Original Article

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The combination of the preoperative albumin-bilirubin grade and the fibrosis-4 index predicts the prognosis of patients with hepatocellular carcinoma after liver resection

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Summary **There is little information regarding the use of a combination of the albumin-bilirubin (ALBI) grade and the fibrosis-4 index (FIB-4) in predicting hepatocellular carcinoma (HCC) patient outcomes after liver resection. In this study, we aimed to analyze the predictive ability of a combination of the ALBI grade and the FIB-4 score (ALBI-FIB-4) for HCC patients within the Milan criteria after liver resection. The data of HCC patients within the Milan criteria who underwent liver resection between 2011 and 2019 at our center were reviewed (n = 544). Patients with an FIB-4 index > 3.25 were considered to have a high FIB-4 index and were given a score of 1, whereas patients with an FIB-4 index ≤ 3.25 were considered to have a low FIB-4 index and were given a score of 0. The ALBI-FIB-4 score was a summary score that combined the ALBI grade and the score based on the FIB-4 index. During the follow-up period, 279 patients experienced recurrence, and 175 patients died. Multivariate analysis showed that tumor size, the presence of multiple tumors, the presence of microvascular invasion and the ALBI-FIB-4 score were four independent risk factors for both postoperative recurrence-free survival (RFS) and overall survival (OS). The 5-year RFS of patients with high ALBI-FIB-4 scores of 1, 2, and 3 were 55.0%, 44.2% and 35.3%, respectively (p = 0.004). The 5-year OS rates of patients with high ALBI-FIB-4 scores of 1, 2, and 3 were 72.9%, 66.4% and 54.8%, respectively (p = 0.011). The ALBI-FIB-4 score may be a surrogate marker for predicting the prognosis of patients with HCC after liver resection. A high ALBI-FIB-4 score was associated with a high incidence of postoperative recurrence and mortality.**

Keywords: Hepatocellular carcinoma, albumin-bilirubin grade, fibrosis-4 index

1. Introduction

Because of the rapidly increasing incidence of hepatocellular carcinoma (HCC), HCC has become the second leading cause of cancer-related death worldwide (*1*). Due to the high prevalence of hepatitis B virus (HBV) infection, more than half of new cases and deaths occurred in China (*2*). Liver resection is one of the methods of curative management for patients with early stage HCC and compensated liver function. However, a high incidence of postoperative recurrence has greatly limited the long-term survival of patients with HCC after liver resection (*3*).

HCC patients are often affected by various degrees of liver fibrosis (*4*). Previous studies have confirmed that severe liver fibrosis or cirrhosis could result in serious postoperative complications, such as postoperative liver failure and poor long-term survival for patients with HCC (*5,6*). Liver biopsy is the standard method to evaluate the degree of liver fibrosis. However, liver biopsy is an invasive management technique that can cause severe complications, such as intra-abdominal bleeding (*7*). Some noninvasive methods based on laboratory measurements have been

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proposed to assess the severity of liver fibrosis (*8,9*). The fibrosis-4 index (FIB-4) is a noninvasive method used to assess the severity of fibrosis in patients that considers four parameters: age, platelet counts, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (*10*). Some investigators have suggested that FIB-4 can predict the outcomes of liver resection (*5*).

In addition to liver fibrosis, liver function also greatly impacts HCC patient outcomes after liver resection. Poor liver function can cause high postoperative morbidity and shorter long-term survival (*11*). Although FIB-4 was recognized for assessing liver fibrosis, it was not able to assess liver function in patients. Recently, the albumin-bilirubin (ALBI) grade was proposed for assessing liver function in patients instead of the conventional Child-Pugh score (*12*). Unlike the Child-Pugh score, the ALBI grade only includes two objective parameters, serum albumin and total bilirubin (*12*). Whether a combination of the FIB-4 score and the ALBI grade could better predict the prognosis of HCC patients after liver resection is not well established. In this study, we tried to clarify this issue.

2. Materials and Methods

We retrospectively reviewed data from patients with HCC within the Milan criteria who underwent liver resection between 2011 and 2019 at our center. The exclusion criteria included reresection, ruptured HCC, receipt of preoperative antitumor treatment, a positive surgical margin, and the presence of other types of tumors. The diagnosis of HCC was confirmed based on the histological examination of resected specimens. This study was approved by the ethics committee of West China Hospital.

2.1. *Follow-up*

All preoperative blood tests were performed one week before the operation. After discharge, patients were followed up regularly every 3 months. Before and after surgery, antiviral drugs (entecavir, lamivudine or tenofovir) were conventionally administered to patients with a positive hepatitis B virus-DNA (HBV-DNA) load. Follow-up assessments included blood cell tests, hepatic function tests, serum measurements of alpha-fetoprotein (AFP), and HBV-DNA tests. Visceral ultrasonography, as well as computed tomography or magnetic resonance imaging and chest radiography, were performed for all patients during each follow-up. Bone scintigraphy was performed whenever HCC recurrence was suspected. Postoperative recurrence was defined as positive imaging findings compared to those obtained during the preoperative examination or was confirmed by biopsy or resection.

2.2. *Definitions*

The FIB-4 index was calculated as the AST (IU/L) × age (years)/[platelet count (10^9/L) × ALT (IU/L)$^{1/2}$]. The ALBI score = (log10 bilirubin ×0.66) + (albumin × −0.085). ALBI grades were defined as grade 1 (score ≤ –2.60), grade 2 (score > –2.60 and ≤ –1.39), and grade 3 (score > –1.39). Preoperative AFP greater than 400 ng/mL was considered a high preoperative AFP level (*3*). An FIB-4 index > 3.25 (cirrhosis) was considered a high FIB-4 index, which was defined as a score of 1 (*8*). An FIB-4 index ≤ 3.25 (noncirrhosis) was considered a low FIB-4 index, which was defined as a score of 0 (*8*). The combined ALBI and FIB-4 score (ALBI-FIB-4) was defined as the combination of the scores of the ALBI grade and the FIB-4 score and ranged from 1 to 4. The neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the lymphocyte count (*13*). The platelet-to-lymphocyte ratio (PLR) was defined as the platelet count divided by the lymphocyte count (*13*).

2.3. *Statistical analysis*

All statistical analyses were performed using SPSS 21.0 (SPSS Company, Chicago, IL) for Windows. All continuous variables were compared using one-way analysis of variance. Categorical variables were compared using the χ^2 test or Fisher's exact test. Recurrence-free survival (RFS) and overall survival (OS) were determined using the Kaplan-Meier method, and comparisons were made using the log rank test. A Cox proportional hazard regression model was generated to evaluate hazard ratios for risk factors OS and RFS. All variables found to be significant ($p < 0.05$) by univariate analysis were included in the multivariate analysis. A p-value less than 0.05 was considered to indicate a statistically significant difference.

3. Results

3.1. *The clinicopathological characteristics*

The clinicopathological data of the 544 patients are shown in Table 1. The mean age was 52.0 ± 11.7 years in the current study, and the patients were predominantly male. Multiple tumors were observed in 43 patients. Microvascular invasion was detected in 74 patients. High preoperative AFP levels were observed in 154 patients. Positive HBV-DNA was detected in 262 patients. In the current study, no patients with an ALBI grade of 3 were observed. A total of 411 patients had an ALBI grade of 1, whereas 133 patients had an ALBI grade of 2. According to the FIB-4 index, 233 patients had a high FIB-4 index, whereas 311 patients had a low FIB-4 index. In the present study, the number of patients who had ALBI-FIB-4 scores of 1, 2, and 3 were

Table 1. Clinicopathological characteristics of present study

Variables	No./mean ± SD
Age (years)	52.0 ± 11.7
Female/male	81/463
Multiple tumors (yea/no)	43/501
Presence of MVI (yea/no)	74/470
Differentiation (well/moderate/poor)	18/373/153
Tumor size (cm)	3.4 ± 1.1
Positive HBV-DNA load (yea/no)	262/282
Preoperative AFP > 400ng/mL (yea/no)	154/390
Preoperative platelet counts (109/L)	116 ± 50
NLR	2.2 ± 1.4
PLR	81.6 ± 37.5
FIB-4 index > 3.25 / ≤ 3.25	233/311
ALBI grade 1/2	411/133
ALBI-FIB-4 score 1/2/3	261/199/84

ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; FIB-4, fibrosis index 4; HBV, hepatitis B virus; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, SD, standard deviation.

261, 199, and 84, respectively. There were no patients with an ALBI-FIB-4 score of 4. Based on a median follow-up of 52.5 months, 279 patients experienced recurrence, and 175 patients died. As shown in Figure 1, the 1-, 3-, and 5-year RFS rates (Figure 1A) were 83.1%, 61.8% and 47.9%, respectively, whereas the 1-, 3-, and 5-year OS rates (Figure 1B) were 97.4%, 83.4% and 67.6%, respectively.

3.2. *Univariate and multivariate analyses for RFS*

Table 2 lists the results of the univariate and multivariate analyses of the predictors of postoperative RFS. Univariate analysis revealed that tumor size, preoperative platelet counts, ALBI-FIB-4 score, presence of MVI, multiple tumors, FIB-4 score, and ALBI grade were significant. However, in the multivariate analysis, only four independent risk factors were identified: tumor size

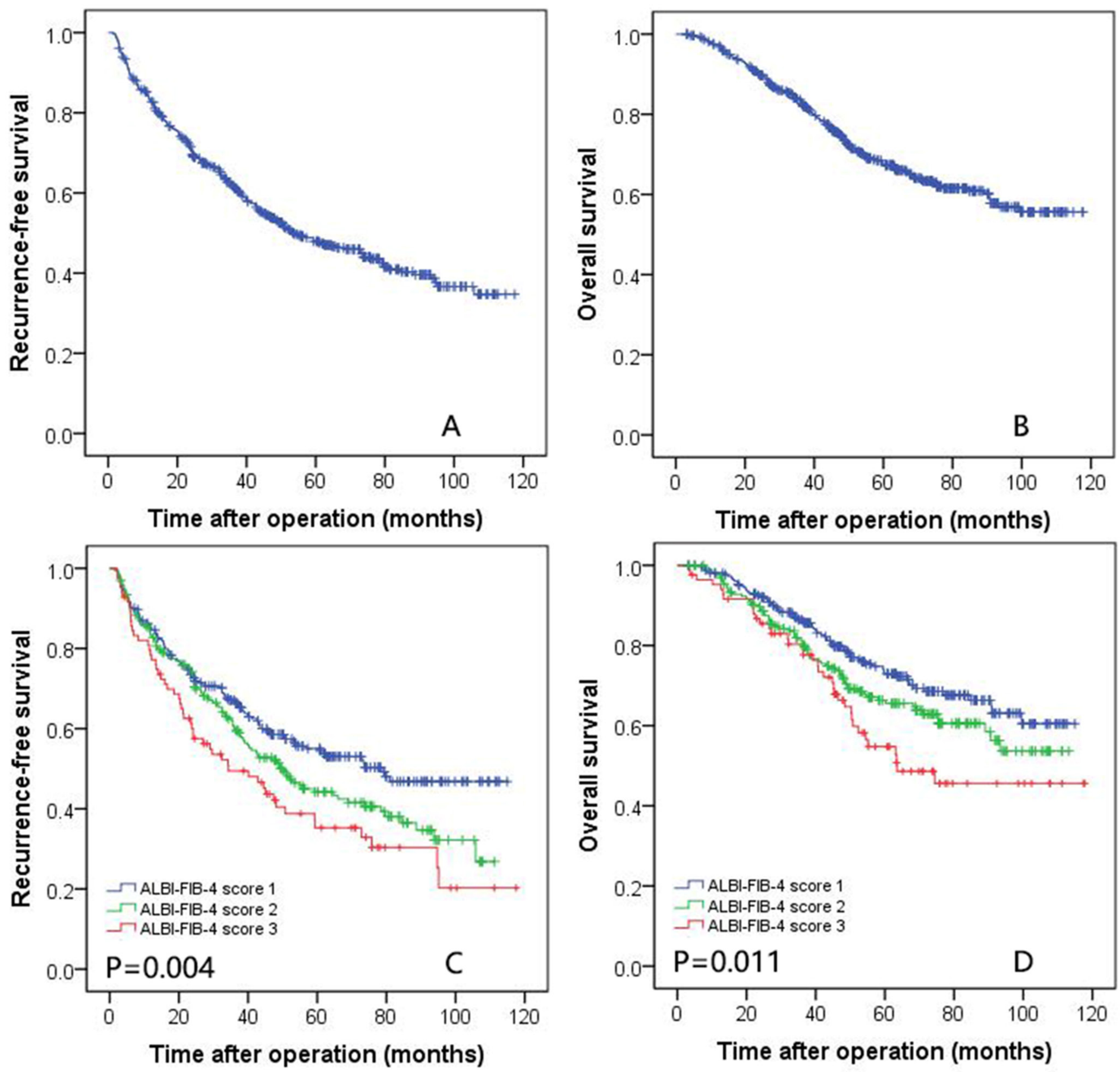

Figure 1. The recurrence-free survival (A) and overall survival (B) curves of the current study. Comparison of the recurrence-free survival (C) and overall survival (D) in patients with different ALBI-FIB-4 scores.

(HR = 1.296, 95% CI = 1.154-1.457, $p < 0.001$), multiple tumors (HR = 2.673, 95% CI = 1.801-3.976, $p < 0.001$), ALBI-FIB-4 score (HR = 1.278, 95% CI = 1.090-1.498, $p = 0.003$), and the presence of MVI (HR = 1.681, 95% CI = 1.225-2.307, $p = 0.001$).

As displayed in Table 3, univariate analysis identified several factors associated with poor OS: tumor size, preoperative platelet counts, ALBI-FIB-4 score, FIB-4 score, positive HBV-DNA, and the presence of MVI. However, the multivariate analysis suggested that only tumor size (HR = 1.386, 95% CI = 1.196-1.607, $p < 0.001$), presence of MVI (HR = 2.090, 95% CI = 1.449-3.015, $p < 0.001$), multiple tumors (HR = 2.436, 95% CI = 1.505-3.943) and ALBI-FIB-4 score (HR = 1.335, 95% CI = 1.091-1.633, $p = 0.005$) were independent risk factors associated with postoperative mortality.

3.3. *Comparison of postoperative RFS and OS in patients with different ALBI-FIB-4 scores*

As shown in Figure 1C, the 1-, 3-, and 5-year RFS rates were 85.0%, 67.1%, and 55.0% for patients with an ALBI-FIB-4 score of 1, 83.2%, 60.1%, and 44.2% for patients with an ALBI-FIB-4 score of 2 and 77.2%, 49.4%, and 35.3% for patients with an ALBI-FIB-4 score of 3, respectively. A significant difference was observed (Figure 1C; $p = 0.004$). As shown in Figure 1D, the 1-, 3-, and 5-year OS rates were 98.1%, 86.0%, and 72.9% for patients with an ALBI-FIB-4 score of 1, 97.4%, 81.4%, and 66.4% for patients with an ALBI-FIB-4 score of 2 and 95.2%, 80.3%, and 54.8% for patients with an ALBI-FIB-4 score of 3, respectively (Figure 1D; $p = 0.011$).

4. Discussion

Previous studies suggested that the severity of fibrosis in patients was associated with both postoperative morbidity and mortality (*6,14*). The FIB-4 index, as a

Table 2. Factors associated with postoperative recurrence-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)	1.005	0.995-1.016	0.319			
Tumor size (cm)	1.257	1.122-1.407	< 0.001	1.296	1.154-1.457	< 0.001
Multiple tumors (yes/no)	2.131	1.457-3.117	< 0.001	2.673	1.801-3.967	< 0.001
Female/male	1.390	0.975-1.981	0.069			
AFP > 400ng/mL (yes/no)	1.096	0.847-1.416	0.486			
Positive HBV-DNA load (yes/no)	1.203	0.951-1.521	0.123			
Differentiation (poor/moerate/well)	0.926	0.735-1.165	0.511			
MVI (yes/no)	1.979	1.313-2.461	< 0.001	1.681	1.225-2.307	0.001
Platelet counts (10^9/L)	0.997	0.995-1.000	0.032			
PLR	0.999	0.996-1.002	0.624			
NLR	1.016	0.942-1.096	0.675			
ALBI grade	1.359	1.049-1.761	0.020			
FIB-4 index	1.387	1.097-1.755	0.006			
ALBI-FIB-4 score	1.304	1.114-1.525	0.001	1.278	1.090-1.498	0.003

ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; FIB-4, fibrosis index 4; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 3. Factors associated with postoperative overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)	1.004	0.991-1.017	0.557			
Tumor size (cm)	1.379	1.194-1.594	< 0.001	1.386	1.196-1.607	< 0.001
Multiple tumors (yes/no)	1.856	1.164-2.959	0.009	2.436	1.505-3.943	< 0.001
Female/male	1.356	0.859-2.139	0.191			
AFP > 400ng/mL (yes/no)	1.253	0.916-1.715	0.158			
Positive HBV-DNA load (yes/no)	1.197	0.889-1.612	0.236			
Differentiation (poor/moerate/well)	0.777	0.581-1.040	0.090			
MVI (yes/no)	2.332	1.625-3.346	< 0.001	2.090	1.449-3.015	< 0.001
Platelet counts (10^9/L)	0.997	0.994-1.000	0.057			
PLR	1.001	0.997-1.005	0.534			
NLR	1.043	0.964-1.127	0.295			
ALBI grade	1.268	0.913-1.761	0.156			
FIB-4 index	1.563	1.162-2.103	0.003			
ALBI-FIB-4 score	1.345	1.105-1.637	0.003	1.335	1.091-1.633	0.005

ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; FIB-4, fibrosis index 4; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

noninvasive marker that could assess the severity of fibrosis, was proven to predict the prognosis of HCC patients after liver resection (*5*). However, the FIB-4 index cannot predict the liver function of patients with HCC. Our study confirmed that the combination of the FIB-4 index and the ALBI score could better predict the outcomes of patients with HCC after liver resection.

In 2015, Johnson *et al*. (*12*) proposed the use of the ALBI grade to assess patient liver function. Compared to the conventional liver function method, the Child-Pugh score, ALBI only included total bilirubin and serum albumin as the two objective factors. However, the Child-Pugh score includes ascites and hepatic encephalopathy, which are two subjective parameters. Subsequently, many investigations confirmed that the ALBI grade may be better than the Child-Pugh score for evaluating patient liver function (*15,16*). A number of studies also revealed that the ALBI grade could predict the prognosis of patients with HCC after liver resection, radiofrequency ablation, liver transplantation, transarterial chemoembolization and other treatments (*17-21*). A large, multicenter study performed by Pinato *et al*. (*22*) confirmed that the ALBI grade showed predictive value for patients with HCC in several Barcelona Clinic Liver Cancer system stages. Studies have even suggested that when the ALBI grade was used instead of the Child-Pugh score, the ALBI-based Barcelona Clinic Liver Cancer staging system and the ALBI-based Japanese Integrated Staging system showed similar or better prognostic prediction power than the Child-Pugh-based Barcelona Clinic Liver Cancer staging system and the Child-Pugh-based Japanese Integrated Staging system (*16,23*). Moreover, poor liver function contributed to a high incidence of postoperative complications, and shorter long-term survival was also found in many studies (*11,24*).

Another explanation for the relationship between a high ALBI grade and a high postoperative recurrence rate is the anti-cancer effect of albumin. Low serum albumin levels may cause a high ALBI grade. Carr *et al*. (*25*) suggested that patients with low serum albumin had larger tumor sizes, higher AFP levels, more tumors and increased portal vein tumor thrombosis. Carr *et al*. (*25*) suggested that decreased serum albumin levels may contribute to the aggressiveness of HCC. A basic research study suggested that albumin plays a direct role in inhibiting the growth of HCC (*26*).

Previous studies have suggested that liver fibrosis is associated with HCC patient outcomes after liver resection. As a noninvasive marker of liver fibrosis, the preoperative FIB-4 index was shown to predict postoperative complications and recurrence in patients with HCC after liver resection (*5*). Previous studies have confirmed a good correlation between FIB-4 index and degree of fibrosis using specimens from liver biopsies (*27*). The FIB-4 index included four parameters: age, ALT, AST and platelet count. These four parameters are also associated with HCC patient outcomes. For example, a national survey confirmed that elderly patients suffered from significantly worse long-term survival than middle-age and young patients (*28*). Kaneko *et al*. (*29*) confirmed that a low preoperative platelet count was associated with high mortality after liver resection. AST and ALT are sensitive and reliable biochemical markers of liver inflammation. A study performed by Zhou *et al* revealed that both AST and ALT could predict early recurrence and OS in patients with HCC following liver resection (*30*).

Our study confirmed that the ALBI-FIB-4 score was better than both the ALBI grade and the FIB-4 index alone in predicting postoperative recurrence and mortality in HCC patients after liver resection. We acknowledge that the ALBI grade can accurately reflect liver function. However, some other situations may also result in a high ALBI grade, such as malnutrition. In this situation, patients may not have severe liver fibrosis. Similarly, some patients with a high FIB-4 score may have good liver function. Accordingly, the ALBI-FIB-4 score may more accurately reflect the patient's status than ALBI grade or FIB-4 index alone. Liao *et al*. (*31*) also suggested the combination of ALBI and FIB-4 could predict postoperative recurrence of patients with HCC after liver resection. Compared with Liao *et al*'s study, our study only included HCC patients within Milan criteria (*31*). Like other centers, patients with HCC beyond Milan criteria may receive some treatments after liver resection. We believe, these treatments may also impact the outcomes of HCC patients after liver resection. Moreover, our study confirmed a combination of ALBI and FIB-4 may not only predict the RFS but also the OS of patients with HCC after liver resection.

There are also some limitations in this study. This is a single center respective study. Additional studies are needed to validate its conclusions. Moreover, in China, more than 90% of HCC cases are HBV-related HCC (*32*). Whether our conclusions pertain to other causes of HCC requires further study.

In conclusion, our study suggested that a combination of ALBI grade and FIB-4 index may better predict the prognosis of patients with HCC after liver resection. Patients with a high ALBI-FIB-4 score may have a higher incidence of postoperative recurrence and poorer long-term survival.

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