



ORIGINAL ARTICLE

Nomogram based on albumin-bilirubin grade to predict outcome of the patients with hepatitis C virus-related hepatocellular carcinoma after microwave ablation

Chao An*, Xin Li*, Xiaoling Yu, Zhigang Cheng, Zhiyu Han, Fangyi Liu, Jie Yu, Ping Liang

Department of Interventional Ultrasound, State Key Laboratory of Kidney Disease, The Chinese PLA General Hospital, Beijing 100853, China

ABSTRACT

Objective: To construct a nomogram based on the albumin-bilirubin (ALBI) grade to provide prognostic value for hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) patients who underwent ultrasound-guided percutaneous microwave ablation (US-PMWA).

Methods: From April 2005 to January 2018, 183 treatment-naïve patients with 251 HCV-related HCCs according to the Milan criteria received US-PMWA subsequently. The overall survival (OS) and recurrence-free survival (RFS) were compared between groups classified by ALBI grade. Cox proportional hazard regression model based on risk factors for survival and recurrence was used to construct the nomogram.

Results: The cumulative OS rates at 1-, 3-, 5- and 10-year were 97.7%, 73.6%, 54.5% and 34.5%, respectively. Stratified according to ALBI grade, the 1-, 3-, and 5-year OS in the ALBI grade 1 group and grade 2 group were 99.2%, 92.4%, 77.9% and 97.7%, 52.3%, 38.6%, respectively, with significant statistical difference ($P < 0.001$). No significant statistical difference was detected in the 1-, 3-, and 5-year RFS rates in the ALBI grade 1 group and grade 2 group ($P = 0.220$). The major complication rate was 1.6%. Multivariate analysis results showed age, α -fetoprotein level, tumor number, platelet count, location, Child-Turcotte-Pugh (CTP) and ALBI grade were associated with OS, which generated the nomograms. Internal validation with 1000 bootstrapped sample sets had good concordance index of 0.769 (95%CI 0.699-0.839) in OS.

Conclusions: This nomogram based on ALBI grade was a visualization risk model, which could provide personalized prediction of long-term outcomes for HCV-related HCC patients after US-PMWA.

KEYWORDS

Nomogram; albumin-bilirubin grade; hepatitis C virus; hepatocellular carcinoma; microwave ablation

Introduction

Hepatocellular carcinoma (HCC) is a common complication related to hepatitis C virus (HCV) infection with considerable mortality and morbidity rates^{1,2}. The incidence of HCV-related HCC, which is lower than that of HCC caused by hepatitis B virus (HBV) in China, however, has increased in a stepwise manner during the past twenty years^{3,4}. Although antiviral therapy, including direct-acting antiviral (DAA) agents and interferon therapy (IFN), has been used as an effective treatment for HCV infection, recurrence of HCC after curative treatment is still critical for

long-term outcomes⁵⁻⁷.

Currently, the treatments for early-stage HCC patients recommended in the guidelines mainly include surgical resection, liver transplantation and local ablation therapy⁸. Nevertheless, many patients have lost the curative opportunity due to poor physical condition and shortage of organ donors. As a slim chance of survival for the patients with HCC, ultrasound-guided microwave ablation (MWA) is superior to radiofrequency ablation (RFA) because of its advantages, including higher intratumoural temperature, shorter operation time and less dependence on the electrical conductivities. As one of the most recent techniques in the field of thermoablation, MWA has been confirmed as a safe and effective treatment for HCC patients with stage 0/A based on the Barcelona Clinic Liver Cancer (BCLC) staging system⁹⁻¹¹. With the recent advances in several interventional assistance technologies (e.g., internally cooled microwave generator, artificial ascites or pleural effusion, three-

*These authors contributed equally to this work.

Correspondence to: Jie Yu and Ping Liang

E-mail: yu-jie301@hotmail.com and liangping301@126.com

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dimensional (3D) visualization preoperative planning and contrast-enhanced ultrasound (CEUS) guidance), the accuracy and effectiveness of treatment for the tumour on the surrounding location have been improved¹²⁻¹⁵. Most studies have reported oncologic outcomes of MWA for patients with HCC and analysed risk factors related to survival and recurrence^{16,17}. However, studies on patients with HCV-related HCC who underwent US-PMWA remain scarce. A nomogram is a visual risk regression model and an ideal tool for predicting HCC patients' prognosis, which is derived from various hazard functions^{18,19}. Moreover, nomograms have been applied to predict outcomes of HCC patients after liver resection, transarterial chemoembolization (TACE) and RFA, while those of HCC patients who underwent MWA have never been reported²⁰⁻²².

Hepatic functional reserve has always been considered to be critical for outcomes of HCC patients due to cirrhosis progression. Child-Pugh grade is the most widely used assessment method for hepatic functional reserve, but highly subjective factors, such as severity of ascites and degree of hepatic encephalopathy, may affect assessment ability²³. Recently, as a simple and objective evaluation method, albumin–bilirubin (ALBI) grade has been applied to assess hepatic functional reserve²⁴⁻²⁶, and a nomogram based on ALBI grade has been used to predict outcomes of patients with HCC after RFA²⁷. Learning from the previous studies, we designed a plan, and the main aim was to construct a nomogram with the ALBI grade to assess the long-term outcomes of patients with HCV-related HCC after US-PMWA. In this way, the tumour recurrence and survival prognosis of patients with HCV-related HCC was further analysed and discussed.

Materials and methods

Patients and clinicopathologic data

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Chinese PLA General Hospital. Because of the retrospective nature of the study, patient consent for inclusion was waived. The medical records of all HCV-related HCC patients between April 2005 and January 2018 were reviewed. For this cohort study, the primary diagnosis of patients with HCV-related HCC was based on HCV-infected individuals with cirrhosis and abdominal ultrasound combined with serum alpha-fetoprotein (AFP) level. The final diagnosis was based on

pathologic findings of needle biopsy samples before ablation. The inclusion criteria were as follows: (a) a single tumour with a maximum size smaller than 5 cm and tumour number less than 3 according to the Milan criteria, (b) no major vascular invasion or extrahepatic metastasis, (c) HCV-infected patients, and (d) absence of ascites. The exclusion criteria were as follows: (a) recurrent HCC; (b) serious medical comorbidities, including heart, lung and renal dysfunction; (c) severe coagulation disorders (i.e., prothrombin time > 25 s, prothrombin activity < 40%, and platelet count < 50 cells × 10⁹/L); or (d) active severe infection.

During the study period, 2632 consecutive patients with HCC underwent percutaneous MWA. Among them, 183 patients with 251 tumours (mean age, 64.6 years ± 9.1; range, 32–84 years) met the inclusion criteria and were included in this study. ALBI score was calculated before treatment using the appropriate clinical parameters, and ALBI grade was defined as follows: (log bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.085); grade 1 ≤ −0.260, −2.60 < grade 2 < −1.39 and grade 3 ≥ −1.39. Stratified according to ALBI grade, clinicopathologic data, including age, gender, tumour characteristics, comorbid disease, pathological differentiation, Barcelona Clinic Liver Cancer (BCLC) grade, Child-Turcotte-Pugh (CTP) grade, α-fetoprotein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), prothrombin time, international normalized ratio (INR), platelet count and creatinine were collected.

The MWA device, procedure and interventional assisted techniques were described in previous reports²⁸⁻³⁰. All ablative procedures were performed percutaneously by three interventional radiologists, namely, P.L., X.L.Y., and Z.G.C., who had 25, 25, and 15 years of experience with MWA, respectively. US-PMWA was performed successfully until all of the tumours were ablated completely. The treatment parameters, including antenna number, insertion number, ablation time, ablation power, treatment session, and interventional assistive techniques, including hydrodissection technique, contrast-enhanced ultrasound (CEUS) guidance and 3D visualization preoperative planning, were collected.

Follow-up and endpoints

Contrast-enhanced images were obtained at 1 and 3 months after ablation and every 3 months thereafter until January 2018. Thereafter, the follow-up visit covered several

evaluations, including routine physical examination, laboratory tests, such as total bilirubin, serum albumin, prothrombin time and tumour marker levels, and contrast-enhanced imaging, including US, CT or MRI. Technique effectiveness was defined as the absence of contrast-enhancement on imaging in any area of the mass after one month.

The endpoints of this study were death and tumour recurrence. In this study, local tumour recurrence, intrahepatic distant recurrence and metastasis all were regarded as tumour recurrence. Local tumour recurrence was defined based on imaging findings of an irregular nodular, scattered, or eccentric pattern of peripheral enhancement around the ablation zone in the patients after US-PMWA. Intrahepatic distant recurrence was defined as the appearance of an irregular, scattered, or eccentric pattern of a peripheral enhancement intrahepatic lesion, which was farther away from the ablation zone after MWA. Once tumour recurrence was found, a second MWA treatment was arranged. Overall survival (OS) was calculated from the date of the first session of MWA treatment to the date of death or last date of follow-up (survival or loss). Recurrence-free survival (RFS) was calculated from the date of the first session of MWA treatment to the date of tumour recurrence or the last date of follow-up (no finding of recurrence or loss). Major complications were defined as events which caused substantial morbidity and disability that increased the level of care, led to hospital admission, or substantially prolonged the hospital stay³¹.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL). Either Pearson χ^2 analysis or Fisher exact tests were performed to compare the categorical variables, and Student's *t*-test was applied to compare the continuous variables. The overall survival (OS) and recurrence-free survival (RFS) rates were assessed by the Kaplan–Meier method with the log-rank test. A Cox proportional hazards model was used to identify the significant effects of risk factors on the survival and recurrence rate. For all tests, a *P* value of less than 0.05 was considered to be statistically significant. Univariate and multivariable analyses of independent prognostic factors were evaluated by means of the forward stepwise Cox regression model. The β coefficients originating from the Cox model were used to construct the nomogram to assess the association of variables with OS and RFS after MWA. Internal validation with 1000

sets of bootstrap samples was performed to evaluate the use of the nomogram for assessment of OS and RFS of patients who undergo MWA. In addition, the performance of the model was evaluated by discrimination and calibration via Harrell's concordance index (C-index) and plotting the Kaplan–Meier curves of the tertile of predictions and the calibration curves using the model. Homogeneity was compared in different statistical models for different stages of HCC, which was generated by means of the parametric survival analysis. The Akaike information criterion, which discloses an overall assessment of different statistical models for serum markers of HCC, was performed with the Cox proportional hazards model. Construction of the nomogram was performed by using R software version 3.0.2.

Results

Baseline characteristics

According to the abovementioned formula, 183 patients with HCV-related HCC were divided into two subgroups according to ALBI grade. In this study, there were 95 patients (28 females, 67 males; average age 63.9 ± 9.0 years) in the ALBI grade 1 group and 88 patients (21 females, 67 males; average age 65.4 ± 9.2 years) in the ALBI grade 2 group. In the ALBI grade 1 group, 147 patients had a single tumour; 36 patients had multiple tumours; and the median maximum tumour diameter was 2.7 cm (range, 0.7–5.0 cm). In the ALBI grade 2 group, 80 patients had a single tumour; 15 patients had multiple tumours; and the median maximum tumour diameter was 2.8 cm (range, 0.8–5.0 cm). The characteristics of the patients and tumours are summarized in **Table 1**. The MWA-related treatment parameters are summarized in **Table 2**.

Midterm oncologic outcome and recurrence

The median follow-up period of patients was 29.9 months (range 3.3–122.2 months). Among 183 patients who underwent US-PMWA, 57 (31.1%) died and 107 (58.5%) experienced recurrence during the observation period. The cumulative OS rates at 1, 3, 5 and 10 years were 97.7%, 73.6%, 54.5% and 34.5%, respectively. The cumulative RFS rates at 1, 3, and 5 years were 61.1%, 37.3% and 6.9%, respectively. The 1-, 3-, and 5-year OS rates in the ALBI grade 1 group and ALBI grade 2 group were 99.2%, 92.4%, and 77.9% and 97.7%, 52.3%, and 38.6%, respectively (**Figure 1A**), showing a statistically significant difference ($P < 0.001$). The 1-, 3-, and 5-year RFS rates in the ALBI grade 1

Table 1 Baseline characteristics of patients undergoing MWA

Characteristics	All	ALBI grade 1	ALBI grade 2	<i>P</i>
Patients, <i>n</i>	183	95	88	
Age (years)*	64.6±9.1	63.9±9.0	65.4±9.2	0.253 ^a
Gender				0.392 ^b
Male	128 (69.9)	67 (70.5)	67 (69.3)	
Female	55 (30.1)	28 (29.5)	21 (30.7)	
Tumor size (cm)†	2.7 (0.7–5.0)	2.8 (0.9–5.0)	2.5 (0.7–5.0)	0.256 ^a
≤ 3	121 (66.1)	54 (61.4)	67 (70.5)	
> 3	62 (33.9)	34 (38.6)	28 (29.5)	
Tumor number	235	130 (55.3)	105 (44.7)	0.170 ^b
Single	147 (80.3)	80 (84.2)	67 (76.1)	
Multiple	36 (19.7)	15 (15.8)	21 (23.9)	
Comorbid disease				0.034 ^c
No	108 (59)	49 (51.6)	59 (67)	
Yes	75 (41)	46 (48.4)	29 (33)	
Pathological differentiation				0.666 ^b
Well/moderately	152 (80.1)	80 (84.2)	72 (81.8)	
Poorly	31 (19.9)	15 (15.8)	16 (18.2)	
Barcelona Clinic Liver Cancer grade				0.214 ^b
0	37 (20.2)	30 (31.6)	7 (8.0)	
A	132 (72.1)	55 (57.9)	77 (87.5)	
B	14 (7.7)	10 (10.5)	4 (4.5)	
CTP grade				0.066 ^b
A	175 (95.6)	88 (92.6)	87 (98.9)	
B	8 (4.4)	7 (7.4)	1 (1.1)	
α-fetoprotein level (ng/mL) †	14.9 (1.4–223.1)	17.8 (2.2–223.1)	12.4 (1.4–66.9)	0.315 ^a
Albumin level (μmol/L) †	37.2 (12.6–54.1)	38.9 (12.6–47.8)	33.5 (13.9–54.1)	0.782 ^a
Total bilirubin level (μmol/L) †	16.2 (4.3–51.6)	11.2 (4.3–44.9)	17.9 (5.1–51.6)	0.812 ^a
ALT level (U/L) †	54.2 (7–234.6)	43.7 (7–77.4)	65.1 (8.9–234.6)	0.032 ^a
AST level (U/L) †	60.1 (14.2–387.0)	41.2 (14.7–221.3)	78.2 (14.2–387.0)	0.016 ^a
GGT (U/L) †	78.6 (15–307.9)	43.1 (15–112.4)	80.2 (17.8–307.9)	0.009 ^a
Prothrombin time international normalized ratio*	1.1±0.1 (0.87–1.49)	1.1±0.2 (0.87–1.38)	1.1±0.1 (0.89–1.49)	0.522 ^a
Platelet count (10 ⁹) †	102.5 (50–569)	99.6 (55–569)	105.1 (50–238)	0.729 ^a
Creatinine level (μmol/L) †	84.6 (14.1–232.1)	88.7 (15.7–201.9)	72.1 (14.1–232.1)	0.791 ^a
Recurrence pattern				
LTP only	48 (26.2)	28 (29.5)	20 (22.7)	0.418 ^b
IDR only	22 (12.0)	14 (14.7)	8 (9.1)	0.117 ^b

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Characteristics	All	ALBI grade 1	ALBI grade 2	P
LTP +IDR	15 (8.2)	9 (9.5)	6 (6.8)	0.533 ^b
Total	85 (46.4)	51 (53.7)	34 (50)	0.239 ^b
Metastasis	22 (12)	14 (14.7)	8 (9.1)	0.102 ^c
Technique effectiveness	183 (100)	95 (100)	88 (100)	1.000 ^b
Major complications	3 (1.6)	1 (1.1)	2 (2.3)	0.609 ^b

Unless otherwise indicated data are number of patients, with percentage in parentheses; ^a Student's *t*-test; ^b Pearson χ^2 -test; ^c Fisher's exact test; * Data are means SD $\pm$ mean; † Data are medians, with data range. MWA, microwave ablation; IDR, intrahepatic distant recurrence; LTP, local tumor progression; ALBI, albumin- bilirubin; CTP, child-turcotte-pugh; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase.

Table 2 The parameters related with ultrasound-guided MWA

Parameter	All	ALBI grade 1	ALBI grade 2	P
Patients, <i>n</i>	183	95	88	
Antenna number	2	2	2	1.000 ^b
Ablation points†	2.4 (2–7)	2.2 (1–5)	2.5 (1–7)	0.612 ^a
Ablation time (s)*	558.3 $\pm$ 23.1 (478–600)	592.5 $\pm$ 21.1 (500–600)	537.1 $\pm$ 11.3 (478–600)	0.328 ^a
Ablation power (W)†	55 (45–60)	55 (45–60)	50 (45–60)	0.772 ^a
Hydrodissection technology				0.256 ^b
Yes	55 (30.1)	25 (26.3)	30 (34.1)	
No	128 (69.9)	70 (73.7)	58 (65.9)	
CEUS guidance				0.530 ^b
Yes	32 (17.5)	15 (15.8)	17 (19.3)	
No	151 (82.5)	80 (84.2)	71 (80.7)	
3D visualization preoperative plan				0.757 ^b
Yes	48 (26.2)	24 (25.3)	24 (27.3)	
No	135 (73.8)	71 (74.7)	64 (72.7)	
Sessions				0.031 ^b
1	165 (90.2)	90 (94.7)	75 (85.2)	
> 1	18 (9.8)	5 (5.3)	13 (14.8)	

Unless otherwise indicated data are number of patients, with percentage in parentheses.^a Student *t* test;^b Pearson χ^2 -test;* Data are means SD $\pm$ mean; † Data are medians, with data range. MWA, microwave ablation ALBI, albumin- bilirubin.

group and ALBI grade 2 group were 62.4%, 46.6%, and 12.2% and, 59.6%, 34.5%, and 0%, respectively (**Figure 1B**), showing no statistically significant difference ($P = 0.220$). Major complications related to the MWA procedure were observed in three patients (1.6%), including one with a liver abscess found in the ALBI grade 1 group and one with a pleural effusion and one with seeding found in the ALBI grade 2 group, showing no statistically significant difference ($P = 0.609$).

Univariate and multivariate analyses

Univariate and multivariate logistic regression analyses were performed to identify predictors influencing the long-term outcome of patients with HCV-related HCC who underwent US-PMWA. The univariate analysis showed statistically significant differences in terms of the OS rate depending on the age (HR = 0.477; $P = 0.009$), tumour size (HR = 1.916; $P = 0.017$), tumour number (HR = 2.167; $P = 0.010$), adjacent

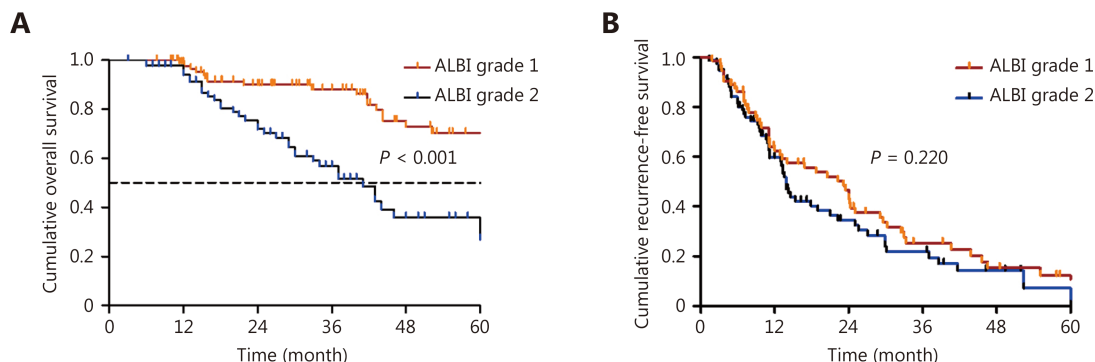


Figure 1 The 1-, 3-, and 5-year OS rates in the ALBI grade 1 group and ALBI grade 2 group were 99.2%, 92.4%, and 77.9%; 97.7%, 52.3%, and 38.6%, respectively, showing significant statistical difference ($P < 0.001$) (A). The 1-, 3-, and 5-year RFS rates in the ALBI grade 1 group and ALBI grade 2 group were 62.4 %, 46.6%, and 12.2%; 59.6%, 34.5%, and difference ($P = 0.220$) (B).

Table 3 Factors associated with overall survival

Factors	Univariate		Multiple regression	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	0.477 (0.275, 0.829)	0.009	0.492 (0.266, 0.909)	0.015
< 65	89			
≥ 65	94			
Gender	0.882 (0.504, 1.543)	0.66	—	—
Male	128			
Female	55			
Differentiation	0.576 (0.312, 1.135)	0.723	—	—
Well/moderately	152			
Poorly	31			
Comorbidities				
Yes	108			
No	75			
Tumor size (cm)	1.916 (1.121, 3.274)	0.017	—	—
< 3	121			
≥ 3	62			
Tumor number	2.167 (1.205, 3.898)	0.01	1.969 (1.010, 3.839)	0.032
Single	147			
Multiple	36			
Adjacent to large vessels	2.571 (1.375, 4.808)	0.003	3.238 (1.508, 6.951)	0.002
Yes	153			
No	30			
α-fetoprotein level (ng/mL)	2.109 (1.231, 3.618)	0.007	1.898 (1.042, 3.456)	0.009
≤ 20	118			
> 20	65			
GGT (U/L)	1.872 (1.178, 2.287)	0.112	—	—

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Factors	Univariate		Multiple regression	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
≤ 50	77			
> 50	106			
Albumin level (g/L)	0.703 (0.405, 1.220)	0.21	–	–
< 35	50			
≥ 35	131			
Total bilirubin level (μmol/L)	1.320 (0.706, 2.466)	0.384	–	–
< 20.5	150			
≥ 20.5	33			
ALT level (U/L)	1.257 (0.740, 2.135)	0.398	–	–
< 40	89			
≥ 40	94			
AST level (U/L)	1.345 (0.743, 2.434)	0.328	–	–
< 40	60			
≥ 40	123			
Platelet count (10 ⁹)	0.772 (0.456, 1.306)	0.334	0.479 (0.258, 0.889)	0.027
<100	99			
≥ 100	84			
Prothrombin time international normalized ratio	1.012 (0.582, 1.760)	0.967	–	–
< 1.1	117			
≥ 1.1	66			
Procedure session	2.148 (1.002, 4.603)	0.049	–	–
1	162			
> 1	21			
Child–Pugh grade	2.119 (0.654, 6.868)	0.211	6.752 (1.728, 26.384)	0.002
A	175			
B	8			
ALBI grade	3.787 (2.117, 6.775)	<0.001	4.814 (2.471, 9.378)	<0.001
1	95			
2, 3	88			

Data in parentheses are 95% confidence intervals. ALBI, albumin- bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

large vessels (HR = 2.571; *P* = 0.003), α-fetoprotein level (HR = 2.109; *P* = 0.007), procedure session (HR = 2.148; *P* = 0.049) and ALBI grade (HR = 3.787; *P* < 0.001) (**Table 3**). The multivariate analysis showed that the factors that significantly affected the OS rate were age (HR = 0.492; *P* = 0.015), tumour number (HR = 1.969; *P* = 0.032), adjacent

large vessels (HR = 3.238; *P* = 0.002), α-fetoprotein level (HR = 1.898; *P* = 0.009), platelet count (HR = 0.479; *P* = 0.027), CTP grade (HR = 6.579; *P* = 0.002) and ALBI grade (HR = 4.814; *P* < 0.001) (**Table 3**). The univariate analysis showed statistically significant differences in terms of RFS rates depending on the age (HR=0.632; *P*=0.022), gender

Table 4 Factors associated with recurrence-free survival

Factors	Univariate		Multiple regression	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)	0.632 (0.427, 0.936)	0.022	0.548 (0.348, 0.862)	0.009
< 65	89			
≥ 65	94			
Gender	1.512 (1.008, 2.267)	0.046	–	–
Male	128			
Female	55			
Differentiation	0.719 (0.428, 1.325)	0.312	–	–
Well/moderately	152			
Poorly	31			
Comorbidities	0.732 (0.495, 1.083)	0.118	–	–
Yes	108			
No	75			
Tumor size (cm)	1.916 (1.121, 3.274)	0.659	–	–
< 3	121			
≥ 3	62			
Tumor number	1.317 (0.835, 2.078)	0.236	–	–
Single	147			
Multiple	36			
Adjacent to large vessels	0.154 (0.870, 2.418)	0.046	–	–
Yes	153			
No	30			
DAA therapy	0.431 (0.211, 0.791)	0.003	0.392 (0.276, 0.836)	0.023
Yes	88			
No	95			
α-fetoprotein level (ng/mL)	1.884 (1.271, 2.793)	0.002	1.760 (1.148, 2.698)	0.002
≤ 20	118			
> 20	65			
GGT (U/L)	1.418 (0.962, 1.712)	0.381	–	–
≤ 50	77			
> 50	106			
Albumin level (g/L)	0.781 (0.518, 1.177)	0.238	–	–
< 35	50			
≥ 35	131			
Total bilirubin level (μmol/L)	0.948 (0.583, 1.542)	0.829	–	–
< 20.5	150			
≥ 20.5	33			

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Factors	Univariate		Multiple regression	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
ALT level (U/L)	0.936 (0.640, 1.368)	0.731	–	–
< 40	89			
≥ 40	94			
AST level (U/L)	0.893 (0.596, 1.336)	0.581	–	–
< 40	60			
≥ 40	123			
Platelet count (10 ⁹)	0.868 (0.592, 1.271)	0.466	–	–
< 100	99			
≥ 100	84			
Prothrombin time international normalized ratio	1.022 (0.682, 1.532)	0.915	–	–
< 1.1	117			
≥ 1.1	66			
Procedure session	1.877 (1.010, 3.488)	0.046	–	–
1	162			
> 1	21			
Child–Pugh score	1.345 (0.493, 3.665)	0.563	–	–
A	175			
B	8			
ALBI grade	1.398 (0.950, 2.058)	0.089	–	–
1	95			
2, 3	88			

Data in parentheses are 95% confidence intervals. ALBI, albumin- bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase.

(HR = 1.512; *P* = 0.046), adjacent large vessels (HR = 0.154; *P* = 0.046), α -fetoprotein level (HR = 1.884, *P* = 0.002), DAA therapy (HR = 1.413; *P* = 0.003) and procedure session (HR = 1.877; *P* = 0.046) (**Table 4**). The multivariate analysis showed that the factors that significantly affected the RFS rate were age (HR = 0.548; *P* = 0.003), α -fetoprotein level (HR = 1.760; *P* = 0.002) and DAA therapy (HR = 0.392; *P* = 0.023) (**Table 4**).

Construction and validation of the nomogram

The nomogram was constructed by using β -coefficients to determine the proportional prognostic effect of the seven independent risk factors to assess their association with OS in the multivariate analysis. Each enrolled patient received one individualized grade, which was the sum of the points from

these seven prognostic variables. The projections from the total points (range, 0–260) shown on the scales in **Figure 2** indicated the estimated probability of OS at 1, 3 and 5 years. The concordance index for the model for assessment of RFS after MWA was 0.769 and with 1000 cycles of bootstrapping (95% CI: 0.699–0.839). The projections from the total points (range, 0–300) shown on the scales in **Figure 3** indicated the estimated probability of RFS at 1 and 3 years. The concordance index for the model for assessment of OS after MWA was 0.637 and with 1000 cycles of bootstrapping (95% CI: 0.582–0.692). Calibration curves plotted with a 1-, 3- and 5-year overall survival were ideal-matched with the idealized 45° line (**Figure 4**), and calibration curves plotted with a 1- and 3-year RFS were ideal-matched with the idealized 45° line (**Figure 5**).

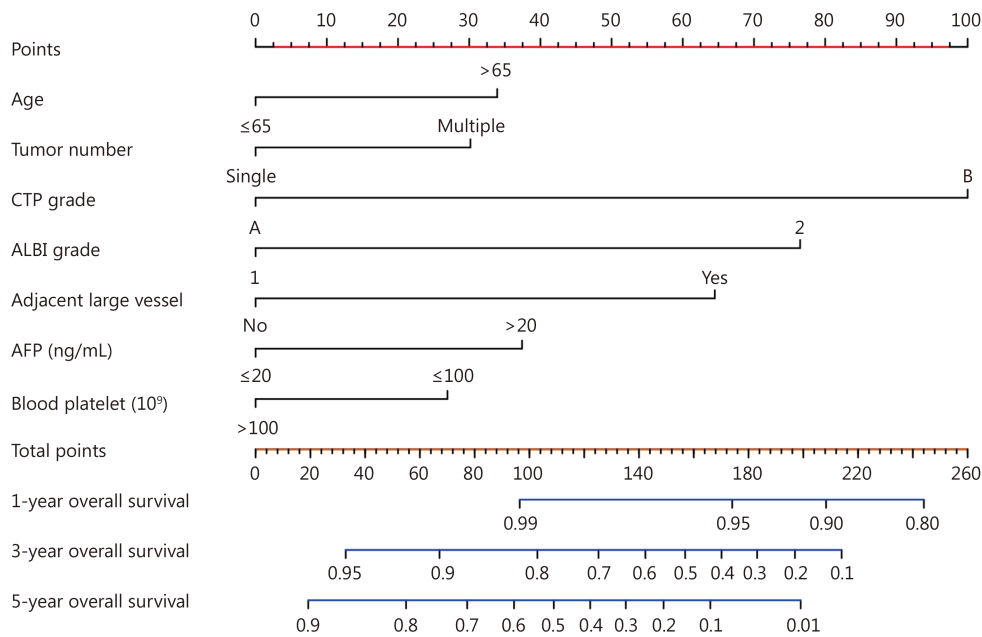


Figure 2 Nomogram shows the assessment of 1-, 3- and 5-year OS of patients with HCV-related HCC who underwent MWA.

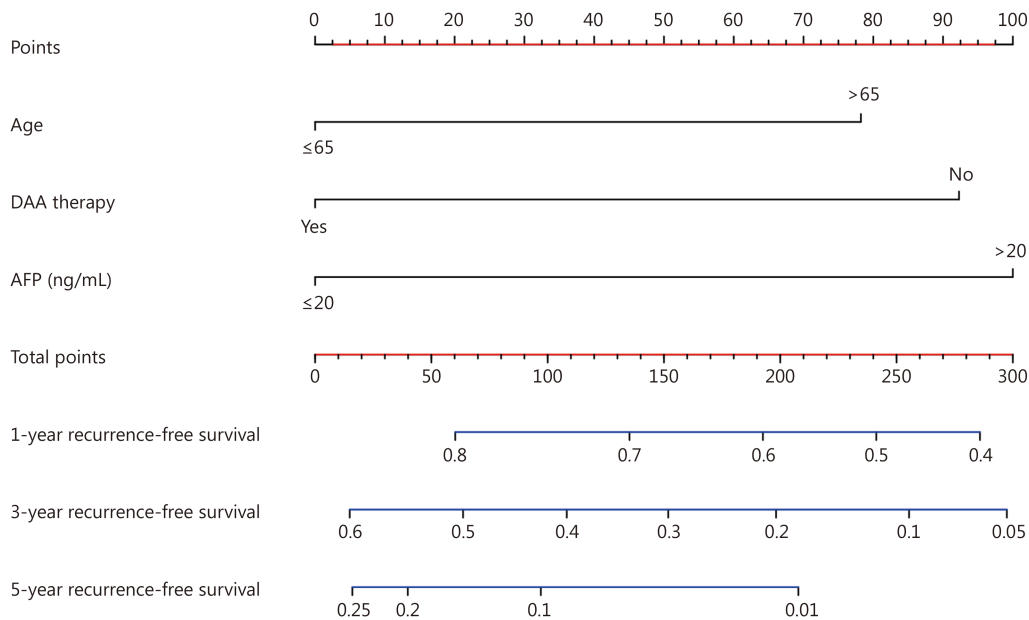


Figure 3 Nomogram shows the assessment of 1-, 3- and 5-year RFS of patients with HCV-related HCC who underwent MWA.

Comparison of markers for associations with OS after MWA

The prognostic performance of ALBI grade, CTP grade, BCLC grade, Model for End-Stage Liver Disease (MELD) grade, α -fetoprotein level, INR, platelet count, AST level and ALT level were evaluated with homogeneity and Akaike information criterion methods. **Table 5** shows that ALBI had

the highest homogeneity and lowest Akaike information criterion value compared with the other criteria.

Discussion

As a mature thermal ablation technology, MWA has been widely used in the treatment for liver malignancy in China. Previous studies have reported much data on MWA in HCC,

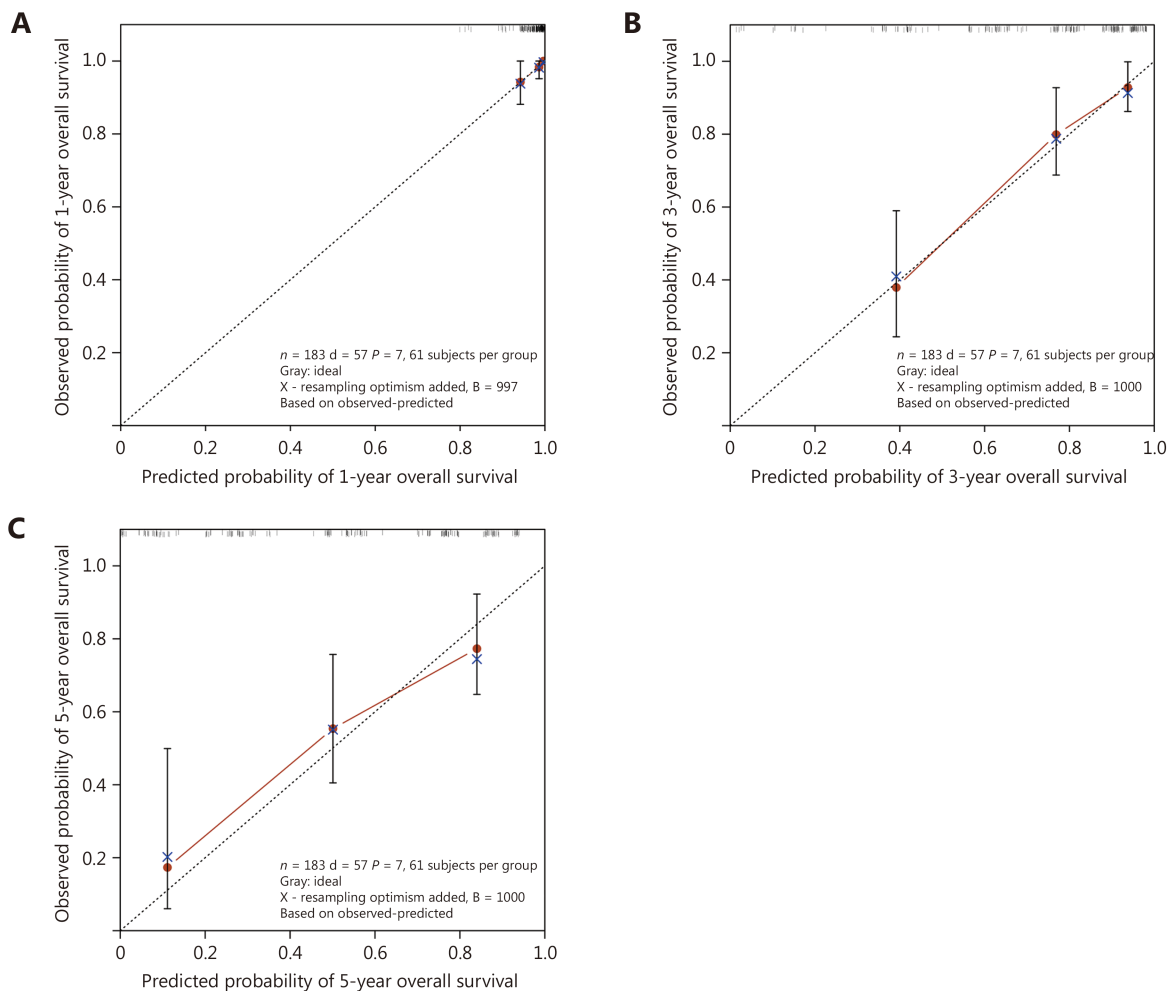


Figure 4 Calibration plot of the nomogram. Calibration curves of the nomogram at 1-year (A), 3-year (B) and 5-year (C) shows good correlation between assessed and observed OS. Calibration curves were close to 45° line.

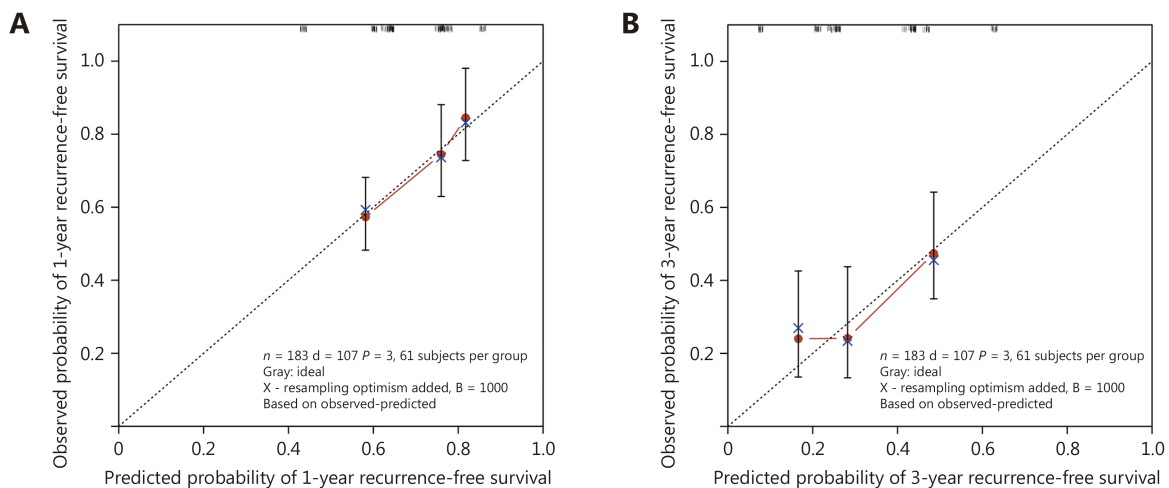


Figure 5 Calibration plot of the nomogram. Calibration curves of the nomogram at 1-year (A) and 3-year (B) shows good correlation between assessed and observed RFS. Calibration curves were close to 45° line.

Table 5 Assessment accuracy of biomarkers and clinical grade for overall survival after MWA

Biomarkers and clinical grade	Discriminatory ability	Homogeneity	Akaike information criterion
ALBI grade	21.237	50.198	2004.881
CTP grade	7.912	22.917	2108.912
Barcelona Clinic Liver Cancer grade	3.223	14.129	2356.781
Model for End-Stage Liver Disease grade	4.812	17.276	2219.023
α -fetoprotein level	11.339	19.281	2121.562
Prothrombin time international normalized ratio	1.012	10.027	2029.21
Platelet count	6.391	7.39	2019.781
AST level	5.123	3.019	2709.681
ALT level	6.812	3.291	2807.812

MWA, microwave ablation; ALBI, albumin- bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase.

but detailed analysis related to the patients with HCV-related HCC has not yet appeared. There were several innovation points in this study. First, patients with HCV-related HCC who underwent MWA were reported initially in the study, while many studies on HBV-related HCC after MWA were previously reported. The long-term outcome of 10-year survival was observed. Second, ALBI grade instead of CTP grade had been the most important criterion for evaluating liver function, which was associated with many advantages, such as being simple, objective and evidence-based. In this study, ALBI grade exhibited excellent discriminative ability for assessment of OS and RFS of patients with HCV-related HCC after MWA but was not applicable to assessment of tumour recurrence. Third, we applied nomograms as prognostic devices in the death of patients with HCV-related HCC, from which a statistical prognostic model can be determined that generates a probability of a clinical event for a particular individual.

Yu et al.³² reported the largest series involving the use of MWA for HCC in a single institution and found that the 1-, 3- and 5-year cumulative survival rates were 93%, 72% and 51%, respectively. Patients with a single tumour, tumour size < 4 cm and Child A cirrhosis had a higher probability of long-term survival. There is a difference in prognosis between HBV-related HCC in previous studies and HCV-related HCC in this study. However, when we considered the differences in patient number, abutting major vessel or organ, liver functional reserve and preoperative treatment, it was not appropriate to compare our study results directly with those of previous studies. In addition, because the CTP grade has a certain subjectivity, we used ALBI grade as an alternative method for assessment of hepatic functional reserve. Many studies have demonstrated the important role

of liver function in the prognosis of HCC. Therefore, we divided the patients into two subgroups according to ALBI grade and compared OS and RFS between the two groups. The results demonstrated that the OS of the ALBI grade 1 group was higher than that of the ALBI grade 2 group, whereby the RFS of the patients had no statistically significant difference. This result suggests that hepatic functional reserve was critical for outcomes of patients with HCC. To further verify the reliability of ALBI grade, among the biomarkers related to OS after MWA, ALBI grade has estimated capability over other criteria according to discriminatory ability, homogeneity and Akaike information criterion, which was an important reference for the treatment of patients and assessment of their outcomes.

In this study, we identified the independent risk factors for OS and recurrence of patients with HCV-related HCC who underwent MWA. Older age, poor hepatic functional reserve (i.e., ALBI grade and CTP grade) and tumour factors (i.e., tumour size, tumour number and α -fetoprotein levels), more treatment sessions and adjacent large vessels were associated with poorer OS, and without DAA therapy, high α -fetoprotein levels and older age were associated with a higher recurrence rate after MWA, which was consistent with the results of previous studies³³. Among the risk factors, patients older than 65 years with high α -fetoprotein levels need to prompt the vigilance of the physician. Based on these risk factors, we constructed a nomogram related to individualized risk estimations for OS of patients who underwent MWA for HCV-related HCC. This nomogram demonstrated a high discriminatory ability with an ideal concordance index of 0.769. Moreover, three calibration curves were used to retest and showed an ideal level of accuracy and better net benefit for the prediction of 1-, 3- and 5-year OS. In addition,

another nomogram demonstrated a lower discriminatory ability with a concordance index of 0.637 in RFS. Depending on the nomogram derived from preoperative clinical variables to assess prognosis for individual patients with HCV-related HCC after MWA, interventional radiologists can easily explain the risk of the operation to the patient's family and set up a detailed treatment schema.

There were several limitations in our study. First, this is a single-center retrospective study with a relatively small sample. Limited sample size might have reduced statistical power in comparative analysis so that some associations were not detected. Second, all of the patients in our cohort were treated at one medical center, therefore referral bias could not be completely avoided. Multi-center prospective study of the application is needed to validate the prognostic accuracy. Final, robust nomogram should be validated externally in different patient cohorts such as patients with HBV-related HCC.

Conclusions

In conclusion, the long-term outcomes of HCV-related HCC patients after MWA were encouraging. The nomogram with ALBI grade may provide prognostic value in 1-, 3- and 5-year RFS and OS for individual patients and was effective in assisting the physician with designing the treatment strategy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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