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The role of hepatic reserve in the mortality of cirrhotic patients with small hepatocellular carcinoma receiving radiofrequency ablation

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Abstract

Although radiofrequency ablation (RFA) is considered a curative treatment for early stage small hepatocellular carcinoma (HCC), the long-term prognosis is suboptimal. The major complications in cirrhotic patients are usually related to poor prognosis and include esophageal variceal bleeding, ascites, and hepatic encephalopathy. This study aimed to evaluate the role of liver reserve on mortality after RFA for early stage HCC among cirrhotic patients, according to the presence of the number of complications. The Taiwan National Health Insurance Database was used to identify 2389 cirrhotic patients with treatment-naïve HCC (<3 cm) undergoing RFA hospitalized between January 1, 2010 and December 31, 2013. Of these, 594 patients had concurrent or a history of cirrhotic-related complications. The 1-year and 3-year survival rates in the cirrhotic patients with complications were 78.5% and 39.8%, respectively, and those in the patients without complications were 92.7% and 65.9% ($P < .001$), respectively. Age (hazard ratio [HR] 1.03, 95% confidence interval [CI] 1.02–1.04, $P < .001$) and cirrhotic-related complications (HR 2.65, 95% CI 2.22–3.16, $P < .001$) significantly increased 3-year mortality. The HR of mortality in patients with 1, 2, or 3 complications compared to those without complications were 2.35 (95% CI 1.92–2.88), 3.27 (95% CI 2.48–4.30), and 4.63 (95% CI 2.82–7.62), respectively (all $P < .001$). In cirrhotic patients with early stage HCC undergoing RFA, poor liver reserve correlates with poor outcome. The presence or history of three cirrhotic-related complications increased 3-year mortality 4-fold.

Abbreviations: CI = confidence interval, HCC = hepatocellular carcinoma, HE = hepatic encephalopathy, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification code, NHIRD = National Health Insurance Research Database, PUB = peptic ulcer bleeding, RFA = radiofrequency ablation, RFI = renal function impairment, VB = variceal bleeding.

Keywords: complications, liver cirrhosis, radiofrequency ablation

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy worldwide.[1,2] HCC usually occurs subsequent to chronic hepatitis infection including hepatitis B or/and hepatitis C and underlying cirrhosis.[1,3,4] Multiple studies have confirmed that radiofrequency ablation (RFA) is an effective treatment for early stage HCC[5–7] and for early stage HCC with compensated cirrhosis.[8–11] In general, surgical resection or RFA is considered a curative treatment for early stage HCC. However, in cirrhotic patients with poor liver function, surgical resection is usually difficult to perform. Fortunately, RFA may be used for these patients because it is less invasive. To our best knowledge, few studies have evaluated the effect of RFA on the long-term prognosis of decompensated cirrhotic patients with early stage HCC.[4]

Using the nationwide population-based dataset in Taiwan, we aimed in this study to determine the effect of liver reserve on mortality in cirrhotic patients with small HCC receiving RFA. In subgroup analysis, we evaluated the mortality in these patients according to the number of liver-related complications.

2. Materials and Methods

2.1. Database and ethical statement

The Taiwan National Health Insurance Research Database (NHIRD) was used for this study. Begun in 1995, Taiwan started the National Health Insurance program that now covers more than 99% of the Taiwanese population. The

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The authors have no conflicts of interest to disclose

All data generated or analyzed during this study are included in this published article.

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NHIRD contains a sample of records from this population for research uses. This study was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital (IRB B10403026). We also approved by Buddhist Tzu Chi Medical Foundation with the registration number: TCMF-A 109-01. The personal information of patients and doctors was removed from the database sample before it was provided for analysis.

2.2. Study sample

This study included patients in the NHIRD who were diagnosed with cirrhosis from January 1 to December 31, 2010 using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 571.5 or 571.2 between January 1, 2010 and December 31, 2013. A total of 2389 patients with treatment-naïve HCC (ICD-9-CM code 155.0) (<3 cm) who were hospitalized and received RFA from January 1, 2010 to December 31, 2013 were enrolled. Among these, 594 patients were identified as having poor liver reserve and 1795 as having good liver reserve. Poor liver reserve in our study was defined as cirrhotic patients with either a history or the concurrent presence of liver cirrhosis-related complications, identified as hepatic encephalopathy (HE, ICD-9-CM code 572.2), variceal bleeding (VB, ICD-9-CM codes 456.0, 456.20), or ascites (ICD-9-CM code 789.5 or procedure code 54.91). Patients with one or more of the above complications were classified into the poor liver reserve group; all others were classified into the good liver reserve group. In order to analyze the effect of liver reserve on the mortality of patients receiving RFA, we compared patients with complications to those who had no complications. We also included the comorbid medical factors of peptic ulcer bleeding (PUB, ICD-9-CM codes 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6), alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03, 571.0–571.3), and renal function impairment (RFI, ICD-9-CM codes 584, 585, 586, 572.4, or other procedure code related to renal failure). In the subgroup analysis, we evaluated the mortality of these patients according to the number of liver-related complications, compared to those with good liver reserve.

2.3. Statistical analyses

All our study analysis were conducted using SPSS version 22 for Windows (IBM Corporation, Armonk, NY). Student test and Chi square test were used to compare continuous and categorical variables. The hazard ratios (HR) and 95% confidence intervals (CI) were calculated at a significance level of 0.05. The Kaplan–Meier log rank test method was used to assess the survival probability of patients with liver cirrhosis by the number of liver-related complications.

3. Results

The study included a total of 2389 patients with treatment-naïve HCC who were hospitalized and had RFA. The demographic characteristics of cirrhotic patients receiving RFA for HCC is provided in Table 1. The overall 1-year and 3-year survival rates in those with poor hepatic reserve were 78.5% and 39.8%, respectively, and the rates in those with good hepatic reserve were 92.7% and 65.9% ($P < .001$), respectively.

The results of Cox regression analysis of the HRs of 3-year mortality based on predisposing factors are provided in Table 2. After adjusting for gender, age, and underlying conditions, the adjusted HR of 3-year overall mortality in the group with poor hepatic reserve compared with the group with good hepatic reserve was 2.65 (95% CI = 2.22–3.16, $P < .001$). After adjusting for other factors, patients with older age (HR 1.03, 95% CI = 1.02–1.04, $P < .001$), male gender (HR 1.05, 95% CI = 0.88–1.25, $P = .598$), alcoholic-related disease (HR 1.33, 95% CI = 0.98–1.79, $P = .067$), PUB (HR 1.80, 95% CI = 0.58–5.62, $P = .310$), and RFI (HR 1.27, 95% CI = 0.86–1.88, $P = .226$) had statistically significantly greater likelihood of 3-year mortality compared with their counterparts without these factors.

Table 1

Demographic characteristics of cirrhotic patients receiving radiofrequency ablation for hepatocellular carcinoma with good hepatic reserve and poor hepatic reserve.

	Good hepatic reserve (n = 1795)	Poor hepatic reserve (n = 594)	*P* value
Male, n (%)	1028 (57.3)	365 (61.4)	.073
Age, yrs	66.0 ± 10.7	63.0 ± 10.9	<.001
Hepatic encephalopathy, n (%)	0 (0)	38 (6.4)	
Ascites, n (%)	0 (0)	145 (24.4)	
EVB, n (%)	0 (0)	31 (5.2)	
Alcohol-related diagnosis, n (%)	77 (4.3)	110 (18.5)	<.001
RFI, n (%)	51 (2.8)	30 (5.1)	.010
PUB, n (%)	6 (0.3)	2 (0.3)	.993

EVB = esophageal variceal bleeding; PUB = peptic ulcer bleeding; RFI = renal failure impairment. Good hepatic reserve was defined as the absence of past or present liver cirrhosis-related complications, identified as hepatic encephalopathy, variceal bleeding, or ascites.

Table 2

Adjusted hazard ratios for mortality in cirrhotic patients receiving radiofrequency ablation for hepatocellular carcinoma during the 3-year follow-up period.

Variable	Hazard ratio	95% Confidence interval	*P* value
Age	1.03	1.02–1.04	<.001
Male	1.05	0.88–1.25	.598
Alcohol-related diagnosis	1.33	0.98–1.79	.067
PUB	1.80	0.58–5.62	.310
RFI	1.27	0.86–1.88	.226
Poor hepatic reserve	2.65	2.22–3.16	<.001

PUB = peptic ulcer bleeding; RFI = renal failure impairment.

To calculate the effect of the number of complications on patient mortality, patients with complications were compared with those having good hepatic reserve (Table 3). The HRs for mortality in patients with 1, 2, and 3 complications compared to those without complications were 2.33 (95% CI = 1.90–2.86, $P < .001$), 3.38 (95% CI = 2.55–4.48, $P < .001$), and 4.41 (95% CI = 2.65–7.34, $P < .001$), respectively. Figure 1 shows the cumulative 3-year survival curve of cirrhotic patients receiving RFA for HCC by the number of complications.

4. Discussion

RFA is considered a curative treatment for small HCC, but the long-term outcome is variable.[12–16] Child-Pugh score, preoperative serum alfa-fetoprotein, and the size and number of tumors are prognosis factors in patients receiving RFA for small HCC.[13,17] Fewer studies, however, have evaluated the role of liver reserve in the mortality of cirrhotic patients receiving RFA for small HCCs. Using a nationwide population-based dataset, this study aimed to characterize the role of liver reserve in these patients in clinical practice.

In this study, the 3-year mortality of cirrhotic patients receiving RFA for small HCC was 40.6%. The result is somewhat lower than that of other studies because many other studied confined themselves to patients with liver cirrhosis with poor liver reservoir.[15,18,19] The other reason is that our enrolled

patients included all inpatients throughout the country, which explains the lower long-term survival rate in our study. In this study, we divided the patients into those with poor liver reserve and good liver reserve. Although the terms "poor" and "good" are relative, the liver reserve in cirrhotic patients is always worse than that of healthy people. According to the Barcelona-Clinic Liver Cancer stage system for HCC, the stage of HCC is grade D in cirrhotic patients with Child-Pugh C stage.[20] RFA is not an indication for these patients. However, in clinical practice, the Child–Pugh score is variable in cirrhotic patients. Many cirrhotic patients may have short-term improvement in their Child–Pugh score after medical treatment. The change in the Child–Pugh score can also change the Barcelona-Clinic Liver Cancer stage of the HCC. In clinical practice, patients may receive the curative treatment of HCC, such as RFA, and subsequently experience a better status of liver reserve. This can explain why many cirrhotic patients receive RFA although they have poor liver reserve status.

In this present study, we primarily demonstrated that cirrhotic patients with early stage HCC and concurrent or a history of three cirrhotic-related complications had a 4-fold higher risk of mortality in the three years after RFA compared to those with no complications. In other words, poor liver reserve in cirrhotic patients undergoing RFA for small HCCs is associated with increased mortality. Previous publications were limited to the effect of RFA on prognosis in compensated cirrhotic patients.[4] In this study, we provide extensive data with a large sample size of decompensated cirrhotic patients undergoing RFA.

Not surprisingly, our findings are similar to previous results. Wakuta et al. pointed out that overall survival, but not recurrence-free survival, was influenced by liver function.[4] Therefore, the presence of more complications in cirrhotic patients would lead to higher morality, despite curative treatment. Some argue that patients with decompensated liver cirrhosis who develop small HCC should not receive RFA. Patients with liver transplants recover more than those receiving RFA. However, clinically, the supply of livers for transplantation is limited. In addition, the stage of liver cirrhosis sometimes may change. In our study, when patients had concurrent or a history of cirrhotic-related complications, the long-term mortality rate

Table 3

Adjusted hazard ratios of the effect of the number of complications on mortality in cirrhotic patients receiving radiofrequency ablation for hepatocellular carcinoma during a 3-year follow-up period.

Variable	Hazard ratio	95% confidence interval	*P* value
Complication conditions			
No complications	Reference		
1 complication	2.33	1.90–2.86	<.001
2 complications	3.38	2.55–4.48	<.001
3 complications	4.41	2.65–7.34	<.001

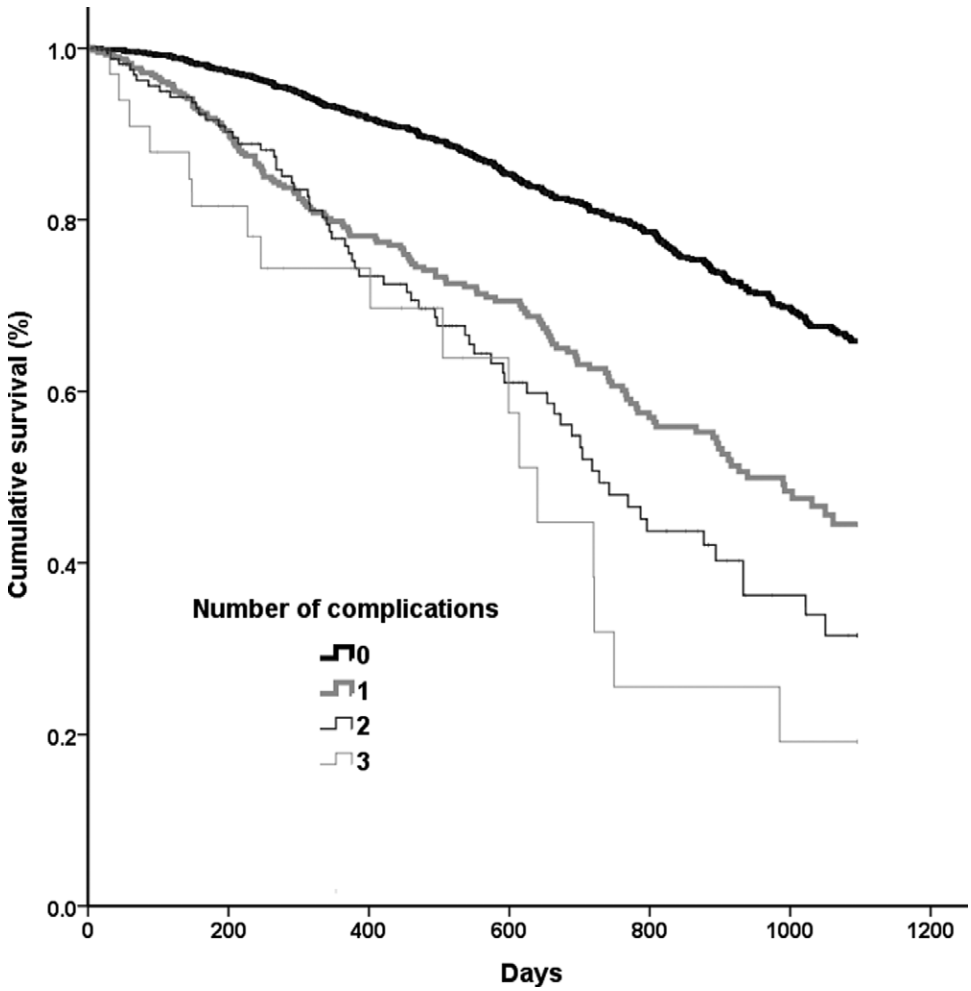

Figure 1. Kaplan–Meier survival analysis for the 3-year follow-up period of cirrhotic patients after radiofrequency ablation for hepatocellular carcinoma by the number of complications.

was increased. If the number of cirrhotic-related complications increases, the liver reserve is worse, and both the short-term and long-term prognosis will be worse. This result shows that, even if the HCC is very small, the important factor for prognosis is the liver function. Although RFA is considered a curative treatment for small HCC, the patient's long-term prognosis ultimately depends on the liver function.

There were some limitations to this present study. First, although the severity of liver cirrhosis is commonly evaluated by the Mayo Clinic model for end-stage liver disease score or the Child–Pugh score, we could not identify laboratory data such as bilirubin, albumin, or prothrombin time in this database by using ICD-9 coding numbers. However, the use of liver cirrhosis clinical stage and the presence of ascites, HE, and VB have been identified in many studies, and the presence of these complications consistently correlates with poor hepatic reserve.[21–23] Second, the coding accuracy of the diagnosis is the main weakness of this kind of population-based study, and it is a limitation of this dataset. However, about four-fifths of hospitalizations were from physicians' service, a result confirmed in a previous study. This correlation may enhance somewhat the reliability of these discharge diagnoses in our study.[24] Finally, the real tumor stage could not be identified in the dataset we used. However, all the patients in this study had small HCCs with tumor size not more than 3 cm and therefore all these patients can be regarded as having early stage HCC. Despite these limitations, this nationwide population-based study is the first to identify the risk of mortality associated with liver reserve in cirrhotic patients with small HCC receiving RFA.

5. Conclusions

In summary, poor hepatic reserve is associated with a poor prognosis in cirrhotic patients with early stage HCC receiving RFA. In such patients, having concurrent or a history of three cirrhotic-related complications increase mortality 4-fold over a three year period.

Author contributions

Tsung-Hsing Hung and Hsing-Feng Lee: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; Chih-Chun Tsai and Tsung-Hsing Hung: statistical analysis.
Conceptualization: Tsung-Hsing Hung.
Data curation: Chih-Chun Tsai.
Formal analysis: Tsung-Hsing Hung, Chih-Chun Tsai.
Methodology: Tsung-Hsing Hung, Chih-Chun Tsai, Hsing-Feng Lee.
Resources: Tsung-Hsing Hung.
Software: Chih-Chun Tsai.
Supervision: Hsing-Feng Lee.
Validation: Hsing-Feng Lee.
Visualization: Hsing-Feng Lee.
Writing – original draft: Tsung-Hsing Hung.
Writing – review & editing: Tsung-Hsing Hung, Hsing-Feng Lee.

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