Original Article

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Preoperative albumin-bilirubin grade combined with aspartate aminotransferase-to-platelet count ratio index predict outcomes of patients with hepatocellular carcinoma within Milan criteria after liver resection

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Summary **There is little information concerning the prognostic significance of combined albumin-bilirubin (ALBI) grade and aspartate aminotransferase-to-platelet count ratio index (APRI) in hepatocellular carcinoma (HCC). Therefore, we performed this study to assess the prognostic utility of combining ALBI and APRI (ALBI-APRI score) for predicting the prognosis of patients with HCC within Milan criteria after liver resection. Two hundred thirty-nine patients were involved in this study. Patients with a high APRI score were allocated a score of 1, whereas patients with a low APRI score were allocated a score of 0. The ALBI-APRI score is the summation of APRI score and ALBI grade. The area under the receiver operating characteristic curve (AUC) was used to estimate the predictive accuracy of different models. During the study period, 132 patients experienced recurrence, and 52 patients died. Multivariate analysis revealed the ALBI-APRI score (HR = 1.753, 95% CI = 1.293-2.377, $p < 0.001$), presence of microvascular invasion (MVI, HR = 2.693, 95%CI = 1.832-3.960, $p < 0.001$) and multiple tumors (HR = 1.973, 95% CI = 1.300-2.995, $p = 0.001$) were all associated with recurrence. In addition, blood transfusion (HR = 3.113, 95% CI = 1.677-5.778, $p < 0.001$), high preoperative alpha-fetoprotein (AFP, HR = 2.272, 95% CI = 1.298-3.976, $p = 0.004$), ALBI-APRI score (HR = 2.046, 95% CI = 1.237-3.382, $p = 0.005$) and presence of MVI (HR = 4.524, 95% CI = 2.514-8.140, $p < 0.001$) were correlated with postoperative mortality. The AUCs of ALBI-APRI score were significantly higher than either ALBI or APRI alone for predicting both postoperative recurrence and mortality. ALBI-APRI score may be a predictor for the prognosis of patients with HCC within Milan criteria following liver resection. A more well-designed and large-scale study are warranted to prove our findings.**

Keywords: Albumin-bilirubin grade, aminotransferase-to-platelet count ratio index, hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is ranked the third most frequent cancer-related mortality worldwide (*1*). Every year, more than 800,000 new cases are diagnosed, and mortality is high due to the poor prognosis of HCC (*2*). Liver resection is widely accepted as a curative treatment for HCC patients with well-compensated liver function. However, the 5-year overall survival for HCC patients after liver resection remains unsatisfactory due to the high incidence of postoperative recurrence (*3*). Some investigations suggest as many as 51.6-70.3% of patients with HCC within Milan criteria will suffer from recurrence after liver resection (*4,5*).

Liver function greatly influences the prognosis of HCC patients. Patients with poor liver function are at high risk for postoperative complications and tend to

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experience poor long-term overall survival. Recently, albumin-bilirubin (ALBI) grade was identified as a simple tool to assess patient liver function (*6*). Compared to Child-Pugh score, ALBI only includes total bilirubin and albumin as the two objective parameters. ALBI measurements may avoid the adverse influence of subjective variables, such as ascites and hepatic encephalopathy. Some studies also demonstrated that ALBI could predict HCC patient prognosis following liver resection (*6-8*). In addition to patient liver function, liver fibrosis or cirrhosis also plays a key role in HCC patient outcomes after liver resection (*9,10*). However, ALBI only reflects patient liver function and cannot indicate the degree of liver fibrosis in HCC patients. Preoperative aspartate aminotransferase (AST)-to-platelet count ratio index (APRI) has been confirmed as a surrogate marker for histological fibrogenesis (*11*). It is unclear whether ALBI incorporated with APRI results could strengthen the prognostic power for HCC patients within Milan criteria following liver resection. To clarify this issue, we conducted this study.

2. Patients and Methods

Patients with HCC within Milan criteria who underwent liver resection between 2013 and 2018 at our center were included in this study. Exclusion criteria included re-resection, ruptured HCC, receipt of preoperative antitumor treatment, a positive surgical margin, and the presence of other types of tumors. HCC was confirmed by postoperative pathological examination. This study was approved by the ethics committee of West China Hospital (No. 2017062).

2.1. *Follow-up*

All preoperative blood tests were performed two days before liver resection. After surgery, patients were followed up regularly every 3 months. Before and after surgery, antiviral drugs (entecavir, lamivudine or tenofovir) were conventionally administered to patients with positive hepatitis B virus-DNA (HBV-DNA) load. During follow-up, blood cell tests, liver function tests, serum alpha-fetoprotein (AFP) measurements, HBV-DNA tests, and visceral ultrasonography, as well as computed tomography or magnetic resonance imaging and chest radiography, were performed for all patients. Bone scintigraphy was performed whenever HCC recurrence was suspected. Postoperative recurrence was defined as positive imaging findings compared to preoperative examination values or as confirmed by biopsy or resection.

2.2. *Definitions*

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) (*12*). APRI was calculated as [(AST value/ULN)/platelet count (10^9/L)] × 100 (*13*). APRI less than 0.5 was considered low APRI, whereas APRI ≥ 0.5 was defined as high APRI (*13*). ALBI-APRI scores were the summation of APRI scores and ALBI grade. ALBI-APRI scores ranged from 1 to 4. A high preoperative AFP was defined as an AFP level greater than 400 ng/mL (*13*). Neutrophil to lymphocyte ratio (NLR) was defined as absolute neutrophil counts divided by the lymphocyte counts (*7*). Platelet to lymphocyte ratio (PLR) as platelet counts divided by the lymphocyte counts (*7*). The preoperative prognostic nutritional index (PNI) was calculated using the following formula: serum albumin (g/L) + 0.005 × total lymphocyte count (per mm^3) (*7*).

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. Multivariable analysis was performed using Cox regression analysis to identify independent risk factors for OS and RFS. All variables found to be significant ($P < 0.05$) by univariate analysis were included in the multivariate analysis. The area under the receiver operating characteristic curve (AUC) was used to estimate the predictive accuracy of ALBI grade, APRI and ALBI-APRI score. A P-value of < 0.05 was considered statistically significant.

3. Results

Two hundred thirty-nine patients were included in this study. Of these, 197 were male, and 42 were female. Mean patient age was 48.86 ± 11.35 years. High preoperative AFP levels were detected in 77 patients. Positive HBV-DNA was observed in 122 patients, and 36 patients received blood transfusions. Multiple tumors were detected in 37 patients, and microvascular invasion (MVI) was observed in 48 patients. High APRI was observed in 208 patients. According to ALBI grade, 165 patients were stratified as grade 1, whereas 74 patients were stratified as grade 2. There were no ALBI grade 3 patients. There were 23 patients with ABLI-APRI score 1, 151 patients with ALBI-APRI score 2, and 65 patients in ALBI-APRI score 3. There were no patients with ALBI-APRI score 4. With a mean of 29.51 ± 13.18 months follow-up, 132 patients suffered from recurrence and 51 patients died.

3.1. *Univariate and multivariate analysis for RFS*

Table 1. Factors associated with RFS

Variables	Univariate	Multivariate	
	P value	HR (95%CI)	*P* value
Age (years)	0.629		
Gender (male)	0.946		
Tumor size (cm)	0.637		
Tumor number > 1	0.002	1.973 (1.300-2.995)	0.001
Differentiation	0.474		
AFP > 400 ng/mL	0.072		
Positive HBV-DNA load	0.495		
Presence of MVI	< 0.001	2.693 (1.832-3.960)	< 0.001
Transfusion	0.003		
Preoperative platelet (10^9/L)	0.029		
High APRI	< 0.001		
ALBI grade	< 0.001		
ALBI-APRI score	< 0.001	1.753 (1.293-2.377)	< 0.001
Preoperative PLR	0.969		
Preoperative NLR	0.691		
Preoperative PNI	0.315		

AFP, alpha-fetoprotein; APRI, aspartate aminotransferase-to-platelet count ratio index; HR, hazard ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; NLR, Neutrophil to lymphocyte ratio; MVI, microvascular invasion.

Table 2. Factors associated with OS

Variables	Univariate	Multivariate	
	P value	HR (95%CI)	*P* value
Age (years)	0.065		
Gender (male)	0.837		
Tumor size (cm)	0.820		
Tumor number > 1	0.829		
Differentiation	0.380		
AFP > 400 ng/mL	0.007	2.272 (1.298-3.976)	0.004
Positive HBV-DNA load	0.162		
Presence of MVI	< 0.001	4.524 (2.514-8.140)	< 0.001
Transfusion	0.001	3.113 (1.677-5.778)	< 0.001
Preoperative platelet (10^9/L)	0.175		
High APRI	0.033		
ALBI grade	< 0.001		
ALBI-APRI score	< 0.001	2.046 (1.237-3.382)	0.005
Preoperative PLR	0.711		
Preoperative NLR	0.741		
Preoperative PNI	0.395		

AFP, alpha-fetoprotein; APRI, aspartate aminotransferase-to-platelet count ratio index; HR, hazard ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; NLR, Neutrophil to lymphocyte ratio; MVI, microvascular invasion.

As shown in Table 1, factors associated with postoperative recurrence included multiple tumors, presence of MVI, transfusion, high preoperative APRI, ALBI grade, platelet counts and ALBI-APRI score by univariate analysis. In multivariate analysis, only ALBI-APRI score (HR = 1.753, 95% CI = 1.293-2.377), presence of MVI (HR = 2.693, 95%CI = 1.832-3.960) and multiple tumors (HR = 1.973, 95% CI = 1.300-2.995) exhibited prognostic power.

3.2. *Univariate and multivariate analysis for OS*

As shown in Table 2, presence of MVI, transfusion, high preoperative APRI, ALBI grade, high preoperative AFP and ALBI-APRI score were significant predictors of OS by univariate analysis. In multivariate analysis, only transfusion (HR = 3.113, 95% CI = 1.677-5.778), high preoperative AFP (HR = 2.272, 95% CI = 1.298-3.976), ALBI-APRI score (HR = 2.046, 95% CI = 1.237-3.382) and presence of MVI (HR = 4.524, 95% CI = 2.514-8.140) remained significant independent predictors of OS.

3.3. *Comparison of RFS and OS of patients with different ALBI-APRI scores*

The 1-, 3-, and 5-year RFS were 100%, 65.1%, and 48.8% for patients with ALBI-APRI score 1; 95.4%, 52.6%, and 12.4% for patients with ALBI-APRI score 2; and 87.7%, 39.0%, and 3.9% for patients with ALBI-APRI score 3, respectively. Significant differences were observed (Figure 1A, $p = 0.005$). The 1-, 3-, and 5-year OS were 100%, 91.7%, and 61.1% for patients

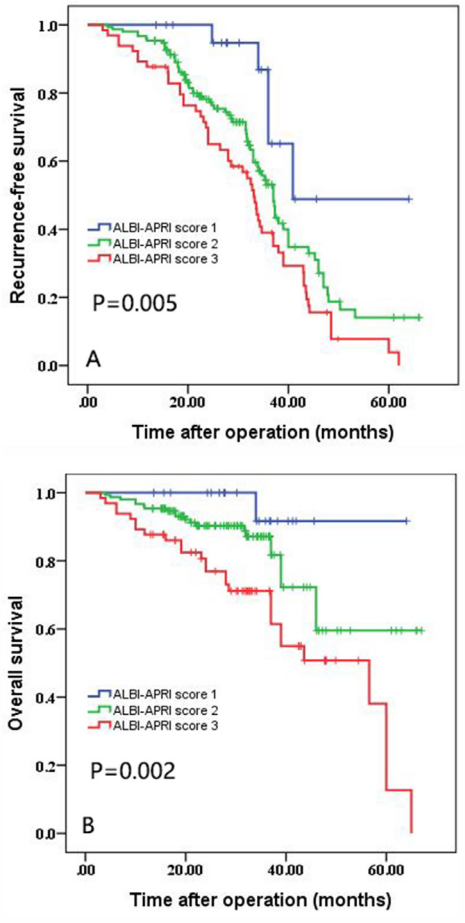

Figure 1. Comparison of recurrence-free (A) and overall (B) survival of patients with different ALBI-APRI scores.

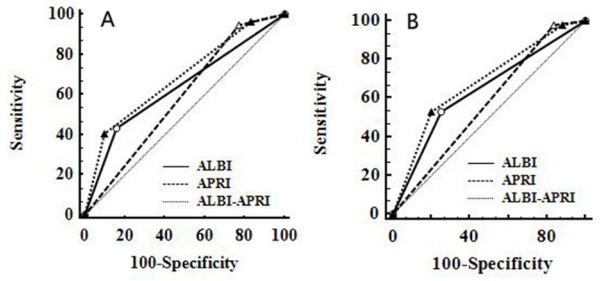

Figure 2. Comparison of the under the receiver operating characteristic curve of ALBI-APRI, ALBI, and APRI in predicting postoperative recurrence (A) and survival (B).

with ALBI-APRI score 1; 95.4%, 87.2% and 59.5% for patients with ALBI-APRI score 2; 87.7%, 71.1%, and 50.7% for patients with ALBI-APRI score 2, respectively (Figure 1B, p = 0.002).

3.4. *Comparison of the predictive abilities of ALBI-APRI, ALBI and APRI*

We compared the AUC of ALBI-APRI, ALBI and APRI, which were 0.686, 0.636 and 0.586, respectively, for predicting postoperative recurrence (Figure 2A). Significant differences were observed between ALBI-APRI versus ABLI ($P_{\text{ALBI-ALBI versus ABLI}} = 0.005$) and ALBI-APRI versus APRI ($P_{\text{ALBI-APRI versus APRI}} < 0.001$). As shown in Figure 2B, for predicting postoperative mortality, ALBI-APRI had the highest AUC (0.683), followed by ALBI (0.640) and APRI (0.570). Significant differences were also observed between ALBI-APRI versus ABLI ($P_{\text{ALBI-APRI versus ABLI}} < 0.001$) and ALBI-APRI versus APRI ($P_{\text{ALBI-APRI versus APRI}} < 0.001$).

4. Discussion

Liver resection is widely accepted as a curative treatment for patients with HCC. However, high postoperative recurrence rate remains an obstacle to long-term survival. Our study suggests that ALBI combined with APRI represent a surrogate marker to predict HCC patient prognosis after liver resection.

Recently, ABLI was confirmed as a superior tool to Child-Pugh score for assessing liver function (*14,15*). Child-Pugh score has some limitations because it includes two subjective variables: ascites and encephalopathy. Additionally, in Child-Pugh score, ascites and albumin may be confounded by their interrelationship. In our clinical practice, we perform liver resection in patients with Child-Pugh A grade. ALBI further discriminates patient liver function in the same Child-Pugh grade. ALBI not only evaluates patient liver function but also predicts HCC patient prognosis after liver resection. For example, Ho *et al*. (*16*) suggested that ALBI is a feasible marker for predicting patient recurrence after liver resection. Dong *et al*. (*7*) confirmed ALBI score significantly impacted both HCC patient RFS and OS after liver resection. However, though ABLI can assess patient liver function, it does not indicate the severity of patient fibrosis. Some patients with severe fibrosis may present with good liver function, and a number of investigations have revealed that severe fibrosis or cirrhosis has an adverse influence on HCC patient prognosis. In contrast, some patients without severe cirrhosis may also exhibit poor liver function, such as patients with malnutrition. The serum albumin level of patients with malnutrition may be very low. Accordingly, patients with malnutrition may have a high ALBI grade.

There are some potential mechanisms of poor ALBI grade contributing to poor prognosis of patients with HCC after liver resection. First, many studies have confirmed that patients with poor liver function may have increased surgical risk, a high incidence of postoperative complications, and a high recurrent rate. Ho *et al*. (*17*) compared the prognostic power of ten liver function models for predicting the prognosis of HCC patients after radiofrequency ablation. Only ALBI was an independent prognostic predictor by multivariate analysis (*17*). Second, some research has suggested that albumin may inhibit the growth of HCC (*18,19*). Carr and colleagues' study indicates that low serum albumin levels are associated with increased variables of HCC aggressiveness, such as larger maximum tumor diameters, increased portal vein thrombosis, higher α-fetoprotein levels and so on (*19*). Basic studies have also confirmed exogenous albumin at physiological concentrations can inhibit the growth of several HCC cell lines *in vitro* (*18*).

In contrast to ALBI, APRI is considered a promising noninvasive alterative to liver biopsy for assessing the stage of fibrosis (*20*). Previous studies have suggested liver fibrosis negatively affects HCC patient outcomes (*10,21*). Gon *et al*. (*22*) even suggested that liver fibrosis is an independent risk factor for rapid progression of portal vein tumor thrombus. Some investigators have also suggested that APRI could predict outcomes of patients with HCC after liver resection (*23,24*). Ichikawa *et al*. (*25*) confirmed that preoperative APRI independently predicts postoperative liver failure. In addition, Cheng *et al*. (*11*) suggested APRI could predict postoperative complications in HCC patients after liver resection. Further, some studies confirmed that postoperative complications may adversely influence both postoperative RFS and OS for patients with HCC after liver resection (*26-28*). Moreover, the preoperative platelet counts of patients with high APRI score may be low. Kaneko *et al*. (*29*) suggested HCC patients with low preoperative platelet counts may suffer from a high incidence of postoperative mortality. Maithel *et al*. (*30*) also confirmed low platelet count was associated with high postoperative mortality. Our study confirmed ALBI

combined with APRI score demonstrates superior predictive ability than either ALBI or APRI alone. ALBI plus APRI score reflect both patient liver function and stage of fibrosis. Recently, Pereya *et al*. (*31*) confirmed ALBI plus APRI score could predict the morbidity, liver dysfunction and mortality for patients who received liver resection for colorectal cancer liver metastases. They suggested ALBI plus APRI score was a good tool to dynamically reflect the chemotherapy-associated liver injury of patients with colorectal cancer liver metastases.

There are some limitations in this study. This is a small sample and single center's retrospective study. Moreover, in China, most HCC are hepatitis B virus-related HCC. Accordingly, whether ALBI+APRI score could predict the prognosis of other causes-related HCC needs further study. We believe that a multicenter prospective study is needed to further validate our conclusions.

In conclusion, our study suggests that ALBI plus APRI score predicts the prognosis of patients with HCC after liver resection. Patients with high ALBI+APRI score experience a high recurrence rate and poor long-term survival.

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