The role of albumin–bilirubin grade in determining the outcomes of patients with very early-stage hepatocellular carcinoma

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Abstract

Background: Patients with hepatocellular carcinoma (HCC) and with a single tumor <2 cm in size are classified as having Barcelona Clinic Liver Cancer (BCLC) stage 0 HCC. We aimed to investigate the role of the albumin–bilirubin (ALBI) grade in predicting outcomes in patients with BCLC stage 0 HCC.

Methods: We retrospectively enrolled patients with BCLC stage 0 HCC in Taipei Veterans General Hospital from 2007 to 2015. Prognostic factors were analyzed using a Cox proportional hazards model and propensity score matching (PSM) analysis.

Results: There were 420 patients enrolled, including 207 with ALBI grade 1, and 213 with ALBI grade 2 or 3. After a median follow-up of 60.0 months (interquartile range, 37.2–84.6 months), 179 patients died. The cumulative 5-year overall survival (OS) rates were 80.6% in patients with ALBI grade 1 and 53.7% in those with ALBI grade 2 or 3, respectively ($p < 0.001$). Multivariate analysis showed that age >65 years, negative hepatitis B surface in serum, creatinine >1.0 mg/dL, platelet count $\leq 10^5/mm^3$, tumor size >1.5 cm, nonsurgical resection (SR) therapy, and higher ALBI grade were independent risk factors related to poor OS. Patients who underwent SR had a better OS and recurrence-free survival than those who received radiofrequency ablation, which was confirmed by a multivariate analysis and PSM analysis.

Conclusion: The ALBI grade can determine OS for patients with BCLC stage 0 HCC. SR can also provide a better outcome than nonsurgical treatment.

Keywords: Barcelona Clinic Liver Cancer; Hepatocellular carcinoma; Prognosis; Radiofrequency ablation; Surgery

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers in the world.[1] The selection of treatment for HCC is mainly based on the cancer stage, liver functional reserve, and performance status.[2] Currently, the most widely applied staging system for HCC is the Barcelona Clinical Liver Cancer (BCLC) staging system.[2] In this system, stage 0 (very early stage) HCC is defined as patients with a single tumor <2 cm in size, with well-preserved liver function and good performance status, and no vascular invasion and extrahepatic metastasis. In this clinical setting, liver transplantation, surgical resection (SR), and local ablation therapy are the recommended treatment modalities based on current HCC management guidelines.[2,3] Although liver transplantation could provide excellent long-term cancer-free survival for patients with early stage HCC, its application is limited because of organ shortages.[2] Thus, SR and local ablation therapy are the most commonly performed treatments for patients with BCLC stage 0 HCC. However, there is no robust evidence to elucidate which treatment is the better for such patients.[4–6] In the daily practice, a substantial number of patients with BCLC stage 0 HCC still undergo noncurative treatment

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modalities, such as transarterial chemoembolization (TACE), or supportive treatment.[7] More studies are required to identify the optimal treatment modality for patients with BCLC stage 0 HCC.

The prognosis of HCC patients is determined by multiple factors such as performance status, treatment modality, tumor burden, and liver functional reserve. The albumin–bilirubin (ALBI) grade is a newly proposed method to assess the degree of liver function in patients with liver cirrhosis or HCC.[8] Several studies have validated that the ALBI grade could be a prognostic predictor for HCC patients.[7–10] However, there is not enough data to confirm whether the ALBI grade can be applied to evaluate the prognosis of patients with very early stage HCC.[11] We hypothesized that the prognostic effect of tumor factors might be less apparent, while liver functional reserve might play a more important role in determining outcomes in patients with very early stage HCC.[11,12] To validate this concept, we aimed to investigate the role of ALBI grade in determining the prognosis of patients with BCLC stage 0 HCC.

2. METHODS

2.1. Patients

This study was prospectively conducted and retrospectively analyzed. From October 2007 to December 2015, 4326 consecutive treatment-naive HCC patients who were diagnosed at Taipei Veterans General Hospital were recorded in the cancer registration system. The diagnosis of HCC was based on the American Association for the Study of Liver Diseases guidelines.[13] For all patients who were newly diagnosed with HCC, their diagnosis and treatment plan were discussed in a weekly multidisciplinary committee meeting.[14] The decision about therapy for HCC was shared with the patient and the physician after explaining to the patient the advantages, disadvantages, prognosis, different treatment modality complications, and recommendations by the multidisciplinary experts.

All patients were followed up every 3 months until their last visit to the hospital, death, or December 31, 2018. Enrolled patients underwent thorough clinical, laboratory, and image assessment. A total of 420 patients who were diagnosed with BCLC stage 0 HCC were included in the final analysis (Fig. 1).

This study fulfilled the standards of Declaration of Helsinki and ethical guidelines and current ethical guidelines. It was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-012AC). Before analysis, consent waivers were obtained, and patient information and data were anonymized and deidentified.

2.2. Statistical analysis

The primary endpoint of this study was overall survival (OS), which was calculated from the HCC diagnosis to patient's death, patient's last visit, or December 31, 2018. Categorical variables, if appropriate, were compared using the Chi-squared test with Yate's correction. Continuous variables were expressed using the median with interquartile range (IQR) and were compared using the Mann–Whitney U test. The cumulative OS rates after treatment were estimated using the Kaplan–Meier method and compared using a Cox proportional hazards model.

Univariate analysis was performed and variables with statistical significance or variables with approximate significance ($p < 0.1$) were then selected for the multivariate analysis using a forward stepwise logistic regression model.

Because the demographic characteristics were not comparable between patients who underwent SR and radiofrequency ablation (RFA), propensity score matching (PSM) was performed to minimize the confounding factors that might affect patient outcomes.[4,7] After matching, the prognosis between patients who underwent SR and RFA were compared again.

A 2-tailed value of $p < 0.05$ was recognized as statistically significant in our analysis. The statistical software was IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY).

3. RESULTS

3.1. Baseline clinical characteristics

The main demographic and baseline clinical data of the study patients are showed in Table 1. Among the 420 patients with BCLC stage 0 HCC, the ALBI grade distribution was as follows:

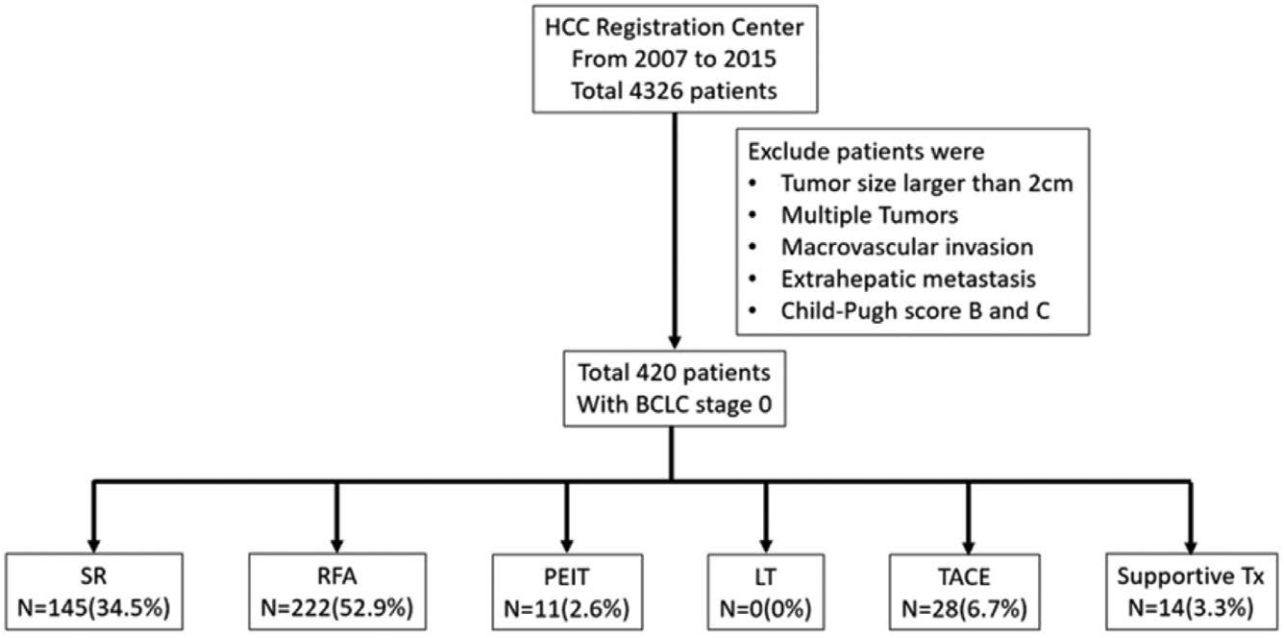

Fig. 1 Study flowchart.

Table 1

Baseline demographic characteristics of the study patients

Variables	All patients (n = 420)	ALBI grade 1 (n = 207)	ALBI grade 2 and 3 (n = 213)	*p*
Patient demographics				
Age (y)	65 (57–72)	62 (54–70)	66 (59–73)	<0.001
Sex (male) (%)	278 (66.2%)	146 (70.5%)	132 (62.0%)	0.080
Serum biochemistry tests and liver function tests				
Albumin (g/dL)	3.9 (3.5–4.2)	4.3 (4.1–4.4)	3.5 (3.2–3.7)	<0.001
Total bilirubin (mg/dL)	0.76 (0.53–1.06)	0.61 (0.48–0.83)	0.97 (0.71–1.44)	<0.001
ALT (U/L)	38 (26–64)	34 (24–50)	47 (29–73)	0.001
AST (U/L)	40 (27–64)	32 (23–46)	51 (36–80)	<0.001
Creatinine (mg/dL)	0.89 (0.74–1.03)	0.89 (0.76–1.04)	0.89 (0.72–1.01)	0.736
Alk-P (U/L)	77 (61–99)	70 (57–80)	93 (66–122.8)	<0.001
Platelets (/mm^3)	116 000 (77 250–169 000)	147 000 (110 000–185 000)	90 000 (61 000–121 000)	<0.001
PT INR	1.07 (1.02–1.14)	1.05 (1.00–1.08)	1.12 (1.06–1.20)	<0.001
Viral factors				
HBsAg (+/–) (%)	207/213 (49.3/50.7)	128/79(61.8/38.2)	79/134 (37.1/62.9)	<0.001
Anti-HCV (+/–) (%)	167/253 (39.8/60.2)	56/151(27.1/72.9)	111/102 (52.1/47.9)	<0.001
Tumor factors				
Tumor size (cm)	1.6 (1.3–1.9)	1.6 (1.3–1.9)	1.6 (1.3–1.8)	0.890
AFP (ng/mL)	14.09 (5.94–85.64)	9.83 (4.50–134.21)	16.80 (8.04–68.05)	0.370
Treatment (resection, local ablation, TACE, supportive treatment) (%)	145/233/28/14 (34.5/55.5/6.7/3.3)	96/100/7/4 (46.6/48.3/3.4/1.9)	49/133/21/10 (23.0/62.4/9.9/4.7)	<0.001
Noninvasive serum markers				
ALBI score	–2.595 (–2.907 to –2.177)	–2.912 (–3.126 to –2.785)	–2.187 (–2.430 to –1.922)	<0.001
MELD	7.79 (6.98–9.23)	7.19 (6.65–7.99)	8.57 (7.42–10.63)	<0.001

Continuous variables are expressed as the median with the 25th and 75th percentiles.

AFP = alpha fetoprotein; ALBI = albumin–bilirubin; Alk-P = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MELD = Model for End-Stage Liver Disease; PT INR = prothrombin time/international normalized ratio; TACE = transarterial chemoembolization.

207 patients (49.3%) were grade 1, 203 patients (48.3%) were grade 2, and ten patients (2.4%) were grade 3. The median age was 65 (IQR, 57–72) years and 278 (66.2%) of patients were male. Additionally, 207 patients (49.3%) had hepatitis B virus (HBV) infection and 167 patients (39.8%) had hepatitis C virus (HCV) infection. The median tumor size was 1.6 cm (IQR, 1.3–1.9), the median ALBI score was –2.595 (IQR, –2.907 to –2.177), and the median Model of End-stage Liver Disease (MELD) score was 7.79 (IQR 6.98–9.23).

For the treatment modalities, 145 patients (34.5%) underwent surgical resection (SR), 233 patients (55.5%) underwent local ablation treatment (222 patients with RFA and 11 with percutaneous ethanol injection therapy), 28 patients (6.7%) received TACE, and the remaining 14 patients (3.3%) chose supportive treatment.

Compared to patients with ALBI grade 2 or 3, those with ALBI grade 1 had a less liver necroinflammation and a better liver functional reserve, which presented as higher serum albumin levels; lower serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphate (Alk-P) levels; a lower prothrombin time international normalized ratio (PT INR); lower MELD score; and higher platelet counts. For tumor factors, there was no significant difference in the tumor size and serum alpha fetoprotein (AFP) levels between the ALBI grade 1 and ALBI grade 2 or 3 groups. However, more patients with ALBI grade 1 underwent SR compared to their counterparts (46.6% vs. 23.0%, $p < 0.001$).

3.2. Factors associated with poor overall survival rates

After a median follow-up of 60.0 (IQR, 37.2–84.6) months, 179 patients died. The cumulative 1-, 2-, 3-, and 5-year cumulative OS rates were 97.1% vs 93.8%, 94.1% vs 83.7%, 89.5% vs 72.1%, and 80.3% vs 53.7% in patients with ALBI grade 1 and those with ALBI grade 2 or 3, respectively (Fig. 2A, $p < 0.001$).

When stratified by treatment modality, the cumulative 1-, 2-, 3-, and 5-year OS rates were 98.6%, 97.2%, 92.1%, and 80.6% in patients who underwent SR, and 93.8%, 84.5%, 74.7%, and 59.6% in those receiving nonsurgical treatments, respectively (Fig. 2B, $p < 0.001$).

Because ALBI scores were calculated using serum albumin and bilirubin levels, we performed two models of multivariate analysis. In model I, the ALBI grade had been entered into the database, but the serum albumin and bilirubin levels were not entered into the multivariate analysis. In model II, we used serum albumin and bilirubin levels, but not the ALBI grade, in the multivariate analysis.

Model I in the multivariate analysis (Table 2) showed that age >65 years (hazard ratio [HR] 1.471, 95% confidence interval [CI]: 1.085–1.994, $p = 0.013$), positive hepatitis B surface antigen (HBsAg) in serum (HR 0.650, 95% CI: 0.474–0.890, $p = 0.007$), creatinine >1.0 mg/dL (HR 1.982, 95% CI: 1.440–2.729, $p < 0.001$), platelet count ≤100 000/mm^3 (HR 1.541, 95% CI: 1.110–2.139, $p = 0.010$), tumor size >1.5 cm (HR 1.482, 95% CI: 1.095–2.005, $p = 0.011$), nonsurgical therapy (HR 1.650, 95% CI: 1.144–2.380, $p = 0.007$), and ALBI grade 2 or 3 (HR 2.226, 95% CI: 1.571–3.156), $p < 0.001$) were associated with OS.

3.3. Subgroup analysis for factors associated with OS

We further compared the prognosis of patients between the ALBI grade 1 and ALBI grade 2 or 3 groups using a subgroup analysis. As shown in Fig. 2C, patients with ALBI grade 1 had a better OS compared to their counterparts in all the subgroup analyses except for patients with a serum albumin levels >4.0 g/dL. Additionally, patients who underwent SR had a significantly better prognosis than those who received nonsurgical treatments except for ALBI grade 1 or serum albumin levels >4.0 g/dL (Fig. 2D).

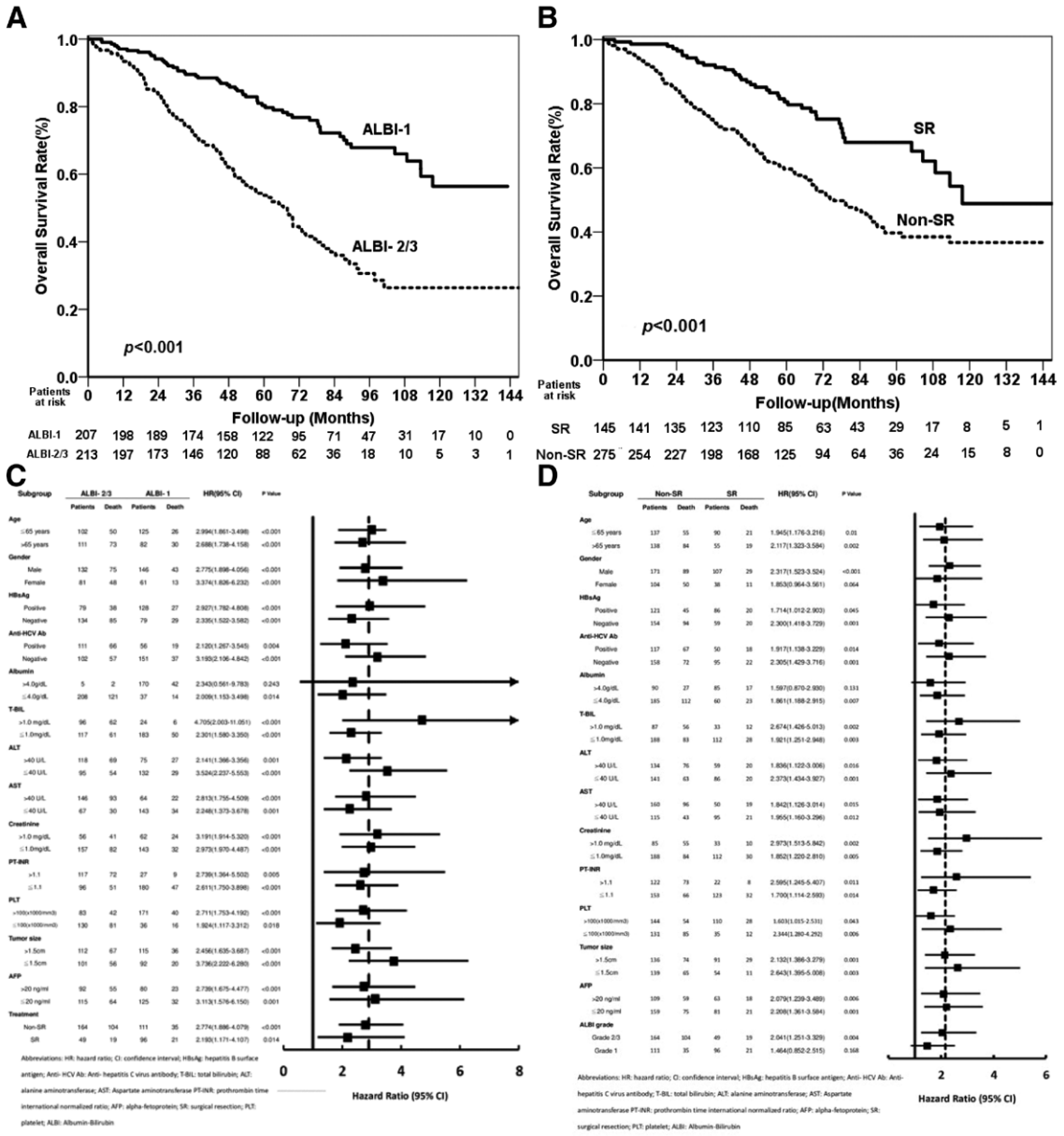

Fig. 2 Outcomes of patients with BCLC stage 0 HCC stratified by ALBI grade and treatment modality. A, Comparison of OS between patients with ALBI grade 1 and those with ALBI grade 2 or 3. B, Comparison of OS between patients who underwent SR and non-SR treatment. C, Comparison of OS between ALBI grade 1 and ALBI grade 2 or 3 by subgroup analysis. D, Comparison of OS between SR and non-SR treatment by subgroup analysis. ALBI = albumin–bilirubin; OS = overall survival; SR = surgical resection.

3.4. Comparison of prognosis between SR and RFA in patients with BCLC stage 0 HCC

Because SR and RFA were the most common treatments in our cohort, we compared the long-term outcomes of patients between these two curative treatments. There were 145 patients who received SR as primary treatment modality and 222 patients who underwent RFA in this cohort. As shown in Supplementary Table S1, http://links.lww.com/JCMA/A71, patients who underwent SR were younger age and more were HBV carriers and had better liver functional reserve, but they also had a larger tumor size than those in the RFA group.

The cumulative 1-, 2-, 3-, and 5-year OS rates were 98.6%, 97.2%, 92.1%, and 80.6% in the SR group and 95%, 85.5%, 75.8%, and 61.7% in the RFA group (Fig. 3A, $p < 0.001$). A multivariate analysis showed that age >65 years (HR 1.431, 95% CI: 1.024–1.998, $p = 0.036$), positive HBsAg in serum (HR 0.560, 95% CI: 0.396–0.793, $p = 0.001$), creatinine >1.0 mg/dL (HR 1.844, 95% CI: 1.290–2.637, $p = 0.001$), platelet count ≤100 000/mm^3 (HR 1.510, 95% CI: 1.042–2.189, $p = 0.030$), tumor size >1.5 cm (HR 1.570, 95% CI: 1.121–2.199, $p = 0.009$), RFA (HR 1.605, 95% CI: 1.101–2.341, $p = 0.014$), and ALBI grade 2 or 3 (HR 2.221, 95% CI: 1.518–3.249, $p < 0.001$) were associated with OS (Table 3).

Additionally, 231 patients had tumor recurrence, including 84 patients in the SR group and 147 in the RFA group. The 1-, 2-, 3-, and 5-year recurrence-free survival (RFS) rates were 85.4%, 74.2%, 62.4%, and 40.6% in SR group and 66.1%, 44.7%, 35.9%, and 27.6% in the RFA group, respectively (Fig. 3B, $p < 0.001$). A multivariate analysis showed that ALBI grade 2 or 3 (HR 2.250, 95% CI: 1.743–2.905, $p < 0.001$) and RFA (HR

Table 2

Univariate and multivariate analysis of factors associated with poor OS in model I

		Univariate analysis		Multivariate analysis	
Variable	**Case No.**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age > 65/≤65 y	193/227	1.752 (1.302–2.358)	<0.001	1.471 (1.085–1.994)	0.013
Sex: female/male	142/278	1.089 (0.799–1.484)	0.589		
HBsAg positive/negative	207/213	0.471 (0.347–0.639)	<0.001	0.650 (0.474–0.890)	0.007
Anti-HCV positive/negative	167/253	1.531 (1.141–2.054)	0.005		
Albumin ≤4.0/>4.0 g/dL	245/175	2.836 (2.015–3.993)	<0.001		
Bilirubin >1.0/≤1.0 mg/dL	120/300	1.930 (1.425–2.613)	<0.001		
ALT >40/≤40 U/L	193/227	1.458 (1.087–1.957)	0.012		
AST >40/≤40 U/L	210/210	2.030 (1.495–2.757)	<0.001		
Creatinine >1.0/≤1.0 mg/dL	118/300	1.604 (1.183–2.177)	0.002	1.982 (1.440–2.729)	<0.001
PT INR >1.1/≤ 1.1	144/276	1.911 (1.422–2.567)	<0.001		
Platelets ≤ 10^5/>10^5/mm^3	166/254	2.279 (1.698–3.060)	<0.001	1.541 (1.110–2.139)	0.010
Tumor size >1.5/≤1.5 cm	227/193	1.299 (0.965–1.749)	0.085	1.482 (1.095–2.005)	0.011
AFP >20/≤20 ng/mL	172/240	1.194 (0.886–1.611)	0.244		
Non-SR/SR	275/145	2.162 (1.521–3.074)	<0.001	1.650 (1.144–2.380)	0.007
ALBI grade 2 or 3/1	213/207	2.911 (2.117–4.004)	<0.001	2.226 (1.571–3.156)	<0.001

[a]In model II, we selected albumin and bilirubin, but the ALBI grade was not included in the multivariate analysis, age > 65 years (HR 1.506, 95% CI: 1.107–2.050, $p = 0.009$); positive HBsAg in serum (HR 0.661, 95% CI: 0.482–0.907, $p = 0.010$); albumin ≤ 4.0 g/dL (HR 2.061, 95% CI: 1.427–2.978, $p < 0.001$); bilirubin > 1.0 mg/dL (HR 1.557, 95% CI: 1.132–2.141, $p = 0.006$); creatinine > 1.0 mg/dL (HR 1.918, 95% CI: 1.394–2.639, $p < 0.001$); platelet count ≤ 100 000/mm^3 (HR 1.522, 95% CI: 1.095–2.117, $p = 0.012$); tumor size > 1.5 cm (HR 1.449, 95% CI: 1.072–1.958, $p = 0.016$); and nonsurgical therapy (HR 1.622, 95% CI: 1.123–2.343, $p = 0.010$) were the independent factors predictive of OS.

AFP = alpha fetoprotein; ALBI = albumin–bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; OS = overall survival; PT INR = prothrombin time/international normalized ratio; SR = surgical resection.

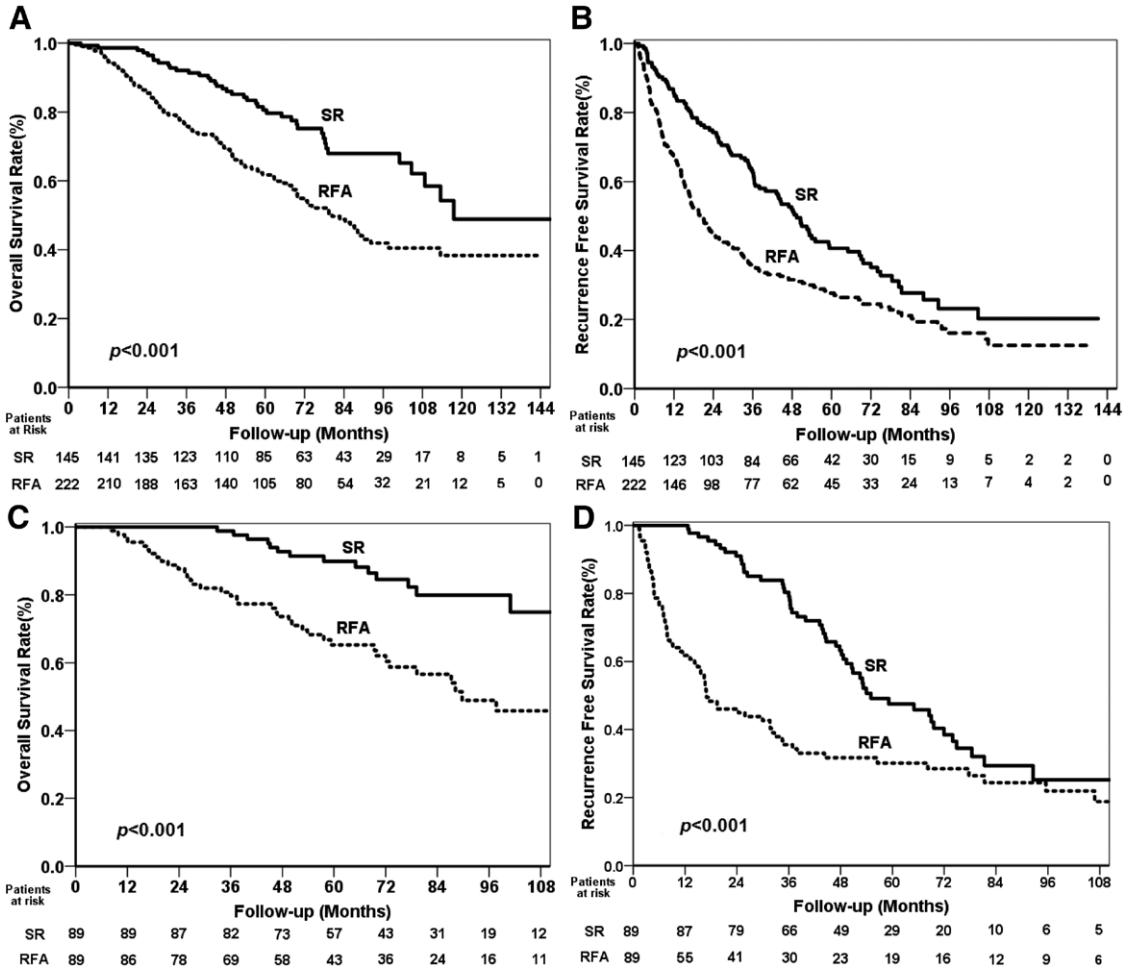

Fig. 3 A comparison of outcomes between SR and RFA. Comparison of OS (A) and RFS (B) between SR and RFA before PSM. Comparison of OS (C) and RFS (D) between SR and RFA after PSM. OS = overall survival; PSM = propensity score matching; RFA = radiofrequency ablation; RFS = recurrence-free survival; SR = surgical resection.

Table 3

The univariate and multivariate analysis of prognostic factors for OS among the patients who received SR or RFA in model I

		Univariate analysis		Multivariate analysis	
Variable	**Case No.**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age > 65/≤65 y	170/197	1.741 (1.257–2.410)	0.001	1.431 (1.024–1.998)	0.036
Sex: female/male	126/241	1.158 (0.827–1.623)	0.393		
HBsAg positive/negative	188/179	0.425 (0.304–0.594)	<0.001	0.560 (0.396–0.793)	0.001
Anti-HCV positive/negative	133/234	1.514 (1.095–2.094)	0.012		
Albumin ≤4.0/>4.0 g/dL	203/164	3.099 (2.139–4.489)	<0.001		
Bilirubin >1.0/≤1.0 mg/dL	102/265	2.088 (1.501–2.905)	<0.001		
ALT >40/≤40 U/L	165/202	1.525 (1.105–2.105)	0.010		
AST >40/≤40 U/L	170/197	2.100 (1.507–2.926)	<0.001		
Creatinine >1.0/≤1.0 mg/dL	98/267	1.443 (1.027–2.029)	0.035	1.844 (1.290–2.637)	0.001
PT INR >1.1/≤1.1	114/253	1.781 (1.284–2.471)	0.001		
Platelets ≤10^5/>10^5/mm^3	138/229	2.427 (1.758–3.351)	<0.001	1.510 (1.042–2.189)	0.030
Tumor size >1.5/≤1.5 cm	208/159	1.490 (1.068–2.079)	0.019	1.570 (1.121–2.199)	0.009
AFP >20/≤20 ng/mL	153/207	1.188 (0.856–1.647)	0.303		
RFA/SR	222/145	2.032 (1.414–2.920)	<0.001	1.605 (1.101–2.341)	0.014
ALBI grade 2 or 3/1	173/194	2.981 (2.115–4.202)	<0.001	2.221 (1.518–3.249)	<0.001

[a]In model II, we selected albumin and bilirubin, but the ALBI grade was not enrolled in the multivariate analysis, age > 65 years (HR 1.426, 95% CI: 1.018–1.998, $p = 0.039$); positive HBsAg in serum (HR 0.551, 95% CI: 0.391–0.776, $p = 0.001$); albumin ≤ 4.0 g/dL (HR 2.455, 95% CI: 1.666–3.616, $p < 0.001$); bilirubin > 1.0 mg/dL (HR 1.738, 95% CI: 1.241–2.434, $p = 0.001$); creatinine > 1.0 mg/dL (HR 1.684, 95% CI: 1.183–2.396, $p = 0.004$); tumor size > 1.5 cm (HR 1.610, 95% CI: 1.150–2.253, $p = 0.006$); and RFA (HR 1.652, 95% CI: 1.137–2.399, $p = 0.008$) were the independent factors predictive of OS.
AFP = alpha fetoprotein; ALBI = albumin–bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; OS = overall survival; PT INR = prothrombin time/international normalized ratio; RFA = radiofrequency ablation; SR = surgical resection.

1.451, 95% CI: 1.121–1.880, $p = 0.005$) were the independent risk factors that were associated with poor RFS (Table 4).

3.5. Propensity score matching analysis to compare the outcomes between SR and RFA

Because the demographic characteristics were diverse between patients who underwent SR and RFA, we performed a PSM analysis to minimize the confounding factors that might determine the prognosis of HCC patients. Using the one-to-one nearest-neighbor matching method, 89 patients were matched in each group. After matching, the demographic characteristics were comparable between these 2 patient groups (Supplementary Table S2, http://links.lww.com/JCMA/A71). After PSM matching, the OS (Fig. 3C) and RFS (Fig. 3D) were still better in patients who underwent SR compared with those received RFA.

4. DISCUSSION

This study had several major findings. First, for patients with BCLC stage 0 HCC, all with Child–Pugh class A liver function, the ALBI grade could be applied as an objective and simple method to further classify the liver functional reserve in these

Table 4

The univariate and model I multivariate analysis of factors for determining recurrence-free survival among the patients who received SR or RFA

		Univariate analysis		Multivariate analysis	
Variable	**Case No.**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age > 65/≤65 y	170/197	1.304 (1.026–1.659)	0.030		
Sex: female/male	126/241	1.016 (0.786–1.313)	0.905		
HBsAg positive/negative	188/179	0.709 (0.556–0.902)	0.005		
Anti-HCV positive/negative	133/234	1.246 (0.972–1.598)	0.082		
Albumin ≤4.0/>4.0 g/dL	203/164	2.271 (1.759–2.933)	<0.001		
Bilirubin >1.0/≤1.0 mg/dL	102/265	1.661 (1.279–2.157)	<0.001		
ALT >40/≤40 U/L	165/202	1.355 (1.064–1.725)	0.014		
AST >40/≤40 U/L	170/197	1.526 (1.199–1.942)	0.001		
Creatinine >1.0/≤1.0mg/dL	98/267	1.073 (0.820–1.403)	0.608		
PT INR >1.1/≤1.1	114/253	1.573 (1.222–2.026)	<0.001		
Platelets ≤10^5/>10^5/mm^3	138/229	1.819 (1.427–2.319)	<0.001		
Tumor size >1.5/≤1.5 cm	208/159	1.085 (0.851–1.384)	0.509		
AFP >20/≤20 ng/mL	153/207	1.381 (1.081–1.764)	0.010		
RFA/SR	222/145	1.622 (1.260–2.089)	<0.001	1.451 (1.121–1.880)	0.005
ALBI grade 2 or 3/1	173/194	2.381 (1.856–3.054)	<0.001	2.250 (1.743–2.905)	<0.001

[a]In model II, we selected albumin and bilirubin, but the ALBI grade was not enrolled in the multivariate analysis, albumin ≤ 4.0 g/dL (HR 1.938, 95% CI: 1.477–2.543, $p < 0.001$), bilirubin > 1.0 mg/dL (HR 1.346, 95% CI: 1.026–1.766, $p = 0.032$), AFP > 20 ng/dL (HR 1.303, 95% CI: 1.018–1.677, $p = 0.035$), and RFA (HR 1.391, 95% CI: 1.070–1.810, $p = 0.014$) were the independent factors predictive of recurrence-free survival.
AFP = alpha fetoprotein; ALBI = albumin–bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; OS = overall survival; PT INR = prothrombin time/international normalized ratio; RFA = radiofrequency ablation; SR = surgical resection.

patients. Second, the ALBI grade could predict the prognosis of patients with very early stage HCC. It was further confirmed by a multivariate analysis and most subgroup analyses. Third, SR provided a better outcome than non-surgical treatments, including RFA, for patients with very early stage HCC. It indicated that patients who had better liver functional reserve and underwent an aggressive curative therapy with SR could have an excellent long-term outcome in this clinical setting.

It is crucial to assess the liver functional reserve to help HCC patients to choose an adequate treatment and to predict their outcomes.[2] The Child–Pugh score and class are widely used to investigate liver function for patients with HCC, and it was used in the BCLC staging system to select a therapy.[13] However, the Child–Pugh score has several weaknesses. First, it is composed of 5 parameters, including serum albumin and bilirubin levels, PT INR, ascites, and hepatic encephalopathy. Among these factors, the assessment for the degree of ascites and the stage of hepatic encephalopathy are relatively subjective. Second, serum albumin level is closely correlated with ascites. Third, all the five parameters have same weight in the Child–Pugh score. These factors decrease its performance ability to predict the prognosis of HCC patients, especially for those with early-stage HCC who underwent SR.[15]

A new method, the ALBI grade, has recently been proposed to assess the liver functional reserve in patients with HCC. The ALBI grade was derived from only 2 objective parameters, serum albumin and bilirubin levels, which were based on a multivariable Cox regression analysis from Japan.[8] Moreover, the ALBI grade was externally validated from different geographic regions and treatment modalities in this study. Thus, the ALBI grade was more objective and evidence-based than the Child–Pugh score. Several recent studies further confirmed the role of ALBI grade in predicting the outcomes of patients with HCC across different BCLC stages and treatment modalities.[14–16] Consequently, in the recent recommendations for the management of HCC, the ALBI grade is included for the evaluation of liver dysfunction in HCC patients.[2]

However, the performance of the ALBI grade in determining the outcomes of patients with BCLC stage 0 HCC is not fully elucidated. Our study showed that for patients with BCLC stage 0 HCC, all of whom were in Child–Pugh class A, the ALBI grade could still stratify patients into the following two distinct prognostic groups. It showed that only around half (49.3%) of the patients were in ALBI grade 1. Patients with ALBI grade 1 had significantly less liver necroinflammation and better liver function compared to their counterparts. Moreover, the long-term OS between the ALBI grade 1 and ALBI grade 2 or 3 groups were significantly different. We also performed multivariate analyses using 2 models to confirm these results. The results showed that the ALBI grade and its components (serum albumin and bilirubin levels) were all correlated with the patients' prognosis, showing the excellent performance of the ALBI grade in distinguishing between the outcomes in patients with BCLC stage 0 HCC (Table 2–4).

SR is no longer the only front-line treatment for patients with early stage HCC, based on the current concept.[17] Ablation may be considered to be a first-line therapy because of the noninferior life expectancy benefit and cost-effectiveness concerns.[18,19] Among local ablation therapies, RFA provided better local tumor control, a lower local recurrence rate, and a higher OS rate when compared with percutaneous ethanol injection therapy.[20] Several studies have been conducted to compare the outcomes between SR and RFA in HCC patients.[4,21–23] Most of the studies showed that although RFA might provide an OS rate that is comparable to or slightly lower than SR, it would lead to a significantly higher incidences of developing recurrence after therapy. However, for patients with a very early stage HCC, the results were not consistent. Several studies showed that RFA and SR might have comparable outcomes in terms of OS and recurrence. Some studies demonstrated that SR provided a significantly better OS and RFS compared to RFA, and other studies showed that SR and RFA had a similar OS rate, but that SR had a lower recurrence rate.[4–6,24] This might be attributed to differences in the study design, demographic characteristics, and etiologies of HCC among these studies. A recent meta-analysis that enrolled 729 patients with very early stage HCC demonstrated that SR offers better long-term oncologic outcomes in terms of OS and RFS compared with RFA.[6] Our study also validated that for patients with BCLC stage 0 HCC, SR could provide a significantly better prognosis than RFA. This was further confirmed by the multivariate analysis and PSM analysis. These results suggest that SR could be a front-line therapy for such patients if there are no contraindications for the operation.

Chronic HBV and HCV infections are the major HCC viral etiology.[25] However, whether the viral etiology would determine the outcomes of patients with HCC remains controversial.[26–30] In patients with chronic HBV infection, HBV DNA can integrate into the host genome, which leads to the host cell genome instability and generates hepatic carcinogenesis in the absence of liver cirrhosis.[31,32] However, for the tumor factors, one recent integrative molecular and pathological HCC classification divided HBV-related HCC into a proliferation class, which might have a more aggressive tumor phenotype, including poorer tumor cell differentiation and a higher frequency of vascular invasion.[33] Several clinical studies also showed that compared to those with HCV-related HCC, patients with HBV-related HCC had lower rates of liver cirrhosis and better liver functional reserve, but they had larger tumor and higher serum AFP levels.[34–36] In our study, patients with HBV-related HCC had significantly higher OS rates compared to their counterparts. Because the impact of tumor factors might decrease in patients with very early stage HCC,[12,37] patients with HBV-related HCC had better OS, which might result from better liver function reserve. However, further prospective studies are warranted to clarify this issue.

There are several limitations in this study. First, it is a retrospective study that was conducted at a single tertiary center. Further prospective study is warranted to validate our concepts. Second, there are some differences in the baseline demographic data between different ALBI grades and treatment modalities. To minimize potential confounding factors, we analyzed the prognostic factors using a multivariate analysis, subgroup analysis, and PSM analysis. All the results demonstrated that the ALBI grade and SR were the crucial factors that were associated with the prognosis for patients with very early stage HCC. Third, the populations in this study were people in Taiwan, which is an HBV-endemic area, and thus, there might be different results in western populations.

In conclusion, the ALBI grade can be used to determine the OS of patients with BCLC stage 0 HCC. Moreover, SR can provide a better outcome than non-surgical treatments for such patients.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at 10.1097/JCMA.0000000000000482.

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