectomy in the Third Affiliated Hospital of Sun Yat-Sen University from January 19, 2009 to December 25, 2014, were analyzed retrospectively. According to the test data, the patients were divided into post-ALBI grade I, post-ALBI grade II, and post-ALBI grade III groups. According to the receiver operating characteristic curves (ROC), the patients were divided into △ALBI (△ALBI >0.71) high and low groups (△ALBI ≤0.71). Baseline clinical data, recurrence-free survival (RFS) and overall survival (OS) rates were compared between the groups.

Results: The 1-, 3-, and 5-year RFS rates and OS rates of patients with post-ALBI grade III were significantly reduced in comparison to those with post-ALBI grade II (P<0.001 both). Between the △ALBI groups, patients with low △ALBI level had significantly reduced 1-, 3-, and 5-year RFS rates and OS rates compared to those with a high △ALBI level (P<0.001 both). Multivariate analyses indicated that higher post-ABLI grade and △ALBI level were significantly independent predictors of an inferior OS and RFS (P<0.05).

Conclusions: This study confirmed for the first time that post-ALBI grade and △ALBI could predict the prognosis of patients with HCC after hepatectomy.

Keywords: Carcinoma; hepatocellular; hepatectomy; albumin-bilirubin (ALBI); prognosis

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and the second leading cause of cancer-related death (1). The large number of hepatitis B patients in China has made HCC one of the most common malignant tumors in China. Hepatectomy, including the resection of HCC and para-carcinoma tissues, remains the preferred treatment for HCC (2). However, because of the high recurrence rate after surgery, the prognosis of HCC patients after hepatectomy is still unsatisfactory (3,4). To accurately determine the prognosis of HCC patients, a large number of studies have described the factors affecting the prognosis of patients with HCC after hepatectomy, including liver function, tumor size, tumor number, vascular invasion, tumor differentiation degree, inflammatory markers, and tumor stage (5-9). The prognosis of patients with HCC is not only related to tumor burden but also closely related to the liver function at the time of diagnosis and treatment of HCC.

Among all predictive factors, Child-Pugh grade, a liver function index, has become a recognized prognostic factor for HCC after hepatectomy. The Child–Pugh score is constituted of five different factors, including the three serological indicators total bilirubin (TB), plasma albumin (ALB) concentration and prothrombin time (PT) extension time; and the two clinical symptom indicators including ascites and hepatic encephalopathy. However, the two clinical symptoms, ascites and hepatic encephalopathy, are strongly subjective, which reduces the accuracy of its application.

Recently, the albumin-bilirubin (ALBI) grade, a new method based on ALB and bilirubin for assessing liver function, was proposed and used for patients with HCC (10). ALBI grade is a combination of two indicators of bilirubin and ALB, which include both the metabolic function (TB) and the synthesis function (ALB) of the liver. The role of ALBI grade in the evaluation of liver function is widely known (11,12). A large number of retrospective studies in Europe and Asia have further confirmed that there is predictive value when using the preoperative ALBI grade for evaluating liver function and predicting the prognosis of HCC (13).

However, there are no reports in the literature concerning the prognostic value of postoperative ALBI (post-ALBI) grade and postoperative ALBI change (△ALBI) in patients with HCC after hepatectomy. Therefore, this study investigated the influence of post-ALBI grade and △ALBI on the prognosis of patients with HCC after hepatectomy.

Methods

Patient inclusion and clinical pathological variables

Patients with HCC who underwent hepatectomy in the Third Affiliated Hospital of Sun Yat-Sen University from January 19, 2009 to December 25, 2014, were included in this study. The inclusion criteria of this study are as follows: (I) preoperative radiological imaging and postoperative histologic diagnosis of HCC; (II) treatment involving curative resection of HCC; (III) no other anticancer treatment before surgery, such as sorafenib treatment, ablation, interventional therapy, etc. The exclusion criteria are as follows: (I) recurrent liver cancer; (II) other anticancer treatment before surgery; (III) loss of follow-up within 3 months after surgery; (IV) missing clinical and experimental data. According to the guidelines of the Asian Pacific Association for the Study of the Liver (APASL) (14), the preoperative diagnosis of HCC in this study was performed by the diagnostic criteria of the typical imaging of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). This study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University.

The clinical pathological data of all the patients were collected from their medical records, including gender, age, tumor size, alpha-fetoprotein (AFP), HBV-DNA, blood cell count, liver function indicators, surgical methods, operation time, intraoperative blood loss, amount of fluid received, blood transfusion, total liver volume, and the size of remnant liver volume.

Total fluid volume = amount of fluid received + blood transfusion;

Net fluid volume = amount of fluid received + blood transfusion − intraoperative blood loss − urine volume.

The total liver volume and the remnant liver volumes after operation were measured by CT or MRI before and after the operation. The plasma ALB concentration and TB concentrations were obtained from the last liver function test before the operation and the first liver function test after the operation.

ALBI and △ALBI were calculated according to the following formula (15).

ALBI = (log10 TB concentration × 0.66) + (ALB concentration × −0.085), (the unit of TB is μmol/L; the unit of ALB concentration is g/L).

According to its calculated value, ALBI was divided into 3 levels: grade I (<−2.60), grade II (−2.60≤ ALBI ≤−1.39), and grade III (>−1.39).

△ALBI = postoperative ALBI (postoperative day 1) − preoperative ALBI (last test before operation).

Follow-up

All patients went through outpatient follow-up. In the first 2 years after surgery, AFP and other serological tests were performed every 3 months, and imaging examinations were performed by CT or MRI, then annually after that according to the standard protocol at our institution.

Postoperative recurrence was defined as the discovery of new star lesions in postoperative imaging examinations. The clinical follow-up was performed after surgery until the patient died or when the end of the follow-up was reached. Patients who were lost during the follow-up period within 3 months after surgery were not included in the study.

Data analysis

All data were analyzed by SPSS 20.0 software. P<0.05 was considered as the standard of statistical significance. Qualitative data were analyzed by χ^2 test or modified Fisher test, and quantitative data were analyzed by independent sample *t*-test. The overall survival (OS) curve and recurrence-free survival (RFS) curve were analyzed by Kaplan-Meier and log-rank tests. Cox regression model was used for hazard ratio assessment and multivariate analysis.

Results

Patients' characteristics and outcomes

A total of 300 patients who underwent hepatectomy of HCC were enrolled in this study. Among them, 275 were males (91.7%), and 25 were females (8.3%). The mean age of all patients was 50.19±11.44 years, and the median follow-up time was 35 months (1.5–87.6 months). Among them, 80 patients (26.7%) had a maximum tumor diameter of 3 cm or less than 3 cm, and 220 patients (73.3%) had a maximum tumor diameter of more than 3 cm. A total of 219 patients (73.0%) had a single tumor, and 81 patients (28.7%) had two or more tumors. During the whole follow-up period, 178 patients (59.3%) had a tumor recurrence, and 72 patients (24.0%) died.

The mean preoperative ALBI of the 300 patients was −2.6428, including 102 patients with ALBI grade I (34.0%), 191 patients with grade II (63.7%), and 7 patients with grade III (2.3%). The first postoperative biochemical result showed that the mean post-ALBI was −1.894, including 219 patients with post-ALBI grade II (73.0%), and 81 patients with grade III (27.0%). The clinicopathological characteristics of the two ALBI groups after surgery are shown in *Table 1*. The incidences of multiple tumors (P=0.002) and tumor invasion of blood vessels (P=0.022) in patients with post-ALBI grade II were lower than those in patients with post-ALBI grade III. The operation duration (P<0.001) was significantly longer in the post-ALBI grade III group, and the remnant liver volume was significantly smaller (P<0.001). The intraoperative blood transfusion volume (P=0.062), blood lose volume (P=0.030), fluid volume (P=0.049) were larger in the post-ALBI grade III group, but it was not statistically significant. And the net fluid volume (P=0.066) of this two groups was similar. Compared with preoperative ALBI, postoperative ALBI increased in 289 patients and decreased in only 11 patients (P=0.608).

The optimal cut-off values of △ALBI for survival analysis

In the receiver operating characteristic (ROC) curves (*Figure 1*), it was determined that the optimal cut-off value of △ALBI was 0.71, and the area under the curve was 0.622 (0.558–0.686), P<0.001, the sensitivity was 0.663, the specificity was 0.549, and the Youden index was 0.152. According to the cut-off value, the patients were divided into △ALBI high (△ALBI >0.71) and low (△ALBI ≤0.71) groups, and the clinicopathological characteristics of the two groups were compared (*Table 2*). The possibilities of patients in the △ALBI high group having multiple tumors (P=0.014) and tumor vascular invasion (P=0.029) was higher than those patients in the △ALBI low group. The operation duration (P=0.015) was longer in the △ALBI high group, and the remnant liver volume was significantly smaller (P<0.001). The intraoperative blood transfusion volume, blood loss volume, and fluid volume were larger in the △ALBI high group, but it was not statistically significant. The net fluid volume was also similar between these two groups.

Correlation between post-ALBI grade/△ALBI and survival prognosis in patients after hepatectomy

The 1-, 3-, and 5-year RFS rates of the 300 patients were 66.3%, 42.4%, and 36.9% respectively. The 1-, 3-, and 5-year OS rates were 92.2%, 78.4%, and 69.9% respectively. The 1-, 3-, and 5-year RFS rates and OS of patients with post-ALBI grade II were significantly increased compared with those of patients with post-ALBI grade III (RFS 72.1%, 49.6%, 44.9% *vs.* 50.6%, 23.1%, 16.2%; P<0.001; *Figure 2A*), (OS 94.0%, 83.7%, 77.7% *vs.* 87.5%, 63.3%, 49.7%; P<0.001; *Figure 2B*). In the △ALBI groups, the 1-, 3-, and 5-year RFS rates and OS of patients in the △ALBI low group was statistically higher than those in the △ALBI high group (RFS 78%, 54.6%, 46.9% *vs.* 57.6%, 33.2%, 29.3%; P<0.001; *Figure 3A*), (OS 95.2%, 89.1%, 84.2% *vs.* 90.0%, 70.2%, 59.7%; P<0.001; *Figure 3B*).

Table 1 Relationship between post-ALBI grades and clinicopathological characteristics

Characteristics	Grade II, n (%)	Grade III, n (%)	P value
Age (years old)			0.205
≤45	72 (32.9)	20 (24.7)	
>45	147 (67.1)	61 (75.3)	
Gender			0.244
Male	198 (90.4)	77 (95.1)	
Female	21 (9.6)	4 (4.9)	
Preoperative NLR			0.089
≤2.89	175 (79.9)	57 (70.4)	
>2.89	44 (20.1)	24 (29.6)	
Preoperative PLR			0.488
≤82.23	72 (32.9)	23 (28.4)	
>82.23	147 (67.1)	58 (71.6)	
Preoperative LMR			0.009
≤3.81	89 (40.6)	47 (58.0)	
>3.81	130 (59.4)	34 (42.0)	
Preoperative TB (μmol/L)	14.40±6.18	21.99±35.49	<0.001
Preoperative ALB (g/L)	40.77±3.69	37.94±5.05	0.002
Postoperative TB (μmol/L)	20.97±8.74	35.92±23.25	<0.001
Postoperative ALB (g/L)	34.37±3.31	28.13±2.98	<0.001
Child-Pugh			
A	212 (96.8)	71 (87.7)	0.04
B	7 (3.2)	10 (12.3)	
Tumor number			0.002
Single tumor	171 (78.1)	48 (59.3)	
Multiple tumors	48 (21.9)	33 (40.7)	
Tumor size (cm)			0.189
≤3	63 (28.8)	17 (21.0)	
>3	156 (71.2)	64 (79.0)	
Vascular invasion			0.022
Yes	71 (32.4)	38 (46.9)	
No	148 (67.6)	43 (53.1)	
Degree of tumor differentiation			0.722
High	27 (12.3)	11 (13.6)	
Moderate	163 (74.4)	62 (76.5)	
Low	29 (13.2)	8 (9.9)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Grade II, n (%)	Grade III, n (%)	P value
Preoperative AFP (ng/L)			1.000
<400	152 (69.4)	57 (70.4)	
≥400	67 (30.6)	24 (29.6)	
Preoperative HBV DNA			0.034
≤10,000	74 (33.8)	17 (21.0)	
>10,000	145 (66.2)	64 (79.0)	
BCLC grade			0.004
0	44 (20.1)	8 (9.9)	
A	88 (40.2)	24 (29.6)	
B	17 (7.8)	15 (18.5)	
C	70 (32.0)	34 (40.2)	
Operation duration (min)	197.80±69.79	261.27±102.96	<0.001
Blood transfusion (mL)	229.68±419.05	325.93±384.80	0.062
Blood loss (mL)	265.39±246.22	327.78±208.27	0.030
Fluid volume (mL, except blood)	2,445.75±695.01	2611.73±488.47	0.049
Total fluid volume (mL)	2,685.48±896.05	2,937.65±690.13	0.011
Net fluid volume (mL)	1,869.27±590.94	1,738.27±402.20	0.066
Total liver volume (mL)	1,077.09±113.40	1,068.93±123.75	0.700
Remnant liver volume (mL)	852.78±117.87	734.12±126.53	<0.001

Net fluid volume = fluid in – fluid out. Post-ALBI, postoperative albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; BCLC, Barcelona clinic liver cancer.

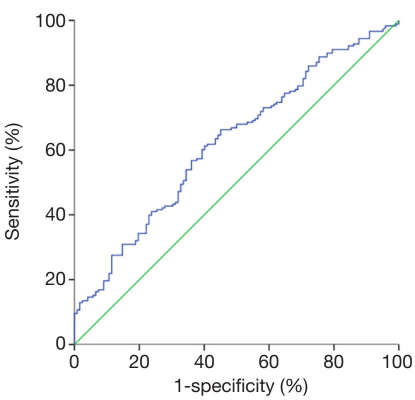

Figure 1 Receiver operating characteristics curve for △ALBI to predict the survival of patients with hepatocellular carcinoma after hepatectomy. △ALBI, albumin-bilirubin change.

Univariate and multivariate analysis of prognostic factors in patients with HCC after hepatectomy

Based on univariate analysis of RFS (*Table 3*), it was found that lymphocyte-to-monocyte ratio (LMR) (P<0.001), tumor number (P<0.001), tumor size (P<0.001), whether there was invasion of the vascular (P=0.001), post-ALBI grade (P<0.001), △ALBI (P<0.001), Barcelona clinic liver cancer (BCLC) grade (P<0.001) and blood loss(P<0.001) were significantly related to the RFS of the patients. Similarly, based on multivariate analysis, it was discovered that tumor number (HR 0.518; 95% CI, 0.348–0.771; P=0.001), tumor size (HR 0.518; 95% CI, 0.338–0.795; P=0.003), blood loss (HR 1.001; 95% CI, 1.000–1.001; P=0.002), post-ALBI grade (HR 0.659; 95% CI, 0.475–

Table 2 Relationship between △ALBI and clinicopathological characteristics

Characteristics	△ALBI ≤0.71, n (%)	△ALBI >0.71, n (%)	P value
Age (years old)			1.000
≤45	39 (30.7)	53 (30.6)	
>45	88 (69.3)	120 (69.4)	
Gender			0.398
Male	114 (89.8)	161 (93.1)	
Female	13 (10.2)	12 (6.9)	
Preoperative NLR			0.330
≤2.89	102 (80.3)	130 (75.1)	
>2.89	25 (19.7)	43 (24.9)	
Preoperative PLR			0.900
≤82.23	41 (32.3)	54 (31.2)	
>82.23	86 (67.7)	119 (68.8)	
Preoperative LMR			0.639
≤3.81	60 (47.2)	76 (43.9)	
>3.81	67 (52.8)	97 (56.1)	
Preoperative TB (μmol/L)	20.34±28.76	13.81±5.73	0.013
Preoperative ALB (g/L)	38.14±4.16	41.40±3.78	<0.001
Postoperative TB (μmol/L)	24.06±16.70	26.41±15.25	0.205
Postoperative ALB (g/L)	34.43±4.15	31.04±4.50	<0.001
Child-Pugh			
A	113 (89.0)	170 (98.3)	0.01
B	14 (11.0)	3 (1.7)	
Tumor number			0.014
Single tumor	102 (80.3)	117 (67.6)	
Multiple tumors	25 (19.7)	56 (32.4)	
Tumor size (cm)			0.114
≤3	40 (31.5)	40 (23.1)	
>3	87 (68.5)	133 (76.9)	
Vascular invasion			0.029
Yes	90 (70.9)	101 (58.4)	
No	37 (29.1)	72 (41.6)	
Degree of tumor differentiation			0.704
High	18 (14.2)	20 (11.6)	
Moderate	95 (74.8)	130 (75.1)	
Low	14 (11.0)	23 (13.3)	

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	△ALBI ≤0.71, n (%)	△ALBI >0.71, n (%)	P value
Preoperative AFP (ng/L)			0.803
<400	87 (68.5)	122 (70.5)	
≥400	40 (31.5)	51 (29.5)	
Preoperative HBV DNA			1.000
≤10,000	38 (29.9)	53 (30.6)	
>10,000	89 (70.1)	120 (69.4)	
BCLC grade			0.136
0	23 (18.1)	29 (16.8)	
A	56 (44.1)	56 (32.4)	
B	11 (8.70)	21 (12.1)	
C	37 (29.1)	67 (38.7)	
Operation duration (min)	201.36±77.78	224.91±88.43	0.015
Blood transfusion (mL)	250.20±407.72	259.68±415.69	0.844
Blood loss (mL)	256.85±251.85	300.87±225.97	0.120
Fluid volume (mL, except blood)	2,393.07±698.33	2,562.14±602.83	0.029
Total fluid volume (mL)	2,643.27±877.79	2,834.54±825.24	0.057
Net fluid volume (mL)	1,813.82±591.62	1,848.64±516.55	0.596
Total liver volume (mL)	1,079.34±114.20	1,071.73±117.20	0.655
Remnant liver volume (mL)	864.28±123.28	792.58±126.38	<0.001

Net fluid volume = fluid in – fluid out. △ALBI, albumin-bilirubin change; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; BCLC, Barcelona clinic liver cancer.

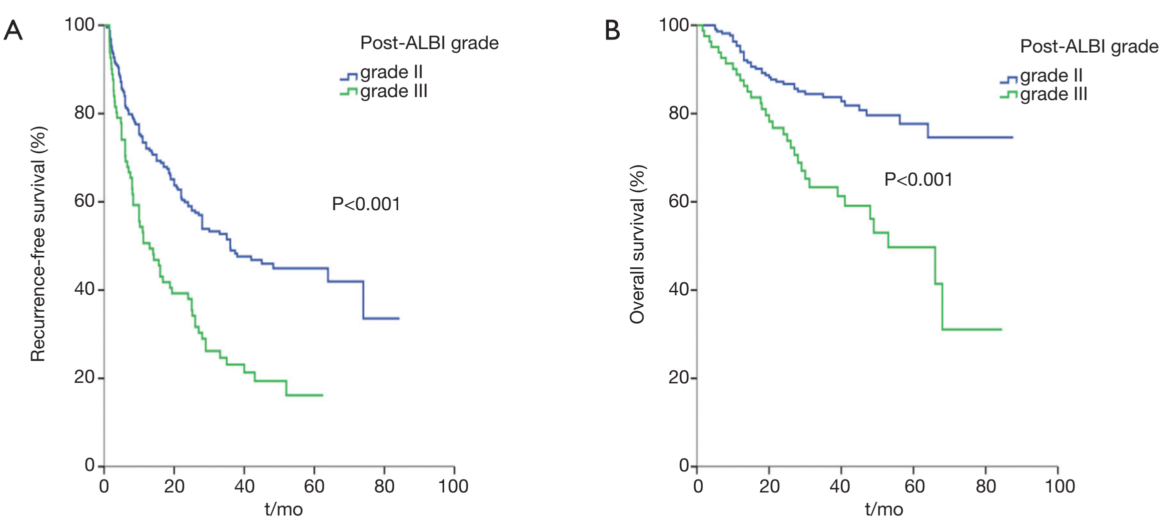

Figure 2 Kaplan-Meier survival analysis of post-ALBI grade in patients with hepatocellular carcinoma after hepatectomy. (A) Recurrence-free survival according to post-ALBI grade; (B) overall survival according to post-ALBI grade. post-ALBI, postoperative albumin-bilirubin.

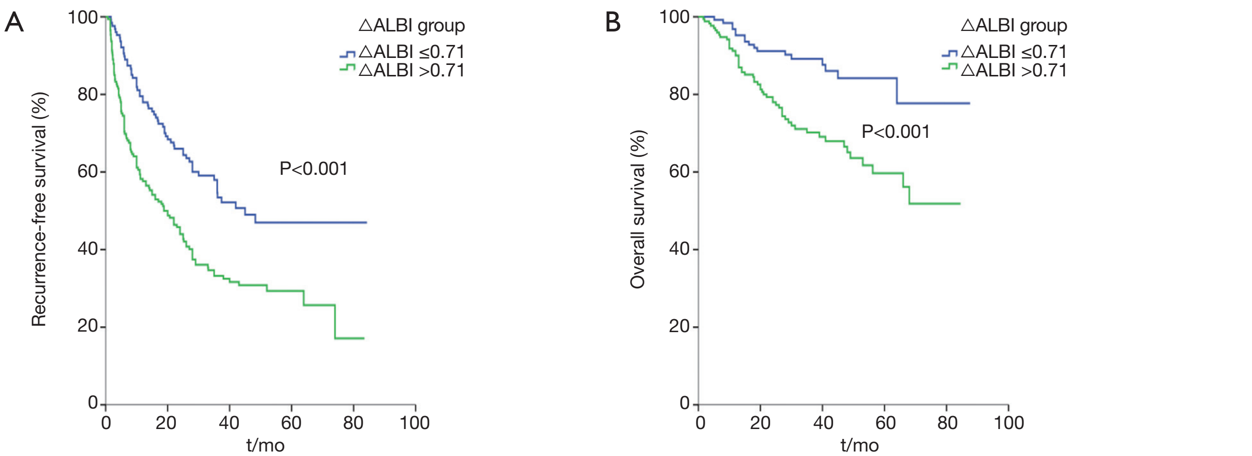

Figure 3 Kaplan-Meier survival analysis of △ALBI in patients with hepatocellular carcinoma after hepatectomy. (A) Recurrence-free survival according to △ALBI; (B) overall survival according to △ALBI. △ALBI, albumin-bilirubin change.

0.914; P=0.008), and △ALBI (HR 0.622; 95% CI, 0.450–0.859; P=0.004) were independent influencing factors of the RFS rates in patients with HCC after hepatectomy.

The results of univariate analysis of OS (*Table 4*) showed that LMR (P=0.001), tumor number (P<0.001), tumor size (P=0.001), whether there was invasion of the vascular (P<0.001), blood loss (P<0.001), post-ALBI grade (P<0.001), △ALBI (P<0.001) and BCLC grade (P<0.001) were significantly related to the OS of the patients. Similarly, multivariate analysis showed that vascular invasion (HR 0.475; 95% CI, 0.228–0.990; P=0.047), blood loss (HR 1.001; 95% CI, 1.000–1.002; P=0.011), post-ALBI grade (HR 0.545; 95% CI, 0.336–0.884; P=0.014), and △ALBI (HR 0.507; 95% CI, 0.288–0.891; P=0.018) were independent influencing factors of the OS in patients with HCC after hepatectomy.

From the results of survival analysis, it was found that post-ALBI grade and △ALBI were important influencing factors for the RFS and OS in patients with HCC after hepatectomy. Meanwhile, both were independent influencing factors for RFS and OS in patients with HCC after hepatectomy. The post-ALBI grade and △ALBI could accurately predict the prognosis of HCC patients.

Discussion

Clinical studies have shown that preoperative and postoperative liver functions of patients with HCC might affect their prognosis and play an important role in tumor recurrence and metastasis (16,17). Liver functions mainly include synthesis and metabolic functions, and the serological reaction mainly includes ALB, a coagulation factor, and bilirubin. A large number of studies have shown that Child-Pugh classification could predict the prognosis of HCC patients (18,19). However, the two clinical indicators as ascites and hepatic encephalopathy are subjective, and there is human error in the assessment, which might affect the accuracy. Johnson (10) reported a simple, objective, and effective indicator of liver function, ALBI grade. This method divides HCC patients into three grades using two cut-off values and has been confirmed in large cohort studies (15,20). In different treatment modalities of HCC, such as sorafenib, interventional therapy, and hepatectomy, preoperative ALBI could also predict the prognosis of patients with HCC (12,15,21). Previous studies have all focused on the predictive value of preoperative ALBI grade in the prognosis of patients.

Before this study, there was no literature on the correlation between post- ALBI grade/△ALBI and the prognosis of patients with HCC. In this study, 300 patients with HCC were enrolled, and all patients had not received any other anticancer treatment before hepatectomy. The results of this study indicated that post-ALBI grade is still an independent influencing factor for postoperative RFS and OS of the patients. The RFS and OS of patients with a higher ALBI grade after operation were worse than those with a lower ALBI grade after the operation. The higher the post-ALBI grade, the worse the postoperative liver function, which is consistent with the poor prognosis. It was also found that not only could △ALBI predict the RFS time well, it was also an independent influencing factor of OS in patients with HCC, while the prognosis of patients

Table 3 Prognostic factors associated with postoperative RFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (y), ≤45 *vs.* >45	1.047 (0.760–1.442)	0.779	–	–
Gender, male *vs.* female	0.655 (0.356–1.207)	0.175	–	–
NLR ≤2.89 *vs.* >2.89	1.621 (1.165–2.254)	0.002	–	–
PLR ≤82.23 *vs.* >82.23	1.381 (0.994–1.919)	0.055	–	–
LMR ≤3.81 *vs.* >3.81	0.547 (0.407–0.735)	<0.001	1.567 (1.155–2.126)	0.004
Preoperative TB (μmol/L)	0.997 (0.987–1.007)	0.543	–	–
Preoperative ALB (g/L)	0.980 (0.948–1.014)	0.244	–	–
Postoperative TB (μmol/L)	1.008 (1.001–1.015)	0.030	–	–
Postoperative ALB (g/L)	0.914 (0.883–0.947)	0.001	–	–
Child-Pugh A *vs.* B	0.806 (0.448–1.451)	0.486	–	–
Single tumor *vs.* multiple tumors	2.169 (1.595–2.951)	<0.001	0.518 (0.348–0.771)	0.001
Tumor size (cm), ≤3 *vs.* >3	2.266 (1.550–3.312)	<0.001	0.518 (0.338–0.795)	0.003
Vessels invasion yes *vs.* no	1.680 (1.245–2.266)	0.001	0.858 (0.540–1.363)	0.516
Differentiation degree low *vs.* high/ moderate	0.993 (0.635–1.553)	0.993	–	–
AFP <400 *vs.* ≥400	1.372 (1.005–1.874)	0.046	–	–
HBV DNA ≤10,000 *vs.* >10,000	1.627 (1.153–2.294)	0.006	–	–
BCLC grade 0 + A *vs.* B + C	1.867 (1.387–2.503)	<0.001	1.341 (0.766–2.345)	0.304
Operation duration (min)	1.002 (1.000–1.003)	0.014	–	–
Blood transfusion (mL)	1.000 (1.000–1.001)	0.007	–	–
Blood loss (mL)	1.001 (1.000–1.001)	<0.001	1.001 (1.000–1.001)	0.002
Fluid volume (mL, except blood)	1.000 (1.000–1.001)	0.013	–	–
Total fluid volume (mL)	1.000 (1.000–1.000)	0.171	–	–
Net fluid volume (mL)	1.000 (1.000–1.000)	0.660	–	–
Total liver volume (mL)	0.999 (0.997–1.000)	0.113	–	–
Remnant liver volume (mL)	0.998 (0.996–0.999)	0.004	–	–
Post-ALBI grade, II *vs.* III	2.086 (1.532–2.841)	<0.001	0.659 (0.475–0.914)	0.008
△ALBI ≤0.71 *vs.* △ALBI >0.71	1.882 (1.378–2.570)	<0.001	0.622 (0.450–0.859)	0.004

Net fluid volume = fluid in – fluid out. RFS, recurrence-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; BCLC, Barcelona clinic liver cancer; post-ALBI, postoperative albumin-bilirubin; △ALBI, albumin-bilirubin change.

with lower △ALBI after the operation was better. Besides this, we also investigated the differences in tumor size, vascular invasion, and tumor number of patients in the two groups divided based on △ALBI. It was found that a large △ALBI was consistent with the results of multiple tumors and tumor invasion in patients, suggesting that an increased degree of postoperative ALBI might be related to the invasiveness of the tumor. Compared with preoperative ALBI grade, postoperative ALBI grade and △ALBI could better reflect the liver condition after surgery and more accurately and objectively predict the prognosis of patients with HCC.

Table 4 Prognostic factors associated with postoperative OS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (y), ≤45 *vs.* >45	1.113 (0.664–1.864)	0.685	–	–
Gender, Male *vs.* female	0.870 (0.398–1.898)	0.726	–	–
NLR ≤2.89 *vs.* >2.89	1.998 (1.223–3.263)	0.006	–	–
PLR ≤82.23 *vs.* >82.23	1.604 (0.940–2.737)	0.083	–	–
LMR ≤3.81 *vs.* >3.81	2.265 (1.412–3.634)	0.001	–	–
Preoperative TB (μmol/L)	0.991 (0.962–1.020)	0.530	–	–
Preoperative ALB (g/L)	0.975 (0.925–1.028)	0.34	–	–
Postoperative TB (μmol/L)	1.010 (0.998–1.021)	0.092	–	–
Postoperative ALB (g/L)	0.896 (0.848–0.946)	0.001	–	–
Child-Pugh A *vs.* B	1.999 (0.490–8.166)	0.355	–	–
Single tumor *vs.* multiple tumors	0.384 (0.241–0.612)	<0.001	0.573 (0.321–1.032)	0.059
Tumor size (cm), ≤3 *vs.* >3	0.325 (0.166–0.637)	0.001	0.526 (0.248–1.116)	0.094
Vessels invasion yes *vs.* no	0.317 (0.198–0.507)	<0.001	0.475 (0.228–0.990)	0.047
Differentiation degree low *vs.* high/moderate	1.631 (0.892–2.982)	0.112	–	–
AFP <400 *vs.* ≥400	1.876 (1.174–3.000)	0.009	–	–
HBV DNA ≤10,000 *vs.* >10,000	1.090 (0659–1.801)	0.738	–	–
BCLC grade 0 + A *vs.* B + C	3.310 (2.012–5.446)	<0.001	1.159 (0.458–2.929)	0.756
Operation duration (min)	1.003 (1.001–1.005)	0.014	–	–
Blood transfusion (mL)	1.001 (1.000–1.001)	0.008	–	–
Blood loss (mL)	1.001 (1.000–1.002)	<0.001	1.001 (1.000–1.002)	0.011
Fluid volume (mL, except blood)	1.000 (1.000–1.000)	0.622	–	–
Total fluid volume (mL)	1.000 (1.000–1.000)	0.051	–	–
Net fluid volume (mL)	1.000 (0.999–1.000)	0.378	–	–
Total liver volume (mL)	0.997 (0.994–1.000)	0.023	–	–
Remnant liver volume (mL)	0.995 (0.992–0.997)	0.004	–	–
Post-ALBI grade, II *vs.* III	0.378 (0.238–0.602)	<0.001	0.545 (0.336–0.884)	0.014
△ALBI ≤0.71 *vs.* △ALBI >0.71	0.369 (0.214–0.635)	<0.001	0.507 (0.288–0.891)	0.018

Net fluid volume = fluid in – fluid out. OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; BCLC, Barcelona clinic liver cancer; post-ALBI, postoperative albumin-bilirubin; △ALBI, albumin-bilirubin change.

In this study, the preoperative ALBI grades of the patients were mainly graded I (34.6%) and grade II (63.2%), and the postoperative ALBI grades of the patients were grade II (70.8%) and grade III (29.2%). The mean ALBI also increased significantly after surgery. ALBI is an important index to evaluate liver function (10). The increase in ALBI after surgery might be related to a reduction in liver function after surgical resection of some normal liver and surgical attack. The increase in postoperative ALBI could also reflect the liver reserve function. The liver reserve function of patients with large postoperative △ALBI was poorer than that of patients with small postoperative

△ALBI, which is consistent with the low RFS and low OS after hepatectomy.

In this study, we collected the data after the operation, the concentration of ALB and TB might be affected by the intraoperative blood loss, amount of fluid received, blood transfusion, and the size of the remnant liver volume. So, we compared the differences of intraoperative blood loss, amount of fluid received, blood transfusion, and net fluid received between the groups. We found that blood loss, amount of fluid received, and blood transfusion were larger in the postoperative ALBI grade III group and △ALBI high group, but these were not statistically significant. We also found the net fluid received between groups was similar. We believe postoperative ALBI grade and △ALBI can predict the outcomes of HCC independently.

The size of liver resection is related to the tumor size and tumor number in patients undergoing hepatectomy for HCC. The volume of liver resection was larger in patients with large tumor volume, and liver function impairment was more significant in large HCC than in small HCC. In our study, we found that patients with post-ALBI grade III and high △ALBI were more likely to have a small remnant liver volume which showed post-ALBI grade and △ALBI could better reflect the liver reserve function. Therefore, they were more statistically significant in prognosis prediction. Our study included patients with all sizes of tumors and did not simply investigate the effects of post-ALBI and △ALBI on the prognosis of patients with small or large HCC, but further confirmed that post-ALBI grade and △ALBI could be used to predict the prognosis of patients with HCC.

Previous studies demonstrated that preoperative ALBI grade combined with tumor T grade (22) and Barcelona grade (13) could better predict the prognosis of patients with HCC. This study simply investigated the effects of post-ALBI grade and △ALBI on the prognosis of patients with HCC. For patients with a high post-ALBI grade or large △ALBI, it could better guide early prevention, diagnosis, and clinical treatment. In future studies, post-ALBI grade and △ALBI combined with tumor staging could be used to evaluate the prognosis of patients with HCC. Therefore, all aspects of different factors could be more comprehensively considered, and it could more accurately predict the prognosis of patients to guide clinical treatment.

The shortcomings of this study are the retrospective nature of the study, the small number of patients enrolled in the study, and that the process of follow-ups and data collection was easily biased, thereby affecting the accuracy of the results. Also, tumor-related factors included in this study were deficient and failed to comprehensively evaluate the role of post-ALBI grade and △ALBI. Large prospective clinical studies would more accurately evaluate the predictive value of post-ALBI grade and △ALBI on the prognosis of patients with HCC after hepatectomy. Post-ALBI grade and △ALBI could also be used in the prognostic prediction of other treatments of HCC.

Conclusions

This study first confirmed that the post-ALBI grade and △ALBI could predict the prognosis of patients with HCC after hepatectomy. Higher post-ALBI grade and higher △ALBI would lead to a worse prognosis of the tumor. In clinical practice, post-ALBI grade and △ALBI could be used as new and valuable prognostic indicators of patients with operable HCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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