Albumin-bilirubin grade may determine the outcomes of patients with very early stage hepatocellular carcinoma after radiofrequency ablation therapy

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Abstract

Background: To assess long-term prognoses of patients with solitary hepatocellular carcinoma (HCC) < 2 cm (the Barcelona Clinic Liver Cancer, BCLC stage 0) after radiofrequency ablation (RFA).

Methods: We retrospectively enrolled 271 patients with BCLC stage 0 HCC who had undergone RFA at Taipei Veterans General Hospital from 2002 to 2016. Factors determining poor overall survival (OS) and recurrence after RFA were analyzed by Cox proportional hazards model.

Results: After a median follow-up duration of 43.4 months, 76 patients had died. The cumulative 5- and 10-year OS rates were 67.1% and 56.4%, respectively. Multivariate analysis disclosed age > 65 years (hazard ratio [HR] 1.608, 95% confidence interval, [CI] 1.015–2.545; p = 0.043), platelet count < 100,000/mm³ (HR 1.704, 95% CI 1.027–2.828; p = 0.039), and albumin-bilirubin (ALBI) grade 2 or 3 (HR 2.191, 95% CI 1.261–3.805; p = 0.005) were the independent risk factors predicting worse OS. One-hundred twelve patients had tumor recurrence after undergoing RFA. Multivariate analysis showed that ALBI grade 2 or 3 (HR 1.825, 95% CI 1.288–2.585; p = 0.001) was the only one independent risk factor associated with poor recurrence-free survival (RFS) after RFA. Most of the subgroup analyses also demonstrated that patients with ALBI grade 2 or 3 had poorer OS and RFS than those with ALBI grade 1.

Conclusion: For patients with BCLC stage 0 HCC, RFA could provide a long-term outcome with a 10-year overall survival rate of 56.4%. Moreover, the ALBI grade can discriminate prognosis in such patients.

Keywords: Albumin-bilirubin grade; Hepatocellular carcinoma; Prognosis; Radiofrequency ablation

1. INTRODUCTION

Hepatocellular carcinoma (HCC) now ranks as the second and sixth leading cause of worldwide cancer mortality in males and females, respectively.1 It is estimated that HCC accounted for 745,500 deaths worldwide in 2012.1 Chronic viral infections, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) are the major HCC etiologies.2,3 In the United States and Europe, HCC incidence and mortality rates are still rising and appear to be due to the high prevalence of hepatitis C virus (HCV) infection and immigration from countries in which hepatitis B virus (HBV) infection is endemic in addition to the rising incidence of NAFLD.4–6 Moreover, although it has been improved, long-term outcome of HCC patients is still unsatisfactory with overall mortality to incidence rate of 0.95.7 To improve the patient outcomes, it is crucial to diagnose HCC at an early stage, in which long-term survival could be achieved by performing curative treatments.8,9

With more awareness and frequent surveillance for patients who bear a high risk of developing HCC, an increasing number of patients are diagnosed with HCC in the early stages.10,11 According to the current the Barcelona Clinic Liver Cancer (BCLC) staging classification for HCC, a solitary tumor < 2 cm in size, good liver functional reserve, excellent performance status, and no vascular invasion or extra-hepatic metastasis is defined as stage 0 (very early stage) HCC.12 The currently recommended treatment modalities for such patients include surgical resection, liver transplantation, and local ablation therapy.13,14 All of these therapies could provide an excellent prognosis with a 5-year survival rate of around 60%–80%.4,15–17 However, the indication of surgical resection for HCC has been limited to patients without clinically significant portal hypertension (CSPH),
and the application of liver transplantation is restricted because of organ shortage.4 Consequently, local ablation therapies have been widely performed for patients who have early-stage HCC and are not good candidates for resection surgery or liver transplantation. Among them, radiofrequency ablation (RFA) therapy is superior to ethanol or acetic acid injection therapy in terms of local tumor control, recurrence, and overall survival (OS).18-20 However, RFA’s efficacy and long-term prognoses for patients with very early stage HCC have not been well studied until now.

Johnson and colleagues recently proposed that albumin-bilirubin (ALBI) scores, which incorporates both serum albumin and bilirubin levels, could provide an objective method for liver functional reserve assessment and could be used to predict the prognoses of patients with HCC.21 However, it was less applicable for patients with very early stage HCC. This study aimed to investigate the long-term outcomes of patients with BCLC stage 0 HCC after RFA. Moreover, we also aimed to investigate the role of ALBI grade in determining these patients’ prognoses.

2. METHODS
2.1. Patients
We retrospectively reviewed 702 consecutive treatment-naïve HCC patients who underwent percutaneous RFA as the initial treatment at Taipei Veterans General Hospital from May 2002 to June 2016. An HCC diagnosis was made in accordance with American Association for the Study of Liver Disease (AASLD) guidelines.13 RFA indications consisted of several parameters: (A) a single tumor with a size < 5 cm or 2–3 tumors all sizes < 3 cm; (B) absence of extra-hepatic metastasis or major vascular invasion; (C) grade A or B Child-Turcotte-Pugh (CTP) classification of liver functional reserve; (D) no ascites; (E) platelet count > 50,000/mm³; and (F) no other major comorbidities (such as infections, arrhythmias, acute myocardial infarction, uncontrolled congestive heart failure, chronic obstructive pulmonary disease with acute exacerbation, recent stroke, and others) that might complicate the RFA procedure.22,23 The RFA device, procedure, and follow-up have been previously described.16,24 Among them, a total of 271 patients with BCLC stage 0 HCC were enrolled for the final analysis (Fig. 1), including 100 (36.9%) patients, who were diagnosed with HCC histologically by liver biopsy, and another 171 patients, who were diagnosed by image modality.13

Our study complied with the standards of Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital. Consent waivers were obtained, and patient information and records were anonymized and de-identified prior to analysis.

2.2. Biochemical and serological tests
Serum biochemistry tests were performed by Roche/Hitachi Modular Analytics System (Roche Diagnostics GmbH, Mannheim, Germany) within one week before the application of RFA. HCV antibody testing was performed using the second-generation enzyme immunoassay (Abbott Laboratories). Serum hepatitis B surface antigen (HBsAg) and AFP levels were measured by radioimmunoassay (Abbott Laboratories, North Chicago, IL. and Serono Diagnostic SA, Coinsin/VD, Switzerland, respectively).

The ALBI score was calculated using the formula: –0.085 × (albumin g/L + 0.666 × log (bilirubin μmol/L). The ALBI grades were classified as grade 1 (score ≤ −2.60), grade 2 (score > −2.60 and ≤ −1.39), and grade 3 (score > −1.39).21

2.3. Statistical analysis
The primary endpoint was OS. It was calculated from the date of HCC diagnosis to the patient’s death, the patient’s last visit, or December 31, 2016. The Fisher exact test or a chi-square test with Yates’ correction was used to compare categorical variables when appropriate, and the Mann-Whitney U-test was used to compare continuous variables. The cumulative OS rates and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method and compared using the Cox’s proportional hazards model. In addition, we confirmed the assumption of proportional hazards by the log-minus-log plot of survival in a Cox regression analysis.

The variables with statistical significance (p < 0.05) or approximate significance (p < 0.1) by univariate analysis were subjected to the multivariate analysis by performing a forward stepwise logistic regression model. As the ALBI grade is calculated by serum albumin and bilirubin levels, we used two models for multivariate analysis. In model I, we selected ALBI grade, but albumin was not entered into multivariate analysis to minimize the confounding effects of these parameters. In model II, albumin, but not ALBI grade was selected for the multivariate analysis. Moreover, subgroup analysis to compare OS and RFS between patients with different ALBI grade stratified by important prognostic factors was performed by Cox proportional hazards model. A two-tailed value of p < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS
3.1. Baseline clinical characteristics
The study population’s main demographic and clinical data are shown in Table 1.

The median age of enrolled patients was 65 years (interquartile range [IQR]: 57–73 years) and the median tumor size was 1.5 cm (IQR: 1.3–1.8 cm). There were 164 (60.5%) males and 107 (39.5%) females. Males were older than females. Males had a higher proportion of chronic HBV infection than females, and females had a higher proportion of chronic hepatitis C than males. Moreover, male patients had higher serum creatinine levels than female patients. Regarding tumor parameters, females had a larger tumor size and a higher serum alpha fetoprotein (AFP) levels than males.

3.2. Factors associated with poor OS rates
After a median follow-up duration of 43.4 months (IQR 25.0–70.3 months), 76 patients had died, and 195 patients were still alive at their last follow-up visit. One hundred and five patients were lost to follow-up sometime before December 31, 2016. For patients who were lost to follow-up, the median follow-up duration after RFA was 32.5 months (IQR 18.5–55.9 months). Additionally, only 29 (10.7%) patients had a follow-up duration < 1 year. During the follow-up period, there were 10 patients who received salvage liver transplantation due to tumor recurrence or liver decompensation.

The cumulative 1-, 3-, 5- and 10-year OS rates were 96.2%, 81.7%, 67.1%, and 56.4%, respectively. Stratified by the status of ALBI grade 1 versus grades 2–3, the 1-, 3-, 5- and 10-year OS rates were 97.4% versus 95.0%, 88.1% versus 77.9%, and respectively.
78.2% versus 54.9%, and 72.3% versus 39.1% \( (p < 0.001, \text{Fig.1 2A}) \). Univariate analysis disclosed that age > 65 years, negative serum HBsAg, serum albumin level ≤ 3.5 g/dL, prothrombin time/international normalized ratio (PT INR) > 1.1, platelet count < 100,000/mm\(^3\), tumor size > 1.5cm, and ALBI grade 2 or 3 were associated with poorer OS for patients with BCLC stage 0 after the RFA procedure (Table 2).

In model I of multivariate analysis, age > 65 years (hazard ratio [HR] 1.608, 95% confidence interval [CI] 1.015–2.545; \( p = 0.043 \)), platelet count < 100,000/mm\(^3\) (HR 1.704, 95% CI 1.027–2.828; \( p = 0.039 \)), and ALBI grade 2-3 (HR 2.191, 95% confidence interval, CI 1.261–3.805; \( p = 0.005 \)) were the independent risk factors predicting worse OS. In model II, serum albumin levels ≤ 3.5 g/dL (HR 1.933, 95% CI 1.179–3.167; \( p \)

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**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 271)</th>
<th>Men (n = 164)</th>
<th>Women (n = 107)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65, 57-73</td>
<td>63, 53-73</td>
<td>68, 61-74</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

*Serum biochemistry and liver function test*

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 271)</th>
<th>Men (n = 164)</th>
<th>Women (n = 107)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>3.90, 3.40-4.20</td>
<td>3.90, 3.50-4.20</td>
<td>3.70, 3.40-4.20</td>
<td>0.120</td>
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<tr>
<td>Cholesterol (mg/dl)</td>
<td>156, 126-173</td>
<td>156, 126-176</td>
<td>155, 131-171</td>
<td>0.887</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.79, 0.50-1.10</td>
<td>0.79, 0.51-1.18</td>
<td>0.71, 0.50-1.03</td>
<td>0.544</td>
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<td>ALT (U/L)</td>
<td>41, 28-73</td>
<td>41, 29-62</td>
<td>42, 27-84</td>
<td>0.663</td>
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<tr>
<td>AST (U/L)</td>
<td>45, 31-70</td>
<td>43, 29-63</td>
<td>50, 32-78</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>95, 85-127</td>
<td>94, 83-121</td>
<td>99, 87-133</td>
<td>0.184</td>
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<td>Creatinine (mg/dl)</td>
<td>0.90, 0.73-1.07</td>
<td>0.97, 0.84-1.10</td>
<td>0.76, 0.65-0.90</td>
<td>&lt; 0.001</td>
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<tr>
<td>ALK-P (U/L)</td>
<td>87, 70-115</td>
<td>83, 71-118</td>
<td>89, 70-115</td>
<td>0.587</td>
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<tr>
<td>Platelet (109/L)</td>
<td>110, 71-153</td>
<td>115, 72-159</td>
<td>101, 69-143</td>
<td>0.374</td>
</tr>
<tr>
<td>PT INR</td>
<td>1.08, 1.02-1.15</td>
<td>1.07, 1.01-1.14</td>
<td>1.09, 1.03-1.16</td>
<td>0.061</td>
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<tr>
<td>ALBI</td>
<td>-2.52, -2.90--2.09</td>
<td>-2.57, -2.90--2.18</td>
<td>-2.44, -2.90--2.03</td>
<td>0.071</td>
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<tr>
<td>ALBI (1/2/3) (%)</td>
<td>117/133/10 (45/51.2/3.8)</td>
<td>74/77/4 (47.7/49.7/2.6)</td>
<td>43/56/6 (41/53.3/5.7)</td>
<td>0.301</td>
</tr>
</tbody>
</table>

*Viral Factors*

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 271)</th>
<th>Men (n = 164)</th>
<th>Women (n = 107)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg (+/-) (%)</td>
<td>116/100 (53.7/46.3)</td>
<td>85/51 (62.5/37.5)</td>
<td>31/49 (38.7/61.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-HCV (+/-) (%)</td>
<td>108/100 (51.9/48.1)</td>
<td>50/64 (43.9/56.1)</td>
<td>58/36 (61.7/38.3)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Alk-P = alkaline phosphatase; PT = prothrombin time; INR = international normalized ratio; ALBI = Albumin-Bilirubin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; AFP = alpha-fetoprotein
Fig. 2  (A) Comparison of OS rates between patients with ALBI grade 1 and those with ALBI grade 2 or 3. (B) Subgroup analysis for the comparison of OS rates between patients with ALBI grade 1 and those with ALBI grade 2 or 3.
During the follow-up period, 112 patients had tumor recurrence after the RFA procedure. The cumulative 1-, 3-, 5- and 10-year RFS rates were 76.4%, 49.0%, 40.1%, and 33.0%, respectively. Stratified by the status of ALBI grade 1 versus grades 2–3, the 1-, 3-, 5- and 10-year RFS rates were 78.3% versus 73.7%, 59.2% versus 37.6%, 52.5% versus 25.8%, and 41.9% versus 21.6% (p = 0.001, Fig. 3A).

As shown in Table 3, model I of multivariate analysis showed that ALBI grade 2–3 (HR 1.825, 95% CI 1.288–2.585; p = 0.001) was the only one independent risk factor associated with poor RFS after RFA. In the model II, serum albumin ≤ 3.5 g/dL (HR 1.645, 95% CI: 1.146–2.360; p = 0.007), and ALT > 40 U/L (HR 1.428, 95% CI: 1.016–2.007, p = 0.040) were correlated to poor RFS by the multivariate analysis.

Subgroup analysis also demonstrated that patients in most of the subgroups with ALBI grade 2 or 3 had a significantly lower RFS rate compared to those with ALBI grade 1 (Fig. 3B).

### 4. DISCUSSION

There are several major findings from our study. First, in our cohort, the cumulative 5-year and 10-year OS rates after RFA were 67.1% and 56.4%, respectively. This result indicated that for patients with very early stage HCC (BCLC stage 0), RFA could provide excellent long-term prognosis. Nevertheless, the recurrence rate after RFA was still high with a 10-year RFS rate of only 33.0%. It suggests that a strict surveillance program to detect the tumor recurrence after RFA is crucial in this clinical setting. In addition, our study demonstrated that ALBI grade could predict the outcomes of patients with HCC who underwent RFA. This clinically applicable marker could help clinical physicians select a suitable treatment modality for patients with very early stage HCC and predict these patients’ outcomes before the RFA application.

For patients with early stage HCC (BCLC stage 0 to A) and with well-preserved liver function, resection surgery and RFA are regarded as first-line treatment modalities. RFA has been reported to produce less non-neoplastic tissue destruction, lower complication rate, lower cost, and a higher repeatability rate for recurrence than resection surgery. On the contrary, resection surgery showed lower tumor recurrence rate due to a higher chance of complete excision for hepatic parenchyma around the tumor, which may contain undetectable satellite tumors, micro-metastases, and micro-vascular invasion. Consequently, the treatment efficacy, complications, and long-term prognoses between RFA and resection surgery in this clinical setting is still under active debate.

For patients with BCLC stage 0 HCC, RFA could provide excellent local tumor control effects with a lower incidence of complications and local tumor recurrence after this procedure. Previous studies have reported that for patients with BCLC stage 0 HCC and who had undergone RFA, they had an acceptable long-term survival rate similar to or slightly lower than resection surgery. In our cohort, the 5-year OS rate after RFA was 67.1%, which was consistent with previous reports. However, the prognoses of patients with BCLC stage 0 HCC after RFA with a longer follow-up duration was not well studied until now. Our study demonstrated that RFA could provide an acceptable 10-year OS rate of 56.4%. Hence, RFA could serve as an effective treatment modality for patients with very early
stage HCC and who are not good candidates for resection surgery or liver transplantation.

Previous studies have demonstrated that tumor factors, liver functional reserve, and field factors in the background liver (such as the degree of inflammation and steatosis and fibrosis stage) all determine the outcomes of patients with HCC outcomes.31,32,35 For patients with early-stage HCC, the impact of tumor parameters diminishes, while liver functional reserve and field factors might play a more important role in predicting the outcomes of patients.30 In our current study, tumor parameters such as size and serum AFP levels were not independent risk factors to be associated with the prognoses of patients with HCC after undergoing the RFA procedure. Instead, elderly age, thrombocytopenia, and higher ALBI grade determined poorer prognosis. The possible mechanism is that RFA could provide an excellent tumor ablation effect for BCLC stage 0 HCC due to the advances in the technique of RFA (such as the application of switching controllers with multiple electrodes, and artificial ascites), as well as the introduction of real-time virtual ultrasonography and contrast-enhanced ultrasonography.23,37-40

Table 3
Univariate and multivariate analysis of factors associated with poor RFS in model I

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case No.</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age &gt; 65/≤ 65 years</td>
<td>131/140</td>
<td>1.310 (0.942-1.820)</td>
<td>0.108</td>
</tr>
<tr>
<td>Sex Female/male</td>
<td>107/164</td>
<td>1.159 (0.830-1.619)</td>
<td>0.386</td>
</tr>
<tr>
<td>HBsAg (+)/(−)</td>
<td>115/116</td>
<td>1.014 (0.727-1.415)</td>
<td>0.935</td>
</tr>
<tr>
<td>Anti-HCV (+)/(−)</td>
<td>163/108</td>
<td>0.827 (0.593-1.153)</td>
<td>0.263</td>
</tr>
<tr>
<td>Albumin ≤ 3.5/&gt; 3.5 g/dL</td>
<td>67/191</td>
<td>1.623 (1.134-2.324)</td>
<td>0.008</td>
</tr>
<tr>
<td>Bilirubin &gt; 1.0/≤ 1.0 mg/dL</td>
<td>81/181</td>
<td>1.265 (0.895-1.788)</td>
<td>0.183</td>
</tr>
<tr>
<td>ALT &gt; 40/≤ 40 U/L</td>
<td>137/131</td>
<td>1.485 (1.063-2.074)</td>
<td>0.020</td>
</tr>
<tr>
<td>Creatinine &gt; 1.0/≤ 1.0 mg/dL</td>
<td>82/184</td>
<td>1.190 (0.837-1.691)</td>
<td>0.332</td>
</tr>
<tr>
<td>PT INR &gt; 1.1/≤ 1.1</td>
<td>104/163</td>
<td>1.317 (0.942-1.841)</td>
<td>0.108</td>
</tr>
<tr>
<td>Platelets &lt; 100/≥100 (109/L)</td>
<td>120/149</td>
<td>1.538 (1.107-2.136)</td>
<td>0.010</td>
</tr>
<tr>
<td>AFP &gt; 20/≤ 20 ng/mL</td>
<td>109/153</td>
<td>1.588 (1.119-2.169)</td>
<td>0.009</td>
</tr>
<tr>
<td>Tumor size &gt; 1.5/≤ 1.5cm</td>
<td>144/322</td>
<td>1.528 (1.097-2.128)</td>
<td>0.012</td>
</tr>
<tr>
<td>ALBI grade 2 or 3/1</td>
<td>143/117</td>
<td>1.804 (1.275-2.551)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In model I, the ALBI grade was enrolled, but albumin and bilirubin levels were not entered into the multivariate analysis. In model II, we selected albumin and bilirubin, but the ALBI grade was not enrolled in the multivariate analysis, serum albumin levels ≤ 3.5 g/dL (HR 1.645, 95% CI: 1.146-2.360, p = 0.007), ALT > 40 U/L (HR 1.428, 95% CI: 1.016-2.007, p = 0.040) were the independent risk factors associated with poor RFS.

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Fig. 3  (A) Comparison of RFS rates between patients with ALBI grade 1 and those with ALBI grade 2 or 3. (B) Subgroup analysis for the comparison of RFS rates between patients with ALBI grade 1 and those with ALBI grade 2 or 3.
correlated to poorer prognosis both in terms of OS and RFA. It suggested that serum albumin levels may play a more important role than bilirubin in determining the long-term outcomes of patients with BCLC stage 0 after RFA.

Besides ALBI grade, platelet-albumin-bilirubin (PALBI) grade has been validated to accurately predict the outcomes of patients with HCC across the different treatment modalities and BCLC stages. Liu and colleagues showed that PALBI grade had a better prognostic performance for patients with HCC who underwent curative therapies when compared to ALBI grade. However, one recent study demonstrated that ALBI grade seemed to have a better discriminative ability than PALBI grade to predict the long-term survival of patients with HCC after RFA. In our study, both ALBI grade and platelet count were the independent risk factors associated with overall survival for patients with BCLC stage 0 HCC after RFA. It needs more prospective studies to investigate the prognostic performance between ALBI and PALBI in determining the outcomes of patients with very early stage HCC.

We acknowledge some limitations to our study. First, our study consisted of a single arm and only enrolled patients with very early stage HCC who had undergone RFA. Therefore, it could not address the long-debate as to whether RFA achieved comparable OS and RFS rates as much as surgical resection did. Second, our study showed results from a single institution. It may not be feasible to compare to directly compare other studies’ results given the potentially different etiologies and demographic characteristics. Third, only 10 patients had an ALBI grade 3 due to the strict inclusion criterion of liver functional reserve for RFA. Consequently, we could not assess the impact of ALBI grade 3 on the long-term prognosis of patients with very early stage HCC who had undergone RFA due to the limited number of patients. Last, our study was retrospective, which could not exclude the selection bias.

In conclusion, for patients with BCLC stage 0 HCC, RFA could provide a long-term outcome with a 10-year overall survival rate of 56.4%. Moreover, the ALBI grade can discriminate the prognosis for such patients.

ACKNOWLEDGMENTS

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