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Efficacy of Percutaneous Thermal Ablation Combined With Transarterial Embolization for Recurrent Hepatocellular Carcinoma After Hepatectomy and a Prognostic Nomogram to Predict Survival

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Abstract

Aim: This study aimed to evaluate the efficacy of percutaneous thermal ablation combined with transarterial embolization for recurrent hepatocellular carcinoma after hepatectomy and establish a prognostic nomogram to predict survival. **Methods:** One hundred seventeen patients with recurrent hepatocellular carcinoma receiving ablation from 2009 to 2014 were included in primary cohort to establish a prognostic nomogram. Between 2014 and 2016, 51 patients with recurrent hepatocellular carcinoma treated by ablation were enrolled in the validation cohort to validate the predictive accuracy of the nomogram. All patients underwent locoregional ablation. Overall survival was the primary end point, and progression-free survival was the second end point. The performance of the nomogram was assessed through concordance index and calibration curve and compared with 5 conventional hepatocellular carcinoma staging systems. **Results:** The 1-, 3-, and 5-year overall survival rates of primary cohort were 88.4%, 70.7%, and 64.1%, respectively. The 1-, 3-, and 5-year progression-free survival rates of primary cohort were 44%, 14%, and 8.7%, respectively. The results of multivariate analysis showed that tumor size ($P = .0469$; hazard ratio, 1.020; 95% confidence interval, 1.0004-1.040), preoperative extrahepatic disease ($P = .0675$; hazard ratio, 2.604; 95% confidence interval, 0.933-7.264), and close to hepatic hilum <2 cm ($P = .0053$; hazard ratio, 3.691; 95% confidence interval, 1.474-9.240) were predictive factors for overall survival. The study established a nomogram to predict survival (concordance index, 0.752; 95% confidence interval, 0.656-0.849). According to the predicted overall survival, patients with recurrent hepatocellular carcinoma were divided into 3 risk classes ($P < .05$): low-risk group (total score <55; predicted 5-year overall survival rate, 82.9%), intermediate-risk group ($55 \leq$ total score < 99; predicted 5-year overall survival rate, 52.8%), and high-risk group (hazard ratio, total score $\geq$99; predicted 5-year overall survival rate, not available). **Conclusion:** Percutaneous thermal ablation appears to be an effective procedure for the treatment of recurrent hepatocellular carcinoma after hepatectomy. The proposed nomogram provides a mechanism to accurately predict survival and could stratify risk among patients with recurrent hepatocellular carcinoma treated by ablation therapy.

Keywords

recurrent hepatocellular carcinoma, hepatectomy, HCC, percutaneous thermal ablation, nomogram

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Abbreviations

AFP, α-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; EHD, extrahepatic disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HH, hepatic hilum; HR, hazard ratio; LT, liver transplantation; MWA, microwave ablation; NA, not available; PFS, progression-free survival; OS, overall survival; PEI, percutaneous ethanol injection; rHCC, recurrent HCC; RFA, radiofrequency ablation; RR, re-resection; SBRT, stereotactic body radiotherapy; TAE, transcatheter embolization; TNM, tumor–lymph node–metastasis

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm and the third cause of cancer death worldwide.[1] Hepatectomy and liver transplantation (LT) are curative surgical treatment modalities for HCC. However, the 5-year HCC recurrence rate after hepatectomy is as higher as 70%[2,3] given the underlying liver diseases, such as chronic hepatitis and cirrhosis. Liver transplantation is considered the most effective option to prevent intrahepatic recurrence, but the recurrence rate is up to 15%.[4-6] Accordingly, how to effectively treat recurrent HCC (rHCC) after resection or LT has assumed greater importance. Re-resection (RR), ablation therapies, transarterial chemoembolization (TACE), and radiotherapy, for example, are reported to show improved clinical outcomes for primary HCC or rHCC. Re-resection improves survival outcomes of isolated recurrent nodule,[7-10] whereas its application can be limited by inadequate functional residual liver tissue and multiple recurrent nodules. Transarterial chemoembolization, for which the rationale is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels will result in a strong cytotoxic and ischemic effect, is considered the first choice for patients with HCC at intermediate stage. However, it shows less effect on preventing new recurrence or distant recurrence.[11-13] Stereotactic body radiotherapy (SBRT) can ablate the target lesion while sparing surrounding normal tissues. It should be noted that the application of SBRT for HCC was limited in patients with solitary nodule.[14] Radiotherapeutic microspheres can deliver high-dose radiation to HCC nodules while sparing the normal liver tissue. Its application has been supported by growing evidence for the treatment of intermediate or advanced HCC. However, a clinical trial comparing the efficacy and safety between selective internal radiotherapy with yttrium-90 resin microspheres and sorafenib in locally advanced and inoperable HCC (SARAH trial) finds that radiotherapy with microspheres is not superior to sorafenib.[15]

Percutaneous ablation, such as radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), and cryoablation, has been considered a safe and applicable means for liver cancer.[16-18] Percutaneous ethanol injection can induce coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. However, intertumoral fibrotic septa or tumor capsule can inhibit the ethanol diffusion and lead to incomplete ablation. A previous meta-analysis illustrated that cryoablation, which induced cytotoxicity by low temperatures, was not superior to RFA.[19] Both RFA and MWA are widely used minimally invasive techniques for the treatment of HCC. The rate of complete necrosis after RFA for HCC smaller than 2 cm in size could be up to 100%, and the 5-year survival rate provided by ablation is comparable to those by hepatectomy.[1] For medium (3-5 cm in diameter) and large (>5 cm in diameter) HCC, some researchers have believed ablation to be a promising technique to prolong survival.[20,21] According to previous clinical evidence and our experience, most rHCCs are small nodules.[22,23] Therefore, percutaneous thermal ablation tends to be a potentially promising therapy for rHCC with a high safety profile.

To our knowledge, the most common staging systems for primary liver tumor include the Barcelona Clinic Liver Cancer (BCLC) staging system[24,25] and tumor–lymph node–metastasis (TNM) classification system.[26] Okuda stage has been used in Japan, but it is limited in discriminating the early-stage and advanced-stage tumors distinctly.[27] Cancer of the Liver Italian Program (CLIP)[28] and the Chinese University Prognostic Index (CUPI) score[29] attempt to address the issue; however, there is no unanimity of opinion regarding their stratified accuracy. These staging classifications are probably to stratify primary patients with HCC and predict survival, but the predictive accuracy and stratified ability for rHCC have not been proved yet. Currently, many investigators have compared nomogram with traditional staging systems for HCC.[30-32] Moreover, a well-established nomogram is helpful to predict overall survival (OS) rate or recurrence rate for patients with rHCC treated by RR[33] or LT.[34]

In the current study, we aimed to evaluate the efficacy of percutaneous thermal ablation for rHCC after hepatectomy and establish a pragmatic staging system to predict the OS in patients with rHCCs.

Materials and Methods

Patients and Study Design

This retrospective study was performed at a single institution with approval from institutional ethics committee, and written informed consent was obtained before treatment.

In total, 237 consecutive patients with intrahepatic rHCC were treated by percutaneous thermal ablation between March 2009 and July 2016. Sixty-nine patients were excluded due to lost to follow-up. The remaining 168 patients with 457 recurrent nodules were included into the current retrospective study.

The inclusion criteria presented as follows: (1) The hepatectomy was defined as complete resection before tumor recurrence. (2) The diagnosis of HCC was confirmed based on the guidelines of the American Association for the Study of Liver Diseases[35] or by needle biopsy. The diagnoses of liver cirrhosis and portal hypertension were confirmed by medical history, clinical manifestations, clinical examinations, pathological findings, and/or radiological findings. (3) Preserved liver function was Child-Pugh A or B, prothrombin time ratio of more than 50%, and platelet count of more than $50^{\circ}000/mm^3$ (50×10^9/L). (4) Patients were not eligible for repeat hepatectomy because of inadequate hepatic functional parameters, such as an indocyanine green retention value, bilirubin level, portal hypertension, and ascites, and extrahepatic comorbidities. Furthermore, patients who refused surgical treatments or those who were waiting for transplantation with unpredictable time were included. (5) Eastern Cooperative Oncology Group status 0-2.

The management of eligible patients was best discussed in a multidisciplinary group that recognized the importance of liver function, as well as patient and tumor characteristics, and was decided eventually based on patients' willingness. One hundred seventeen patients receiving ablation from 2009 to 2014 were included in primary cohort to establish a prognostic nomogram. Between 2014 and 2016, 51 patients with rHCC treated with ablation were enrolled in the validation cohort to validate the predictive accuracy of the proposed nomogram.

Ablation Equipment

The RFA system (RITA Medical Systems, Mountain View, California) and MWA system (FORSEA MTC-3CA; Qinghai Microwave Electronic Institute, Nanjing, China) were used in the current study. The radiofrequency generator with 46 kHz provided maximum output power of 200 W. The MWA was performed with a frequency of 2450 MHz and an output power of 0 to 120 W. The modality of imagine guidance was 16-slice computed tomography (CT) scanner (Aquililion; Toshiba Medical Co, Tokyo, Japan).

Preoperative Preparation

In this study, bland transcatheter embolization (TAE) was performed before RFA to evaluate tumor burden and vascularity. Furthermore, preoperative TAE was helpful to increase the detection rate of HCC and find satellite lesions. Tumor-feeding arteries were embolized by 4 to 10 mL lipiodol (Huaihai Pharmaceutical Factory, Shanghai, China). The RFA or MWA was performed within 2 weeks after TAE. One hundred fifty-eight patients received TAE in the study.

Ablation Procedure

The RFA or MWA was performed in the study based on the characteristics of target lesion. For large rHCC or a lesion with proximity to large vessel, MWA was a viable choice; RFA was considered a preferable technique for rHCC abutting digestive tract, diaphragm, or gallbladder. Procedures were performed by 2 radiologists specializing in liver ablation (experience more than 5 years). Patients in an appropriate position (prone, supine, or lateral decubitus position according to tumor location) were under local anesthesia with 1% lidocaine. Vital signs were continuously monitored during and for 24 hours following the procedure. Under the guidance of CT, an appropriate approach of antenna/electrode insertion was determined. A 22-G needle was advanced into the target lesion and was used to lead antenna/electrode to the target. Single session of ablation was performed for recurrent lesion less than 2 cm, while multipoint overlapping ablations were carried out for recurrent nodules more than 2 cm. Repeat CT scan to confirm the right position of antenna/electrode. Remove the antenna/electrode while the track had been ablated with the intention of avoiding tumor seeding along the electrode route. Postprocedural contrast-enhanced CT scanning was performed to access tumor response and treatment-related complications.

Assessment of Therapeutic Efficacy

The primary end point was OS. The second end point was progression-free survival (PFS). Overall survival was defined as the interval between the initial ablation and death or the last time of follow-up. Progression-free survival was defined as the time elapse from the first ablation to first postablation intrahepatic HCC recurrence. Complete tumor ablation was defined as a hypoattenuating zone surrounded with an ablative margin with 0.5 to 1.0 cm in diameter, and no enhancement was detected during arterial and portal venous phase. If hypervascularization in arterial phase was found, it was assessed as residual tumor and incomplete ablation.

Complications were classified based on the Society of Interventional Radiology classifications.[36] Major complication was defined as the event which prolonged the hospital stay, or substantially increased the mortality and/or disability. Other complications were identified as minor complications.

Follow-Up

For assessing the response of RFA and complications, contrast-enhanced CT or contrast-enhanced magnetic resonance imaging and laboratory tests including serum α-fetoprotein (AFP), liver function tests, blood biochemistry tests, and blood coagulation tests were performed on the day following treatment, at 1 month from initial discharge, every 3 months during the first years, and every 6 months thereafter.

Table 1. Demographics and Characteristics of Primary Cohort and Validation Cohort With Intrahepatic Recurrent HCC.

Demographics and Characteristics	Primary Cohort, n = 117	Validation Cohort, n = 51	*P* Value
Categorical variables			
Gender			.193
Male	103	41	
Female	14	10	
Liver cirrhosis			.525
No	59	23	
Yes	58	28	
HBsAg (serum)			.798
Negative	18	8	
Positive	99	43	
HBeAg (serum)			.626
Negative	87	41	
Positive	30	10	
Preoperative TAE			.752
No	6	4	
Yes	111	47	
Close to HH <2 cm			.822
No	77	32	
Yes	40	18	
Tumor margin			.877
Regular	93	40	
Irregular	24	11	
Residual tumor tissue ≥30%			.054
No	11	0	
Yes	106	51	
Portal hypertension			.200
No	83	41	
Yes	34	10	
Vascular invasion			.072
No	103	50	
Yes	14	1	
Satellite lesions			1.000
No	112	49	
Yes	5	2	
Preoperative EHD			.106
No	98	45	
Yes	18	3	
Ascites			1.000
No	108	47	
Yes	9	4	
Lymph node metastasis			.407
No	105	46	
Yes	11	2	
Major complications			.933
No	111	50	
Yes	2	1	
Child-Pugh			.578
A	108	45	
B	9	6	
Continuous variables			
Age, years, median (range)	53.88 (25-82)	56.8 (37-73)	.138
ALT, U/L, median (range)	27.57 (2-280)	32.79 (8-147)	.652
AST, U/L, median (range)	28.8 (13-289)	29.2 (11-102)	.598
TBIL, μmol/L, median (range)	13.95 (4-57)	14.9 (5-55)	.148
Albumin, g/L, median (range)	40.8 (28-49)	41.8 (31-52)	.952
Prealbumin, g/L, median (range)	156.25 (14-285)	139.3 (41-279)	.354
GGT, U/L, median (range)	48.3 (12-769)	50.47 (16-280)	.959
PT, seconds, median (range)	11.63 (9-15)	11.15 (10-15)	.047
AFP, μg/L, median (range)	16.06 (1-12100)	13.49 (2-26990)	.912
CEA, μg/L, median (range)	2.38 (1-16)	2.93 (1-18)	.511
CA 19-9, U/mL, median (range)	18.63 (1-601)	17.57 (1-98)	.624
Number of rHCC, median (range)	1.9 (1-10)	1.82 (1-10)	.552
Max diameter of rHCC, mm, median (range)	22.33 (2-115)	22.8 (6-64)	.644

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, γ-glutamyl transferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; EHD, extrahepatic disease; HH, hepatic hilum; rHCC, recurrent hepatocellular carcinoma; PT, prothrombin time; TAE, transcatheter embolization; TBIL, total bilirubin.

Categorization of Patients in Current Prognostic Staging Systems

Five conventional classification systems, including BCLC staging system, TNM classification system, Okuda stage, CLIP, and CUPI score, were introduced to predict survival and compare with the proposed nomogram.

Statistical Analysis

Data were analyzed using SPSS 17.0 for Windows. Chi-square test or Fisher exact test was used to compare the categorical variables between the primary cohort and the validation cohort, and *t* test or Mann-Whitney *U* test was used to compare the differences of continuous variables. Survival time was calculated using Kaplan-Meier method and compared by log-rank test. Cox proportional hazards regression model was used for multiple analysis. The final Cox model was selected by bidirectional elimination process according to Akaike information criterion.

According to the results of Cox proportion hazard regression, a nomogram to predict OS was established by the package of *rms* in R version 3.3.1 (http://www.r-project.org/), and concordance index (C-index) was used to estimate the accuracy of the nomogram. The C-index was calculated by rcorrp.cens

Table 2. Univariate and Multivariate Analysis of Prognostic Factors for Primary Cohort.

Univariable	Number of Patients	75% OS (Months) Estimated or Hazard Ratio	*P* Value
Categorical variables and ranked data			
Gender			.32
Male	103	29.175	
Female	14	NR	
Liver cirrhosis			.931
No	59	32.69	
Yes	58	33.22	
HBsAg (serum)			.776
Negative	19	32.69	
Positive	88	35.08	
HBeAg (serum)			.96
Negative	87	32.69	
Positive	30	35.84	
Preoperative TAE			.565
No	6	NR	
Yes	111	33.22	
Tumor margin			.006
Regular	24	7.66	
Irregular	93	48.16	
Close to HH			.002
No	77	49.84	
Yes	40	17.906	
Residual tumor tissue ≥30%			.01
No	11	1.64	
Yes	106	35.09	
Portal hypertension			.532
No	83	35.844	
Yes	34	25.528	
Vascular invasion			.008
No	103	35.84	
Yes	14	7.2	
Satellite lesions			.053
No	112	35.09	
Yes	5	24.05	
Ablation margin			.102
>5 mm	21	NR	
≦5 mm	93	25.52	
Ascites			.565
No	108	33.21	
Yes	9	20.37	
Lymph node metastasis			.163
No	105	35.09	
Yes	11	7.66	
Preoperative EHD			.013
No	98	35.84	
Yes	18	7.66	
Continuous variables			
Age		0.999	.973
ALT		1.005	.187
AST		1.001	.753
TBIL		1.025	.214
Albumin		0.934	.127
PT		1.07	.664
AFP		1.000153	<.001
Number of tumors		1.118	.044
Max diameter of tumor		1.01	.001

(continued)

Table 2. (continued)

Univariable	Number of Patients	75% OS (Months) Estimated or Hazard Ratio	*P* Value
Multivariable	HR	95% CI	*P* Value
Close to HH <2 cm	3.691	1.474-9.240	.0053
Size of tumor (mm)	1.020	1.0004-1.040	.0469
Preoperative EHD	2.604	0.933-7.264	.0675

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; CI, confidence interval; EHD, extrahepatic disease; GGT, γ-glutamyl transferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HH, hepatic hilum; HR, hazard ratio; NR, not reached; OS, overall survival; PT, prothrombin time; TAE, transcatheter embolization; TBIL, total bilirubin.

package in Hmisc in R. It was used to compare the predictive accuracy between the nomogram and current staging systems. There was positive relation between C-index and prognostic accuracy (higher C-index indicates better predictive accuracy). Calibration curves were depicted to describe the concordance between actual survival and predicted outcome by nomogram. $P < .05$ was considered statistically significant.

We performed subgroup analysis based on the results of multivariate analysis and clinical experience. The subgroup analysis consisted of 18 variables: the max diameter of tumor (>2 cm or ≤2 cm), the sum of diameter of total rHCC (>3 cm or ≤3 cm), number of tumors (>2 or ≤2), ablation margin (<5 mm or ≥5 mm), tumor border (regular or irregular), vascular invasion (yes or no), preoperative TAE (yes or no), the level of γ-glutamyl transferase (>54 U/L or ≤54 U/L), and the level of AFP (<400 μg/L or ≥400 μg/L). The C-index was calculated to access predictive accuracy of the nomogram utilized in the above 18 groups.

Results

Patients Clinicopathologic Characteristics

In total, 117 and 51 patients were enrolled into the primary cohort and the validation cohort, respectively. There were 95 and 30 patients underwent RFA in primary cohort and validation cohort, respectively. There were 22 and 21 patients underwent MWA in primary cohort and validation cohort, respectively. Demographics and characteristics for the study population are shown in Table 1. There were 103 males and 14 females in primary cohort and 41 males and 10 females in validation cohort ($P = .193$). The median age in primary cohort and validation cohort was 53.88 years (range, 25-82 years) and 56.8 years (range, 37-73 years), respectively ($P = .138$). The difference of prothrombin time between the 2 cohorts was significant ($P < .05$), but both of them were within normal level. The primary cohort and validation cohort did not differ significantly in terms of the rest variables.

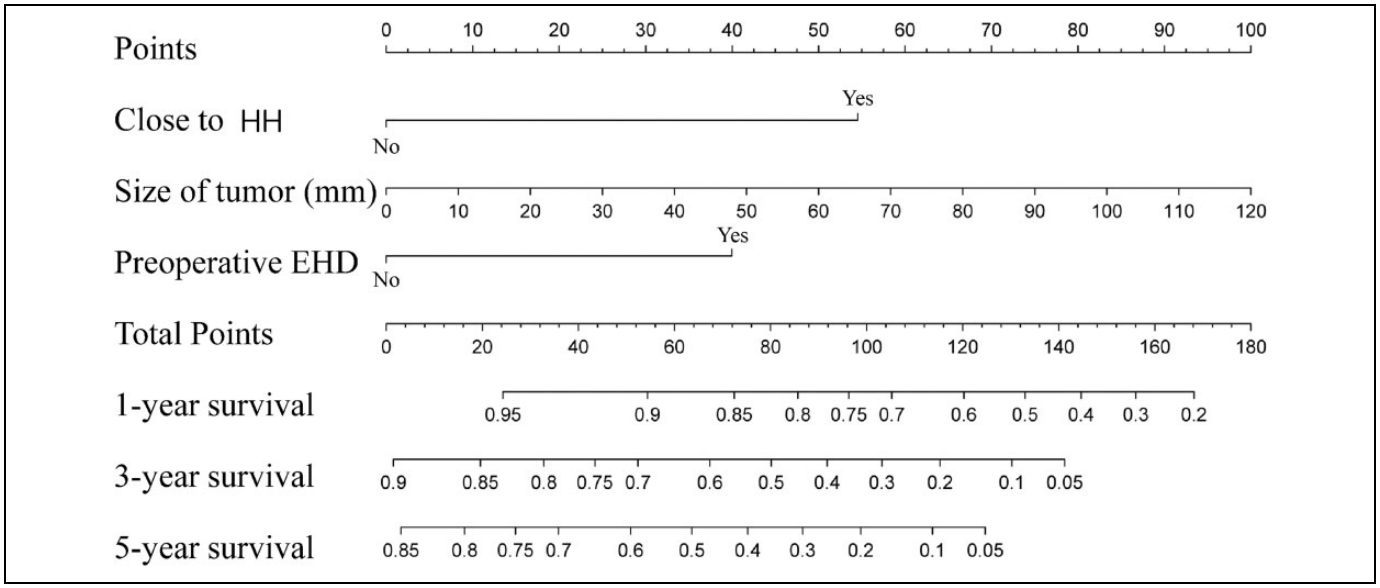

Figure 1. Recurrent hepatocellular carcinoma prognostic nomogram. (To use the nomogram, a patient's values are located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total point axis, and a line is drawn downward to the survival axes to determine the likelihood of 1-, 3-, and 5-year survival.) EHD indicates extrahepatic disease; HH, hepatic hilum.

Progression-Free Survival, OS, and Safety

The 1-, 3-, and 5-year OS rates of primary cohort were 88.4%, 70.7%, and 64.1%, respectively. In the validation cohort, the 1-, 3-, and 5-year OS rates were 85.8%, not available (NA), and NA, respectively. No significant difference concerning OS rate was observed ($P = .763$).

The 1-, 3-, and 5-year PFS rates were 44%, 14%, and 8.7%, respectively, in primary cohort, and 29.1%, NA, and NA in validation cohort, respectively. There was no significant difference concerning PFS rate ($P = .299$).

No perioperative death was found in the current study. Three patients (3/168, 1.79%) had major complications (all were severe infection) and were cured by anti-infective therapy. The median duration of hospitalization was 5.77 days (range, 2-35 days) in primary cohort and 5.94 days (range, 2-17 days) in validation cohort.

Univariate and Multivariate Analysis in the Primary cohort

The results of univariate and multivariate analysis are listed in Table 2. Univariate analysis of primary cohort showed that postoperative TAE, tumor margin, close to the HH <2.0 cm, residual tumor tissue ≥30%, vascular invasion, preoperative extrahepatic diseases (EHDs), the level of AFP, number of rHCC, and the max diameter of rHCC were significant factors for OS.

At multivariate analysis, predictors for OS included the following: close to HH <2.0 cm (hazard ratio [HR], 3.691; 95% confidence interval [CI], 1.474-9.240; $P = .0053$), the max diameter of rHCC (HR, 1.020; 95% CI, 1.0004-1.040; $P = .0469$), and preoperative EHD (HR, 2.604; 95% CI, 0.933-7.264; $P = .0675$).

Prognostic Nomogram for Patients in the Primary Cohort and Performance of Nomogram in Subgroups

Figure 1 showed the prognostic nomogram integrating all predictors of OS from multivariate analysis. The C-index was 0.752 (95% CI, 0.656-0.849), indicating a good performance of predicting OS for patients with rHCC. The calibration plot for survival probability at 1 and 3 years after ablation displayed an optimal agreement between the prediction by nomogram and actual observation (Figure 2A and B).

Close to HH <2.0 cm (yes, 55 points; no, 0 point), size of tumor (point: [100/120] × tumor size), and preoperative EHD (yes, 40 points; no, 0 point) constituted the proposed nomogram. A total point accumulated by the points of the 3 prognostic factors was used to predict the 1-, 3-, and 5-year OS rates. The total score of nomogram was divided into 3 classes: the low-risk group (total score <55), the intermediate-risk group (55 ≤ total score < 99), and the high-risk group (total score ≥99). The OS rates among the 3 degrees differed significantly ($P = .001$; Table 3).

The C-indices of the primary cohort nomogram in 18 subgroups ranging from 0.673 to 0.800 (Figure 3) indicated a promising predictive ability. Only 1 subgroup showed a C-index of 1.0 due to limited sample size (4 patients without preoperative TAE).

Comparison of Predictive Accuracy Between the Nomogram and Single Variable

The nomogram was more accurate than single independent factor on the basis of the calculated C-indices (nomogram, 0.752; max diameter of rHCC, 0.554; vascular invasion, 0.628; preoperative EHD 0.687), and all P value <.01.

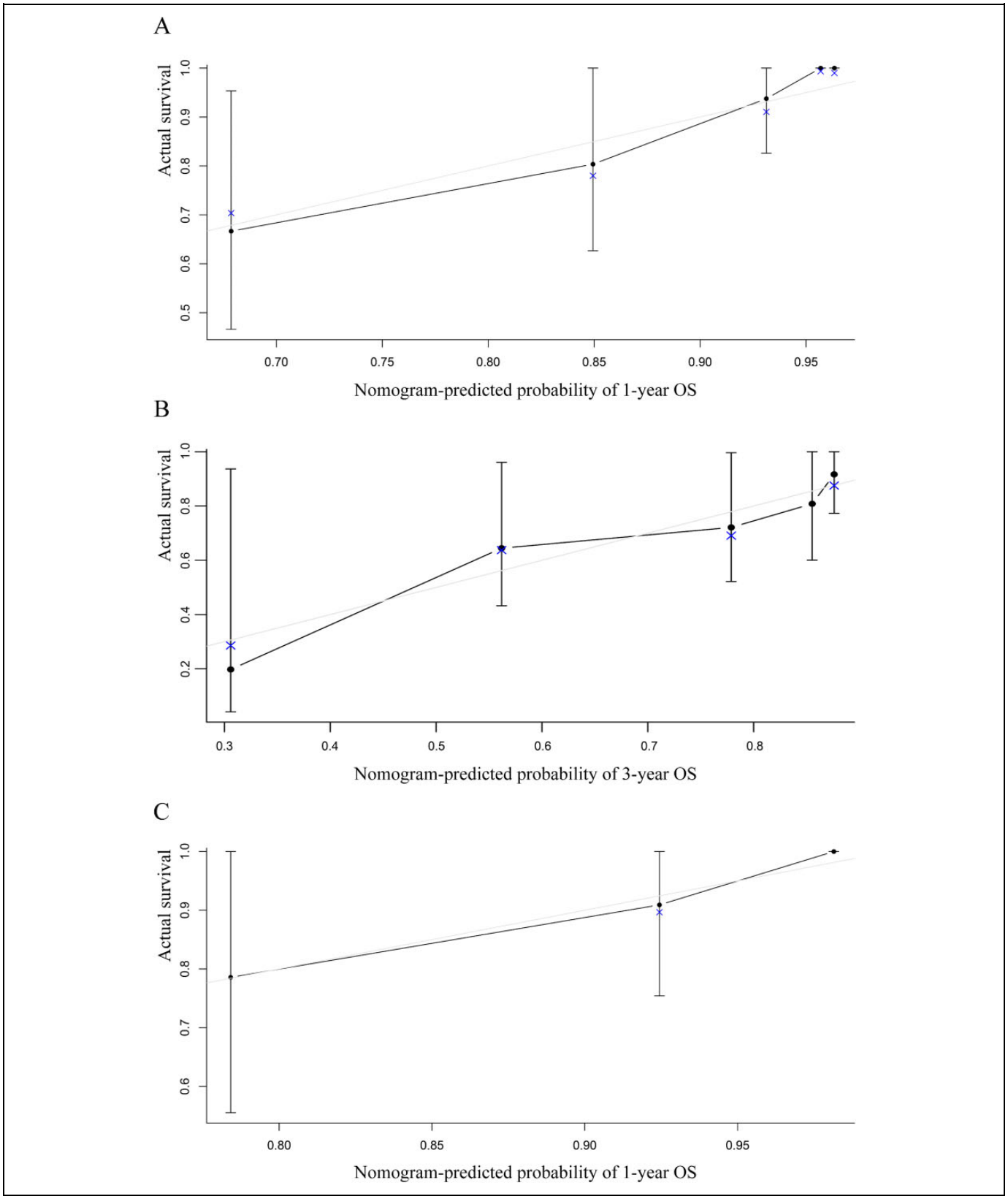

Figure 2. Recurrent hepatocellular carcinoma survival nomogram calibration curves. Nomogram-predicted overall survival is plotted on the *x* axis; actual overall survival is plotted on the *y* axis. A-B, One- and 3-year survival in the primary cohort. C, One-year survival in the validation cohort.

Table 3. Patient Survival by BCLC Stage, TNM Stage, Okuda Stage, CLIP Stage, CUPI Score, and Nomogram Stage of Primary Cohort.

	Number		OS (%)			
	Patient (%)	Death (%)	1-Year	3-Year	5-Year	*P*
BCLC stage						.296
0	13 (11.3)	3 (23.1)	92.3	92.3	73.8	
A	51 (44.3)	12 (23.5)	87.8	78.9	73.3	
B	28 (24.3)	5 (17.9)	100	79.2	47.5	
C	23 (20.0)	5 (21.7)	76.9	54.7	NR	
TNM stage						.592
I	40 (34.2)	10 (25.0)	86.4	82.1	73.9	
II	49 (41.9)	12 (24.5)	95.8	77.8	60.4	
IIIa	NR	NR	NR	NR	NR	
IIIb	5 (4.3)	1 (20.0)	50	NR	NR	
IIIc	NR	NR	NR	NR	NR	
IVa	4 (3.4)	0 (0.0)	100	NR	NR	
IVb	18 (15.4)	3 (16.7)	83.3	74.1	74.1	
Okuda stage						.823
I	102 (87.2)	24 (23.5)	88.9	79.0	65.2	
II	15 (12.8)	2 (13.3)	100.0	76.2	NR	
III	NR	NR	NR	NR	NR	
CLIP score						.334
1	38 (32.5)	10 (26.3)	85.8	85.8	77.2	
2	53 (45.3)	10 (18.9)	95.8	79.3	61.0	
3	18 (15.4)	5 (27.8)	78.4	61.8	NR	
4	5 (4.3)	1 (20.0)	100.0	66.7	NR	
5	1 (0.9)	0 (0.0)	NR	NR	NR	
6	NR	NR	NR	NR	NR	
CUPI score						.426
LR	114 (97.4)	26 (22.8)	89.9	78.4	65.6	
IR	3 (2.6)	0 (0.0)	100	NR	NR	
HR	NR	NR	NR	NR	NR	
Nomogram of PC						.001
LR	64 (87.5)	8 (12.5)	97.8	86.7	82.9	
IR	41 (70.7)	12 (29.3)	84.6	76.8	52.8	
HR	12 (50.0)	6 (50.0)	75.0	50.0	NR	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; HR, high risk; IR, intermediate risk; LR, low risk; NR, not reached; OS, overall survival; PC, primary cohort; TNM, tumor–lymph node–metastasis.

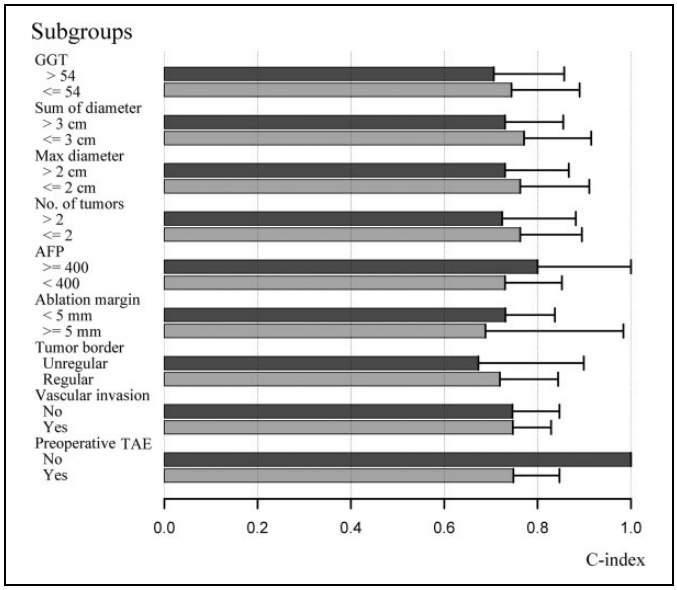

Figure 3. C-indices of the proposed nomogram in different subgroups in the primary cohort. The C-indices of the primary cohort nomogram in 18 subgroups ranging from 0.673 to 0.800. Only 1 subgroup showed a C-index of 1.0 due to limited sample size (4 patients without preoperative TAE). AFP indicates α-fetoprotein; C-index, concordance index; GGT, γ-glutamyl transferase; TAE, transcatheter embolization.

Comparison Between the Nomogram and Conventional Liver Cancer Staging Systems in Primary Cohort

The BCLC stage, TNM stage, CLIP score, Okuda stage, and CUPI score were included to compare with the proposed nomogram. As demonstrated in Table 3 and Figure 4, the BCLC stage (Figure 4A), TNM stage (Figure 4B), Okuda stage (Figure 4C), CLIP score (Figure 4D), and CUPI score (Figure 4E) were all unsatisfactory in stratifying patients with rHCC, and *P* values were .296, .592, .334, .823, and .426, respectively. However, the proposed nomogram showed a good performance in stratifying patients with rHCC through 3 risk grades ($P = .001$; Figure 4F).

The proposed nomogram presented better accuracy in predicting the OS for primary cohort: The C-index of nomogram (0.752) was higher than other staging systems (BCLC stage, 0.653; TNM stage, 0.662; Okuda stage, 0.538; CLIP score, 0.589; CUPI, 0.511; $P < .05$, for all; Figure 5).

Predictive Performance of the Nomogram for OS in the Validation Cohort

Fifty-one patients were contained in validation cohort. The C-index of validation cohort nomogram was 0.773 (95% CI, 0.582-0963), and the predictive ability of the nomogram was more accurate than the single independent factor of tumor diameter (C-index, 0.566; $P < .001$). The calibration curve for 1-year OS showed good concordance between the prediction and actual observation (Figure 2C).

Discussion

The treatment strategies and the stratification for rHCC are controversial. Re-resection, salvage liver transplantation, RFA, TACE, and sorafenib, for example, are considered alternative treatments with considerable clinical empirical supporting. Re-resection was suggested as an optimal choice for isolated recurrent nodule. The 5-year OS rate after RR was ranging from 37% to 70% without postoperative mortality.[7-10] However, for patients with inadequate functional residual liver tissue or multiple recurrent nodules, the application of RR was limited. According to the outcome of survival analysis of the current study, ablation therapy is comparable to RR with promising survival outcomes. Furthermore, not only the patients with solitary nodule but also those with multiple nodules, large rHCC, or vascular invasion could be treated by thermal

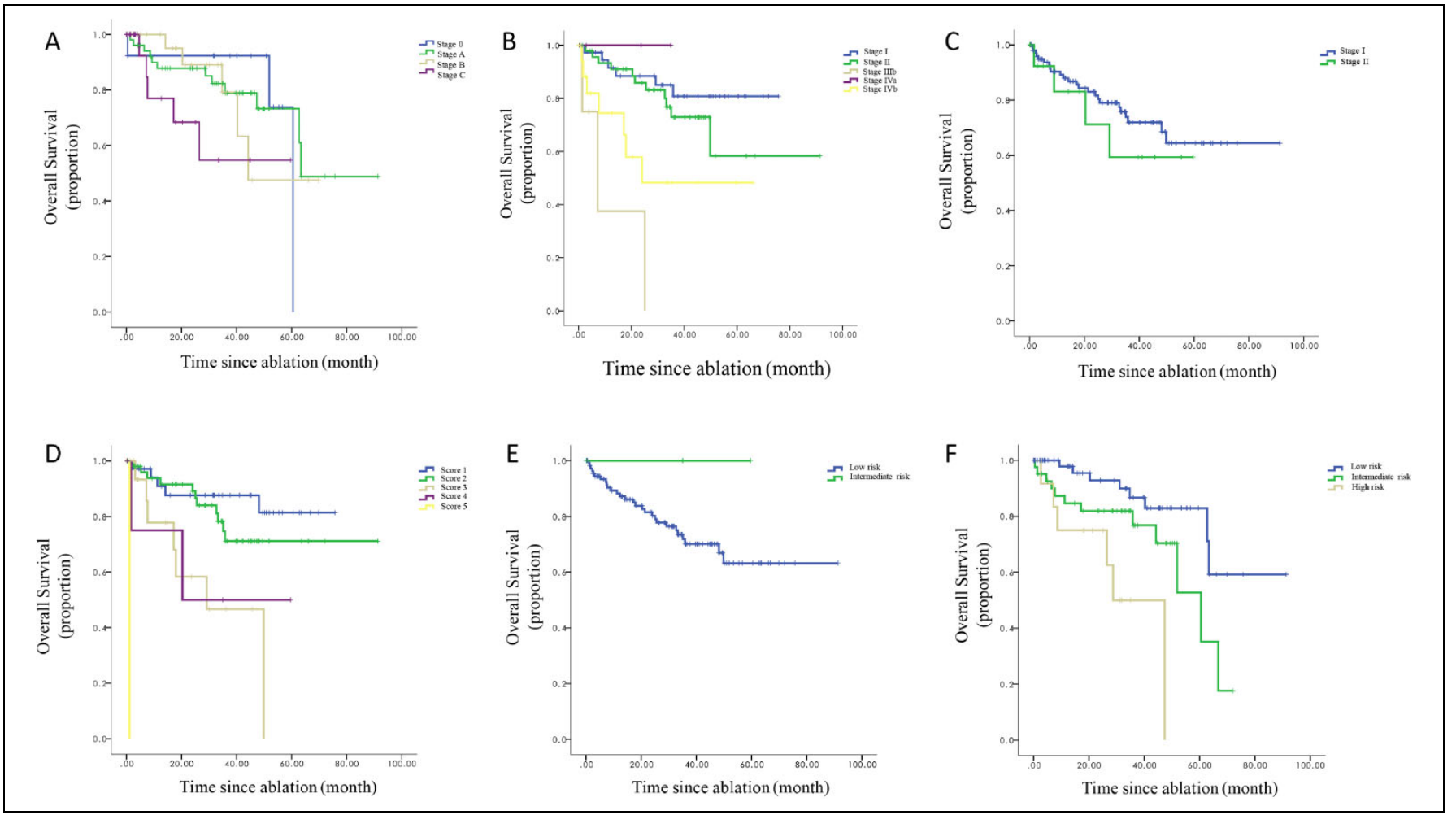

Figure 4. Kaplan-Meier estimates of overall survival: (A) The Barcelona Clinic Liver Cancer (BCLC) staging system ($P = .296$); (B) TNM classification system ($P = .592$); (C) Okuda stage ($P = .334$); (D) Cancer of the Liver Italian Program (CLIP; $P = .823$); (E) the Chinese University Prognostic Index (CUPI) score ($P = .426$); (F) the proposed nomogram ($P = .001$). The proposed nomogram showed a good performance in stratifying patients with recurrent HCC through 3 risk grades ($P = .001$).

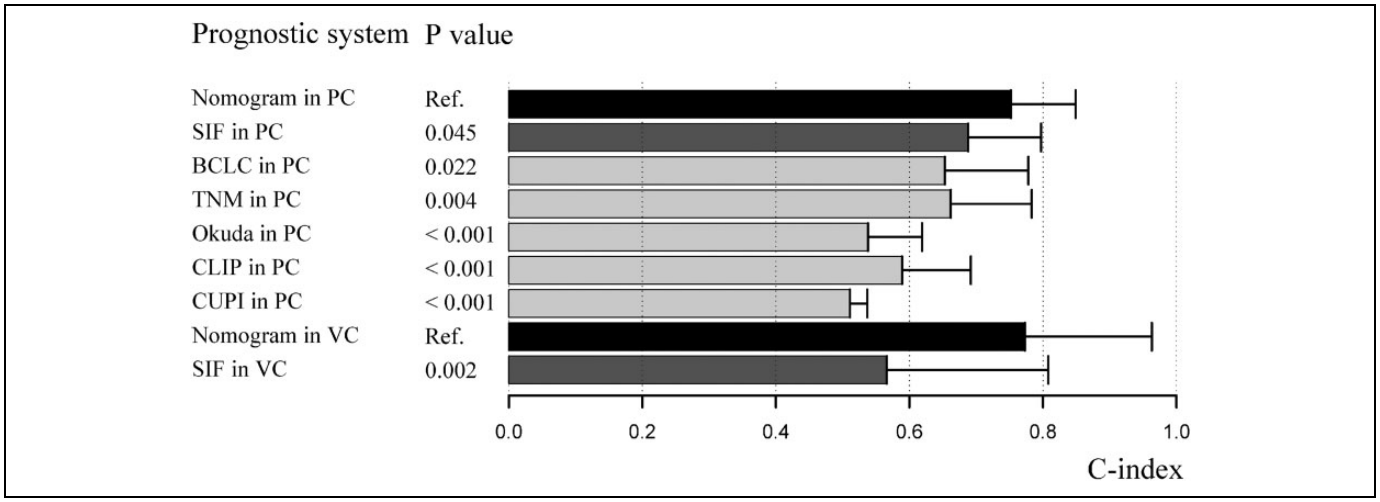

Figure 5. C-Indices of the proposed nomogram and the current prognostic systems for recurrent hepatocellular carcinoma. The C-index of nomogram (0.752) was higher than those of SIF (max diameter of tumor size, 0.687) and conventional staging systems (BCLC stage, 0.653; TNM stage 0.662; Okuda stage, 0.538; CLIP score, 0.589; CUPI, 0.511; *P*s < .05). BCLC indicates Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; PC, primary cohort; ref, reference; SIF, single independent factor (max diameter of rHCC); VC, validation cohort.

ablation with high safety profile. Indeed, in contrast to hepatectomy, patients with multiple nodules, large tumor, or vascular invasion could obtain more benefit from ablation than resection.[37-41]

Transarterial chemoembolization could treat patients with rHCC, but the repeat recurrence rate was as higher as 75% and 93% in 3- and 6-month follow-up, respectively. Thus, TACE might be a good approach to control the progression of macroscopic nodules, instead of preventing new recurrence.[11-13] Conversely, thermal ablation is recommended as a curative treatment for small HCC.[1,42] When RFA and TACE were used to treat rHCC, both the OS and PFS after RFA are higher than TACE alone.[42] In our study, 94.9% of patients in primary cohort underwent preoperative TAE. Hence, TAE combined with percutaneous thermal ablation for the treatment of rHCC might have some underlying effects on the clinical outcomes, and these effects need to be validated in further research.

The current study proposed an accurate nomogram which predicted the prognosis of patients after thermal ablation. Previous study has established a prognostic model[33] to predict clinical outcomes of RR for rHCC. The predictive ability was similar between our nomogram and the surgical prognostic model (C-index, 0.752 vs 0.77). In the proposed nomogram, 3 prognostic factors were involved, including the size of tumor, preoperative extrahepatic metastases, and close to HH <2.0 cm. Several published studies have reported tumor size to be an independent risk factor for patients with HCC or rHCC.[43-45] In the current study, target lesion with large tumor size predicted a poor prognosis. In addition, 2 cm was a cutoff value based on the findings of subgroup analysis. It should be noted that the C-indices were 0.730 and 0.763 in >2 cm group and ≤2 cm group, respectively. It is indicated that the predictive accuracy of the nomogram was more concordant with actual observation in rHCC ≤2 cm.

Second, tumor close to HH <2 cm was a significant risk factor for OS of patients with rHCC. A few reports have established nomogram to predict the survival of patients with rHCC[33,34]; however, the association between tumor site and survival remains unknown. Indeed, the influence of tumor site, especially closing to HH, has been discussed in many investigations. Tumor cell diffusion through portal vein could be an underlying origin of recurrence in follow-up period.[46] Furthermore, close to portal vein could enhance the "heat sink" effect and decrease ablation temperatures. Some reporters proposed that hepatic pedicle clamping minimized the risk of recurrence after curative resection.[47-49] We assumed that the distance between tumor location and HH may affect OS by certain mechanism. However, in this study, the variable was designed as a categorical variable instead of a continuous variable, and the underlying mechanism should be discussed in further trials.

Third, preoperative EHD before ablation may impact OS after ablation. The 75% survival time for 18 patients with EHD in primary cohort was 7.66 months and for patients without EHD was 35.84 months. A significant difference between the patients with EHD and individuals with un-EHD about accumulative OS was observed in univariate analysis ($P = .013$). In multivariate analysis, EHD was not an independent predictor for OS ($P = .0695$), but according to the clinical experience, preoperative EHD could induce poor survival. Although RFA was not the first choice for patients with intermediate- and advanced-stage HCC, its application had been reported by many established medical evidence. Some researchers reported that RFA and TACE were both efficient for unresectable HCC, but RFA could provide a better rate of tumor control and a short-term survival than TACE.[50] Besides, according to our previous clinical experience and investigations, RFA combined with TACE-treated patient with HCC with vascular invasion could provide a median survival time of 29.5 months,[51]

whereas the median survival time did not exceed 12 months after TACE, chemotherapy, and radiation.[52-54]

In order to validate the predictive accuracy and discriminative ability of the nomogram, we compared the proposed nomogram with 5 common staging/score systems. We calculated the C-indices of the BCLC stage, TNM stage, Okuda stage, CLIP score, CUPI score, and the nomogram. The nomogram with the highest C-index (0.752) presented a predictive accuracy and indicated that it was more concordant with the actual survival than conventional staging/score systems (Ps < .05). The predictive ability of the nomogram was supported by the calibration curves.

In this study, conventional staging systems were limited in stratifying patients with rHCC. The stratification classified by BCLC stage system had no effect on survival rate of patients with rHCC ($P = .296$), but the 75% survival of rHCC presented a declined tendency. Hence, the accuracy of stratified rHCC through BCLC stage system should be validated in further study. The proposed nomogram in this study showed a good ability to stratified rHCC. The total score of nomogram was divided into low, intermediate, and high risk. If a patient with rHCC with a total score <55, the survival after ablation is encouraging; conversely, if the score ≥90, the therapy of ablation would not be a proper choice for prolonging OS. One study found that a nomogram with accurate prediction could be helpful for monitoring in follow-up period, guiding treatment, and designing trials.[33] They built 2 nomograms (pre-RR and post-RR) with 6 predictions (tumor diameter on pathology and imaging, tumor number on pathology and imaging, time to recurrence after initial resection, hepatitis B virus [HBV]-DNA) and stratified the total score of nomogram into 4 quartiles, each quartile has 6 different cutoff score. This model was complex. The other conventional staging systems in this study may not be appropriate for stratifying rHCC.

There are several limitations in the current study. First, this is a single-center retrospective study, of which selection bias may exist. In the current study, many patients with rHCC had hepatitis B surface antigen and were noncirrhotic. In previous studies, the baseline characteristics of included population showed a prevalence of HBV of about 90%[55,56] and a rate of noncirrhosis ranging from 35.4% to 55.1%.[43,45,56,57] It should be noted that, in some area with high prevalence of HCV infection, such as Japan, the rate of patients with rHCC with HBV is only 19.6% to 20.6%.[58,59] This may be because of the differences in terms of the geographical distribution, genetics, ethnicity, and different chronic viral infection in patients with HCC. Hence, in our study, the prevalence of HBV (84.5%) and cirrhosis (51.2%) reflect the baseline characteristics of patients with rHCC in Eastern Asia, and a multicenter, randomized, controlled trial that enrolled variable ethnic groups from different countries is required to expand our findings. In the retrospective study, many patients underwent liver resection for primary HCC in other hospitals, and the histology outcomes of primary HCC were limited. Finally, the assessment of tumor response was evaluated based on imaging findings. A multicenter, randomized, controlled trial is required to analysis and pathological confirmation to further interpret these outcomes.

Conclusion

In conclusion, this study presented a preferable clinical outcome of percutaneous thermal ablation for the treatment of patients with rHCC after resection and established an intriguing prognostic nomogram for predicting survival. The proposed nomogram accurately predicted the survival of patients with rHCC, which was the first prognostic model for patients with rHCC treated by percutaneous thermal ablation, and the relative contribution of the nomogram should be validated in further study.

Authors' Note

This study was approved by the institutional review board of You'an Hospital Ethics Committee. Informed consent was obtained from all individual participants included in the study (approval number: Beijing Youan Hospital, Capital Medical University, Approval Certificate of Ethical Review [2017] No. 28).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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