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RESEARCH ARTICLE

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Prognostic utility of albumin-bilirubin grade for short- and long-term outcomes following hepatic resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 706 patients

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Abstract

Background: The objective of the current study was to define the impact of albumin-bilirubin (ALBI) grade on short- as well as long-term outcomes among patients with intrahepatic cholangiocarcinoma (ICC).

Methods: Patients who underwent hepatectomy for ICC between 1990 and 2016 were identified using an international multi-institutional database. Clinicopathologic factors including ALBI score were assessed using bivariate and multivariable analyses, as well as standard survival analyses.

Results: Among 706 patients, 453 (64.2%) patients had ALBI grade 1, 231 (32.7%) ALBI grade 2, and 22 (3.1%) had ALBI grade 3. After adjusting for all competing factors, patients with ALBI grade 2/3 had higher odds of a prolonged length-of-stay (>10 days, odds ratio [OR] = 2.37, 95% confidence interval [CI]:1.47-3.80), perioperative transfusion (OR = 2.15, 95% CI:1.45-3.18) and 90-day mortality (OR = 2.50, 95% CI:1.16-5.38). Median and 5-year overall survival (OS) for the entire cohort was 41.5 months (IQR:15.7-107.8) and 39.8%, respectively. Of note, median OS incrementally worsened with increased ALBI grade: grade 1, 49.6 months (IQR:18.3-NR) vs grade 2, 29.6 months (IQR:12.6-98.4) vs grade 3, 16.9 months (IQR:6.5-32.4; $P < 0.001$). On multivariable analysis, higher ALBI grade remained associated with higher hazards of death (grade 2/3: hazard ratio = 1.36, 95% CI:1.04-1.78).

Conclusion: The ALBI score was associated with both short- and long-term outcomes following resection for ICC and could prove a useful surrogate marker to identify patients at risk for adverse outcomes.

KEYWORDS
albumin, bilirubin, complications, ICC, overall survival

1 | INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare cancer with an increasing incidence in the United States (US) and worldwide over the last three decades.[1,2] Surgery remains the mainstay of treatment and the only chance for cure among patients diagnosed with ICC. Prognosis of patients remains dismal, however, even after curative-intent resection with a median survival ranging from 24 to 36 months.[3,4] In addition, liver resection for ICC is associated with a high perioperative morbidity reaching up to 45% and a mortality rate as high as 5%.[5] As such, development of risk stratification schemas is necessary to improve preoperative patient selection and identify patients who might benefit the most from surgery or other treatment strategies in a multidisciplinary setting.

To date, there are only a few prognostic tools available for patients with ICC.[6-8] In addition, most of these tools rely on factors known only after surgery as only a few models have utilized preoperative factors to stratify the long-term prognosis.[6] Most commonly, tumor-associated factors such as tumor number, size, major vascular invasion as well as serum biomarkers, such as the carcinoembryonic antigen (CEA) and the cancer antigen (CA) 19-9 have been correlated with clinical outcomes.[6,7] Apart from tumor factors, assessment of the underlying liver function is crucial in determining the outcomes of patients undergoing liver surgery for ICC.[9-12] Of note, the albumin-bilirubin (ALBI) grading system has been proposed to provide a simple and objective method to evaluate the liver function reserve and, in turn, predict patient outcomes following liver surgery.[13] Since its introduction in 2015, there has been a growing interest of the prognostic utility of ALBI grade, mainly focusing on patients undergoing surgery for hepatocellular carcinoma (HCC).[14,15] The prognostic utility of the ALBI score among patients undergoing resection for ICC has, however, not been assessed. As such, the objective of the current study was to examine the ability of ALBI score to predict short- and long-term outcomes among patients undergoing resection for ICC. In addition, we sought to investigate whether the ALBI grading system could stratify prognosis of ICC patients in the presence or absence of cirrhosis.

2 | METHODS

2.1 | Study population and data collection

Patients undergoing curative-intent liver resection for histologically confirmed ICC between January 1990 and December 2016 were identified in a multi-institutional database incorporating data from 15 tertiary institutions (The Ohio State University Comprehensive Cancer Center, Columbus, OH; Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VS; Winship Cancer Institute, Emory University, Atlanta, GA; Fundeni Clinical Institute, Bucharest, Romania; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; Beaujon Hospital, Clichy, France; Erasmus University Medical Centre, Rotterdam, Netherlands; University of Ottawa, Ontario, Canada; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Yokohama City University School of Medicine, Yokohama, Japan; and Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia). Patients who did not undergo curative-intent resection or had missing data on the laboratory values of interest, such as albumin and bilirubin, as well as missing follow-up data were excluded. The Institutional Review Board of all participating institutions approved this study.

2.2 | Variables and outcomes of interest

The primary outcome of interest was overall survival (OS); OS was defined as the time interval between the date of hepatectomy for ICC and the date of death or last follow-up. Secondary outcomes included complication rate (overall, major, minor), length-of-stay (LOS) >10, perioperative transfusion, 90-day mortality, and 30-day readmission rates. The primary independent variable was ALBI grade. The ALBI score was calculated using the following formula: [$\log_{10}$ bilirubin (μmol/L) x 0.66] + [albumin (g/L) x −0.085], as previously described.[13] Similar to previous reports, patients were categorized into three groups; grade 1 (≤−2.60), grade 2 (>−2.60 and ≤−1.39), and grade 3 (>−1.39).[13] Due to the limited number of patients with ALBI grade 3, short- and long-term outcomes of ALBI grade 2 and 3 patients were cumulatively assessed and compared with ALBI grade 1 patients.

Demographic and clinicopathologic data included age, sex, race, American Society of Anesthesiologist (ASA) class, preoperative serum level of bilirubin, albumin and carbohydrate antigen (CA) 19-9, presence of cirrhosis, type of resection (ie, minor, major), tumor location (ie, unifocal, multifocal), tumor size, T stage, N stage, margin status, morphological type (MF: mass-forming; IG: intraductal growth; PI: periductal infiltrating), tumor grade, presence of major or microvascular invasion, receipt of adjuvant chemotherapy, and LOS. Tumor T- and N stage were defined according to the American Joint Committee on Cancer (AJCC) 8th edition staging manual.[16] Major hepatectomy was defined as the resection of three or more Couinaud segments.[17] Major vascular invasion was defined as invasion of the first- and second-order branches of the portal vein or hepatic arteries, or as invasion of one or more of the three hepatic veins. In contrast, microvascular invasion was defined as intraparenchymal vascular involvement identified on histological examination.[16] Urinary tract or surgical site infections were categorized as minor complications, whereas all other complications constituted major complications, as previously reported.[18]

2.3 | Statistical analysis

Descriptive statistics were presented as median (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. A logistic multivariable regression model was used to examine the association between the ALBI grade and outcomes of interest, including complications, LOS, perioperative transfusion,

30-day readmission, and 90-day mortality. OS was calculated by creating Kaplan–Meier curves and differences in survival between different groups were assessed using the log-rank test. The association of clinicopathologic variables with OS was evaluated by using a Cox proportional hazards model. Statistical significance was assessed at $\alpha = 0.05$. All statistical analyses were performed with the SPSS, version 25 statistical package (IBM Corp, Armonk, NY).

3 | RESULTS

3.1 | Baseline characteristics of the entire cohort

A total of 706 patients with ICC met the predefined inclusion criteria and were included in the analysis. Median patient age at the time of surgery was 57.9 years (IQR: 49.3-66.0) and more than half of patients were male (n = 419, 59.4%). Only a minority of patients had cirrhosis (n = 90, 13.8%). The median bilirubin, albumin, and CA19-9 levels preoperatively were 0.9 mg/dL (IQR: 0.6-1.4), 4.2 g/dL (IQR: 3.8-4.4), and 45.6 UI/mL (IQR: 17-206), respectively. Overall, 453 (64.2%) patients had ALBI grade 1, 231 (32.7%) ALBI grade 2, and 22 (3.1%) had ALBI grade 3 (Table 1). The majority of patients had unifocal disease (n = 614, 87.1%) with a median tumor size of 6.0 cm (IQR: 4.0-8.1). According to the 8th AJCC staging system, 56.5% (n = 399) of patients had T1a/T1b disease, while 22% (n = 155) and 19.5% (n = 138) had N0 and N1 disease, respectively. In addition, most patients had an R0 resection (n = 619, 88.3%), MF or IG morphologic ICC type (n = 581, 88.8%), well to moderately differentiated tumors (n = 574, 84.3%); only a small subset of patients had major vascular invasion (n = 91, 12.9%). On histological examination, 27.1% (n = 190) of cases had microvascular invasion. Median LOS was 14 days (IQR: 9-14). A minority of individuals received adjuvant chemotherapy (n = 181, 26.2%).

3.2 | Short-term outcomes

ALBI grade was associated with short-term outcomes. Specifically, after adjusting for age, sex, ASA class, cirrhosis, and type of resection, patients with ALBI grade 2/3 had higher odds of a prolonged LOS (>10 days, OR = 2.37; 95% CI, 1.47-3.80; $P < 0.001$), as well as perioperative transfusion (OR = 2.15; 95% CI, 1.45-3.18; $P < 0.001$) and 90-day mortality (OR = 2.50; 95% CI, 1.16-5.38; $P = 0.019$; Table 2, Figure 1). ALBI grade 2/3 was also associated with higher 30-day readmission on bivariate analysis (OR = 2.03; 95% CI, 1.03-3.98; $P = 0.036$).

3.3 | Long-term outcomes

After a median follow-up of 20.7 months (IQR: 10.8-39.9), the median and 5-year OS for the entire cohort was 41.5 months (IQR: 15.7-107.8) and 39.8%, respectively. Of note, median OS incrementally worsened with increased ALBI grade: ALBI grade 1, 49.6 months (IQR: 18.3-NR) vs ALBI grade 2, 29.6 months (IQR:12.6-98.4) vs ALBI grade 3, 16.9 months (IQR: 6.5-32.4, $P < 0.001$; Figure 2). After

TABLE 1 Clinicopathologic features of patients (n = 706)

Variables	Total, n (%)
Age, median (IQR)	57.9 (49.4, 66.0)
Male	419 (59.4)
ASA	
≤2	474 (70.9)
>2	195 (29.1)
Bilirubin (mg/dL), median (IQR)	0.9 (0.6, 1.4)
Albumin (g/dL), median (IQR)	4.2 (3.8, 4.4)
CA19-9 (UI/mL), median (IQR)	45.6 (17, 206)
Cirrhosis	90 (13.8)
Type of resection	
Minor resection	330 (47)
Major resection	372 (53)
Location	
Unifocal	614 (87.1)
Multifocal	91 (12.9)
Tumor size, cm; median (IQR)	6.0 (4.0, 8.1)
AJCC 8th edition T stage	
T1a/T1b	399 (56.5)
T2/T3/T4	307 (43.5)
AJCC 8th edition N stage	
Nx	413 (58.5)
N0	155 (22)
N1	138 (19.5)
Margin status	
R0	619 (88.3)
R1	72 (10.3)
R2	10 (1.4)
Morphologic type	
MF, IG	581 (88.8)
PI, MF+PI	73 (11.2)
Grade	
Well to moderate	574 (84.3)
Poor to undifferentiated	107 (15.7)
Major vascular invasion	
No	613 (87.1)
Yes	91 (12.9)
Microvascular invasion	
No	510 (72.9)
Yes	190 (27.1)
Adjuvant chemotherapy	
No	509 (73.8)
Yes	181 (26.2)
LOS, median (IQR)	14 (9, 18)
ALBI grade	
Grade 1	453 (64.2)

(Continues)

TABLE 1 (Continued)

Variables	Total, n (%)
Grade 2	231 (32.7)
Grade 3	22 (3.1)

Abbreviations: AJCC, American Joint Committee on Cancer; ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologist; CA, Carbohydrate antigen; IG, intraductal growth; IQR, interquartile range; LOS, length-of-stay; MF, mass-forming; PI, periductal infiltrating

stratifying by the presence of cirrhosis, cirrhotic patients with ALBI grade 1 undergoing resection for ICC had better 5-year OS compared with ALBI grade 2/3 patients (54.5% vs 25.8%, $P = 0.033$; Figure 3A). The same relationship was evident among noncirrhotic patients (5-year OS: 45.8% vs 35.8%, $P = 0.013$; Figure 3B).

On multivariable analysis, after controlling for competing factors, higher ALBI grade remained associated with higher hazards of death (referent grade 1: grade 2/3: hazard ratio [HR] = 1.36; 95% CI, 1.04-1.78; $P = 0.027$). Perhaps not surprisingly, CA19-9 >200 (HR = 2.49; 95% CI, 1.88-3.30; $P < 0.001$), N1 disease (HR = 2.16; 95% CI, 1.40-3.33; $P < 0.001$), higher T stage (referent T1: T2/T3/T4, HR = 1.91; 95% CI, 1.36-2.69; $P < 0.001$), R1/R2 resection (HR = 2.01; 95% CI, 1.28-3.13; $P = 0.002$) and poor/undifferentiated tumor grade (HR = 1.56; 95% CI, 1.09-2.24; $P = 0.014$) were also associated with poor OS (Table 3).

4 | DISCUSSION

ICC is a highly aggressive tumor with an increasing incidence over the last few years, especially in Western countries.[1,4] Despite advances in the understanding of the biologic behavior of this tumor and perioperative techniques, patients with ICC exhibit a 5-year OS of approximately 30% even after curative-intent resection.[1] To date, several prognostic schemas and nomograms have been proposed to stratify outcomes of patients with ICC.[6-8] These have largely focused on tumor-specific factors, including tumor number, size, major vascular invasion, lymph node status as well as serum CEA and

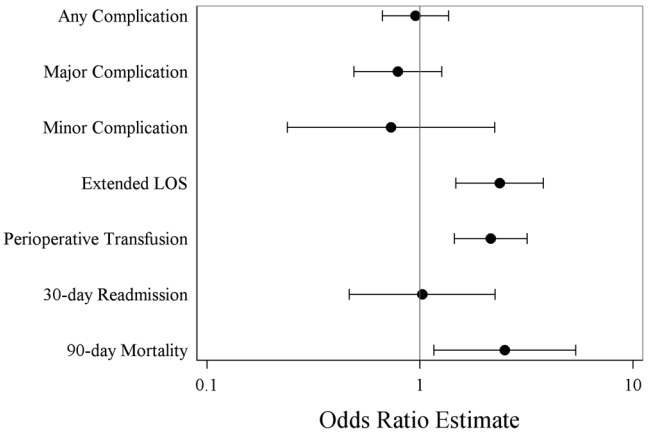

FIGURE 1 Association of albumin-bilirubin (ALBI) grade with short-term outcomes

CA19-9 levels.[7,8] Apart from tumor-specific characteristics, assessment of underlying liver function is important to accurately predict the risk of patients undergoing liver surgery for hepatobiliary malignancies. The current study was important, because we specifically examined the ability of a simple metric—the ALBI grade—to predict the outcomes of patients undergoing surgery for ICC using an international multi-institutional database. Of note, patients with ALBI grade 2 or 3 had higher odds of a prolonged LOS, perioperative transfusion, and 90-day mortality compared with ALBI grade 1 patients. Perhaps of more interest, OS incrementally worsened with increased ALBI grade, reaching a median OS as low as 1.5 year among grade 3 patients. Importantly, the ALBI grade was able to stratify prognosis of both cirrhotic and noncirrhotic patients. To the best of our knowledge, this is the first study to validate the prognostic utility of ALBI grade for both short- and long-term outcomes among patients undergoing surgery for ICC.

First proposed by Johnson et al[13] in 2015, the ALBI grading system attempted to assess hepatic function reserve of patients diagnosed with HCC. The ALBI model is solely based on laboratory parameters, namely albumin and bilirubin, without taking into account the other factors included in the calculation of the Child-Pugh score, such as the prothrombin time and the presence of ascites

TABLE 2 Albumin-bilirubin grade and short-term outcomes

Variable (ALBI Grade 2/3 vs 1)	Bivariate OR, 95% CI	*P*-value	Multivariable[a] OR, 95% CI	*P*-value
Any complication	1.17 (0.84, 1.63)	0.33	0.95 (0.67, 1.37)	0.80
Major complication	0.60 (0.38, 0.95)	0.020	0.79 (0.49, 1.27)	0.33
Minor complication	1.20 (0.35, 3.82)	0.73	0.73 (0.24, 2.24)	0.58
LOS >10	1.15 (0.81, 1.65)	0.42	2.37 (1.47, 3.80)	<0.001
Perioperative transfusion	2.45 (1.71, 3.50)	<0.001	2.15 (1.45, 3.18)	<0.001
30-d readmission	2.03 (1.03, 3.98)	0.036	1.02 (0.47, 2.25)	0.95
90-d mortality	2.99 (1.50, 6.12)	<0.001	2.50 (1.16, 5.38)	0.019

Abbreviations: ALBI, albumin-bilirubin; CI, confidence interval; LOS, length-of-stay; OR, odds ratio
[a]Adjusted for age, gender, ASA class, cirrhosis, type of resection minor complications: SSI, UTI.

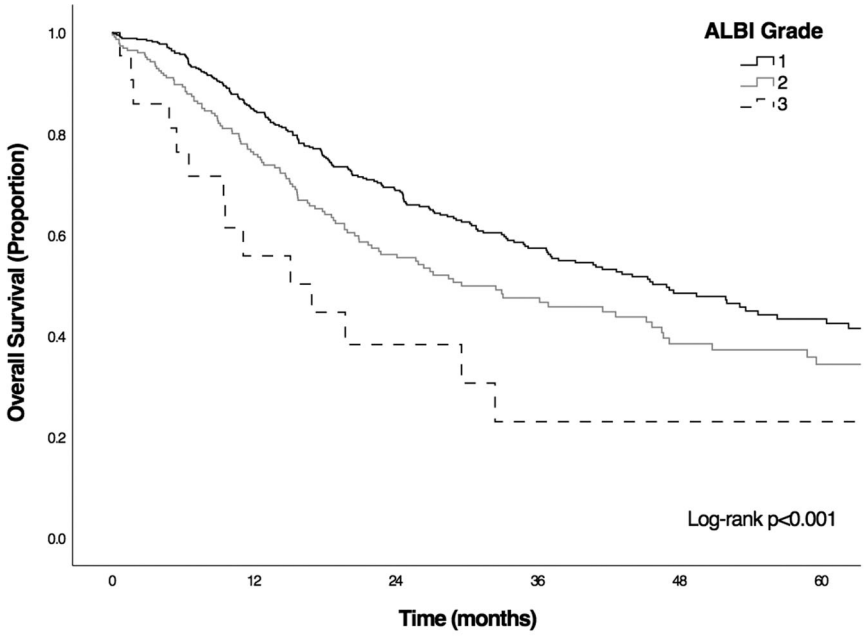

FIGURE 2 Kaplan–Meier curve demonstrating differences in overall survival (OS) among patients with ALBI grades 1, 2, and 3. ALBI, albumin-bilirubin

or encephalopathy.[9,13] Previous studies had examined the prognostic accuracy of ALBI grade, mainly focusing on patients diagnosed with HCC.[13,15,19] In analyzing patients with HCC from an international multi-institutional database, Pinato et al[15] reported that ALBI grade stratified prognosis of patients with HCC across all tumor stages, irrespective of the treatment employed (ie, surgery, transarterial chemoembolization, or sorafenib). The authors suggested the routine use of ALBI grade to stratify liver functional reserve among patients.[15] While several studies have examined ALBI grade and HCC, there are little data on the prognostic impact of ALBI for other hepatobiliary malignancies. Recently, Wang et al[20] investigated the utility of ALBI grade in predicting OS of patients with advanced extrahepatic cholangiocarcinoma. The authors demonstrated that ALBI grade could stratify the prognosis of patients, with a predictive value greater than the Child-Pugh score.[20] To date, however, there has been no study to validate the prognostic utility of the ALBI metric among patients undergoing surgery for ICC. In the current study, among 706 patients undergoing surgery for ICC, we noted that patients with ALBI grade 3 had markedly worse prognosis compared with ALBI grade 2 and grade 1 patients (median OS: 16.9 months vs 29.6 months vs 49.6 months; $P < 0.001$). In fact, patients with ALBI grade 2/3 had a worse prognosis even after controlling for all measured competing risk factors (HR = 1.36; 95% CI, 1.04-1.78; $P = 0.027$). Importantly, this difference was also evident among both cirrhotic and noncirrhotic patients, thus demonstrating that this metric had a good prognostic ability irrespective of the presence of cirrhosis. As such, data from the current study strongly suggest that ALBI score may be a useful preoperative tool to identify patients at risk for adverse outcomes and, thus, help guide the management of these patients.

Apart from long-term survival, the ALBI grade has also been associated with perioperative outcomes.[18,21,22] A recent analysis of

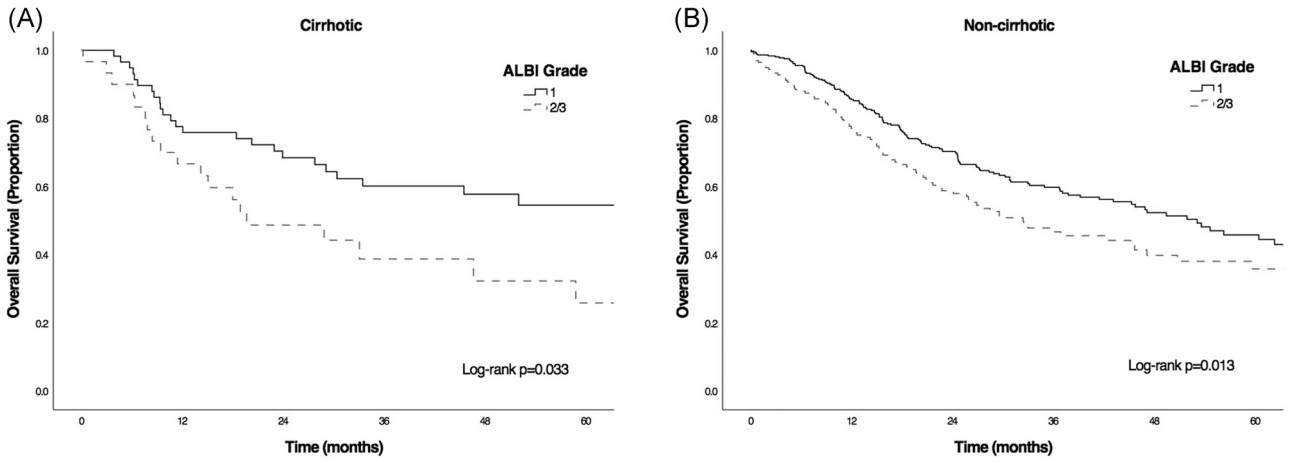

FIGURE 3 Kaplan–Meier curve demonstrating differences in OS among patients with ALBI grade 1 vs grade 2/3 among cirrhotic (A) and noncirrhotic patients (B). ALBI, albumin-bilirubin; OS, overall survival

TABLE 3 Bivariate and multivariable analyses of survival

	Bivariate		Multivariable	
Variables	**HR, 95% CI**	***P*-value**	**HR, 95% CI**	***P*-value**
Age				
≤60	Ref			
>60	1.10 (0.87-1.38)	0.424	-	-
Sex				
Male	Ref			
Female	1.11 (0.88-1.40)	0.348	-	-
ASA score				
≤2	Ref		Ref	
>2	1.29 (1.02-1.65)	0.035	1.10 (0.79-1.51)	0.58
CA 19-9				
≤200	Ref		Ref	
>200	2.51 (1.96-3.23)	<0.001	2.49 (1.88-3.30)	<0.001
Cirrhosis				
No	Ref			
Yes	0.88 (0.64-1.21)	0.44	-	-
AJCC 8th edition N stage				
N0	Ref		Ref	
N1	2.56 (1.80-3.63)	<0.001	2.16 (1.40-3.33)	<0.001
Nx	1.26 (0.93-1.72)	0.133	2.23 (1.46-3.40)	<0.001
AJCC 8th edition T stage				
T1a/T1b	Ref		Ref	
T2/T3/T4	1.86 (1.49-2.31)	<0.001	1.91 (1.36-2.69)	<0.001
Margin status				
R0	Ref		Ref	
R1/R2	1.64 (1.19-2.25)	0.002	2.01 (1.28-3.13)	0.002
Morphologic type				
MF, IG	Ref		Ref	
PI, MF+PI	1.56 (1.13-2.15)	0.007	0.81 (0.51-1.29)	0.384
Grade				
Well to moderate	Ref		Ref	
Poor to undifferentiated	1.63 (1.24-2.16)	0.001	1.56 (1.09-2.24)	0.014
Microvascular invasion				
No	Ref		Ref	
Yes	1.35 (1.06-1.71)	0.015	0.76 (0.52-1.11)	0.162
Adjuvant chemotherapy				
No	Ref			
Yes	1.23 (0.96-1.56)	0.098	-	-
ALBI grade				
Grade 1	Ref		Ref	
Grade 2/3	1.47 (1.17-1.84)	0.001	1.36 (1.04-1.78)	0.027

Abbreviations: AJCC, American Joint Committee on Cancer; ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologist; CA, carbohydrate antigen; IG, intraductal growth; MF, mass-forming; PI, periductal infiltrating

the National Surgical Quality Improvement Program database from our own group revealed that ALBI grade 2/3 was associated with higher odds of posthepatectomy liver failure (PHLF; OR = 1.57, 95% CI, 1.08-2.27), bile leak (OR = 1.35; 95% CI, 1.02-1.80), perioperative transfusion (OR = 2.08; 95% CI, 1.69-2.55), and 30-day mortality (OR = 2.40; 95% CI, 1.25-4.60) following liver surgery for benign and malignant diseases.[18] In another study, Wang et al[22] reported that ALBI grade predicted both short- and long-term outcomes of patients undergoing liver resection for HCC with a higher accuracy than the traditional Child-Pugh score. Indeed, ALBI grade may overcome the limitations of the traditional Child-Pugh scoring system, namely the use of interrelated variables (ie, albumin and ascites), the use of subjective variables (ie, ascites and encephalopathy), and the arbitrary selection of cut-off values for continuous variables (ie, bilirubin, albumin, and prothrombin time), thus eliminating "ceiling" and "floor" effects.[13-15] In line with the aforementioned findings, our study revealed a strong association between an increased ALBI grade and the short-term outcomes of patients undergoing surgery for ICC; patients with ALBI grade 2/3 had higher odds of prolonged LOS, perioperative transfusion and 90-day mortality compared with ALBI grade 1 patients. Collectively, the data suggest—for the first time in the literature—that ALBI grade could be an efficient tool in predicting

both short- and long-term outcomes among patients undergoing surgery for ICC.

The current study had certain limitations that should be considered when interpreting the results. The retrospective nature of the study may have introduced some selection bias (ie, selection of patients for surgery). In addition, the lack of a comparison group (ie, patients treated with treatments other than surgery) did not allow us to draw definitive conclusions about the prognostic utility of the ALBI grade among patients undergoing another type of therapy for ICC; as such, the results should only be applied to a surgical population. Finally, an analysis of the association between the ALBI grade and specific complications of interest, such as PHLF or bile leak was not feasible due to the large number of missing values for these variables.

In conclusion, long-term outcomes of patients undergoing curative-intent resection for ICC were relatively poor with a 5-year OS of approximately 40%. Prognosis of patients was associated with tumor-specific factors such as serum CA19-9 levels, lymph node status, T stage, and tumor differentiation. After controlling for these factors, higher ALBI grade was independently associated with worse outcomes. In fact, median OS incrementally worsened with increased ALBI grade, with patients who had ALBI grade 3 surviving less than 1.5 years. This association was evident among both cirrhotic and noncirrhotic patients. Apart from OS, higher ALBI grade also predicted worse short-term outcomes, including prolonged LOS, perioperative transfusion, and 90-day mortality. ALBI score may be a useful surrogate marker to identify patients at risk for adverse outcomes following resection for ICC and, thus, help guide the management of patients with ICC.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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