Am J Cancer Res 2021;11(10):5126-5140
www.ajcr.us /ISSN:2156-6976/ajcr0136290

Original Article

A novel prognostic nomogram for hepatocellular carcinoma after thermal ablation

Qiang Tao[1,2*], Qingjing Zeng[3*], Wenwu Liu[2,4*], Jia Liu[5], Lingmin Jiang[1,2], Xinyue Tu[1,2], Kai Li[3], Peng Zhao[1,2], Xiang Tang[1,2], Zonghao Liu[1,2], Liang Wang[6], Qilin Xu[7], Yun Zheng[1,2]

[1]Department of Liver Surgery, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong, China; [2]State Key Laboratory of Oncology in South China and Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong, China; [3]Department of Ultrasound, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510635, Guangdong, China; [4]Department of Gastric Surgery, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong, China; [5]Department of Neurology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518000, Guangdong, China; [6]The First Department of General Surgery, The First People's Hospital of Kashi Prefecture, Kashi 844000, The Xinjiang Uygur Autonomous Region, China; [7]The Second Department of General Surgery, The First People's Hospital of Kashi Prefecture, Kashi 844000, The Xinjiang Uygur Autonomous Region, China. [*]Equal contributors.

Received June 11, 2021; Accepted August 31, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: It remains impossible to accurately assess the prognosis after thermal ablation in patients with hepatocellular carcinoma (HCC). Our aim was to build a nomogram to predict the survival rate of HCC patients after thermal ablation. We developed and validated a nomogram using data of 959 HCC patients after thermal ablation from two centers. Harrell's concordance index (C-index), calibration plot and Decision curve analysis (DCA) were used to measure the performance of the nomogram, and we compared it with the Barcelona Clinic Liver Cancer (BCLC) staging system and a previous nomogram. Six variables including age, serum albumin, operation method, risk area, tumor number and early recurrence were selected to construct the nomogram. In the training cohort, internal validation cohort, and external validation cohort, the nomogram all had a higher C-index to predict survival rate than both the BCLC staging system and the previous nomogram (0.736, 0.558 and 0.698, respectively; 0.763, 0.621 and 0.740, respectively; and 0.825, 0.551 and 0.737, respectively). Calibration plots showed a high degree of consistency between prediction and actual observation. Decision curve analysis (DCA) presented that compared with BCLC system and the previous nomogram, our nomogram had the highest net benefit. In all three cohorts, the nomogram could accurately divide patients into three subgroups according to predicted survival risk. A nomogram was developed and validated to predict survival of HCC patients who underwent thermal ablation, which is helpful for prognostic prediction and individual surveillance in clinical practice.

Keywords: Hepatocellular carcinoma, thermal ablation, nomogram, prognostic, BCLC

Introduction

Globally, hepatocellular carcinoma (HCC) turns out to be one of the most common malignancies, with a large number of patients dying every year [1]. The incidence and mortality of HCC have been emerging rapidly on the background of increased alcohol abuse, cirrhosis, aflatoxin exposure, diabetes, metabolic syndrome and obesity [2]. Hepatectomy and liver transplantation are potentially curative therapies, which are the preferred treatments for patients with HCC. However, due to various reasons, such as limited liver function reserves, insufficient organ donors, high complication rates resulting from surgery, and refusal of treatment, only a small percentage of patients qualify as candidates at the time of diagnosis [3]. In the past decade, thermal ablation, as one of the curative and standard therapies for early HCC, has been widely applied in clinical practice [4]. Nevertheless, a high postoperative recurrence rate is still the main factor influencing long-term prognosis [5].

We already have several staging or grading systems, including the Barcelona Clinic Liver Cancer (BCLC) staging system, which can be

used to predict survival as well as guide therapy choice in patients with HCC [6]. According to previous study, clinical outcomes vary widely even among patients at the same stage who receive similar treatment strategies. Therefore, these systems have significant limitations in predicting the outcome of patients receiving thermal ablation [7].

To date, nomograms have been established for predicting the prognosis of various tumors [8, 9]. They are also used to assess survival in HCC patients [10, 11]. However, only a few models are available to predict prognosis after thermal ablation of HCC. And also, these tools usually only focused on patients who received either radiofrequency ablation (RFA) or microwave ablation (MWA) [12, 13]. As RFA and MWA are the two most commonly used ablation treatments, it is necessary to develop a model to predict the prognosis of HCC treated by RFA and MWA at the same time for clinical convenience and accurate application. Furthermore, results of several previous studies showed that early recurrence after radical therapy related to invasive tumor features, including high alpha-fetoprotein (AFP), large tumor, microvascular invasion (MWI), and high albumin-bilirubin (ALBI) grade and usually led to poor survival in HCC patients [14, 15]. Few previous nomograms take the influence of early recurrence after thermal ablation on survival into account, which may result in poor prediction performance, especially for patients with recurrent HCC. In addition, tumors located in risk areas can affect the prognosis of HCC patients due to difficulty in the procedure of ablation and more complications [16, 17]. However, so far, no previous study has included the variable whether tumor located in risk area to develop nomogram. Hence, it is necessary to construct a nomogram based on ablation methods, early or late recurrence after ablation, whether tumor located in risk area and other individual risks to more accurately predict the outcome of HCC after thermal ablation. To build a nomogram, validation is a necessary process for obtaining unbiased estimates of model performance. As the gold standard, external validation should be performed whenever possible [18]. Unfortunately, most previous prognostic nomograms often report results with only internal validation.

In the present study, we established a nomogram of prognosis integrating ablation methods, early or late recurrence after ablation and whether tumor located in risk area using data of 565 HCC patients underwent thermal ablation from our center. Then the nomogram was internally validated using data of 240 patients from the same center and externally validated using data of 154 patients from another center.

Materials and methods

The study was approved by the institutional ethics committee of the participating institutions. We obtained written informed consent from all patients.

Patients and study design

All newly diagnosed HCC patients who received curative-intent thermal ablation at Sun Yat-sen University Cancer Center (SYSUCC) from January 2002 to January 2017 were identified. Initially, 856 consecutive patients entered in the study. Inclusion criteria as follows were used: (a) Complete ablation for primary HCC as mentioned in another study [19]; (b) Liver function of Child-Pugh class A or B; (c) No evidence of extrahepatic metastasis; (d) No history of other treatment for primary HCC both before and after thermal ablation alone or preoperative transcatheter arterial chemoembolization (PreTACE) combined thermal ablation; (e) No other tumor medical history. The following exclusion criteria were applied: (a) Major hepatic/and portal vein branch invasion; (b) Incomplete clinical data; (c) No imaging efficacy evaluation after ablation. Finally, 805 patients were identified. Then, we randomly divided these patients into a training cohort (n=565) and an independent internal validation cohort (n=240), with a ratio of 7:3. We included 227 patients who received ablation therapy in the Third Affiliated Hospital of Sun Yat-sen University (TAHSYSU) from December 2010 to December 2015 into our study for external verification. Among these patients, 154 patients entered our study by using the same exclusion and inclusion criteria, and served as an external validation cohort (n=154) (**Figure 1**).

We collected the following clinical data of patients, including age, gender, preoperative transcatheter arterial chemoembolization (pre-

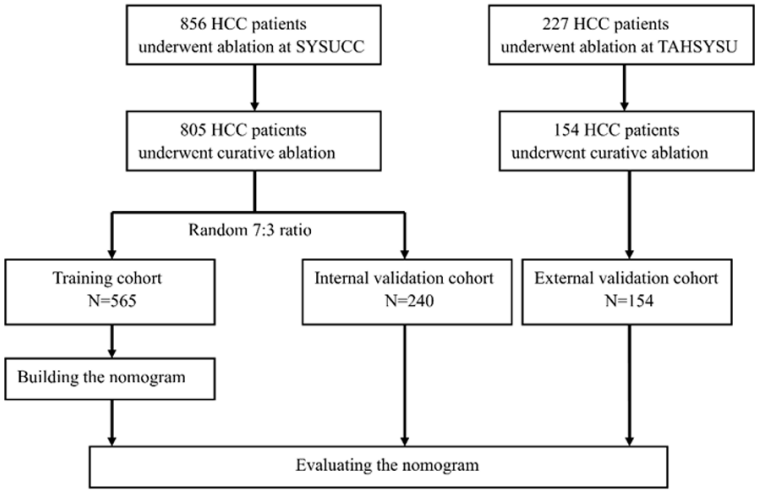

Figure 1. Flowchart.

TACE), operation methods, tumor number, tumor size, tumor location, alpha-fetoprotein (AFP), hemoglobin (Hb), white blood cell (WBC), red blood cell (RBC), platelet count (PLT), albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), albumin-bilirubin (ALBI) grade, Child-Pugh grade, liver function (0, ALBI grade 1 and Child-Pugh grade A; 1, ALBI grade 1 or Child-Pugh grade A; 2, ALBI grade 2 or 3 and Child-Pugh grade B), prothrombin time (PT), hepatitis (hepatitis B virus or hepatitis C virus), cirrhosis, risk area (A tumor located in risk areas was defined as one that was adjacent to the hepatic capsule, cavity viscera, large vessels or right or left bile duct less than 1 cm [20, 21]), BCLC stage, early recurrence (time from ablation to recurrence less than 12 months).

Diagnosis and ablation procedure

The diagnosis of HCC in most patients was according to the American Association for the Study of Liver Diseases (AASLD) clinical criteria [22], which had been confirmed by biopsy in a few patients.

Both RFA and MWA were operated by surgeons with no less than 15 years of operation experience. The choice of ablation method (RFA or MWA) was determined by the treating surgeon based on factors such as the availability of the device at that time. After intravenous anesthesia by an anesthetist, patients were performed ablation therapies under real-time ultrasound guidance. The details of ablation procedures were reported in our previous studies [23-25].

Follow-up and study endpoints

We recommended that all patients should receive follow-up regularly after ablation therapies. Patients were generally followed up for the first time about one month after treatment to assess the therapeutic effect, subsequently once every 3 to 6 months until death or loss of follow-up. A comprehensive physical examination and a detailed medical history record were carried out during each follow-up. We also performed serum AFP, routine blood tests, liver function tests as well as computed tomography (CT) or magnetic resonance imaging (MRI). If there were clinical indications, further investigation was performed. Overall survival (OS) rates were the primary endpoint of the study. Overall survival time was defined as the time elapsed between the time ablation was performed and the time of death or the last follow-up. We censored this research on January 1, 2019.

Statistical analysis

Student t-test or Mann-Whitney U-test was used to compare continuous variables. Chi-square test or Fisher exact test was used to compare binary categorical variables, and Kruskal-Wallis test was used to compare ordinal variables. The Kaplan-Meier method was used to construct survival curves, and the comparison was made by log-rank test. We converted categorical variables from continuous variables by optimal cut points which were selected based on clinical reference values, judgments of clinical experts, and the statistics results of the maximum selected rank from "maxstat" R package. A nomogram was developed with "rms" R package based on the results of multivariate as well as univariate analyses. In univariate analyses, the variables with *P* values less than 0.10 were selected into the multivariate Cox proportional hazard model.

The variables entered into the final model were selected based on *P* values less than 0.10 in multivariate analyses. To assess the discrimination performance of the nomogram, we applied the Harrell's concordance index (C-index) resulted from comparing the actual observed survival probability with that nomogram-predicted. Decision curve analysis (DCA) was performed by using the source file "stdca.R" to evaluate the clinical utility and net benefit of this model. The Kaplan-Meier curves of three subgroups divided by predictions were also used to assess the discrimination performance of the nomogram. We assessed the nomogram calibration with calibration plots. In validation cohorts, C-index, calibration plot as well as Kaplan-Meier curve of the tertile of predictions were obtained based on the developed nomogram. Comparisons of C-index of the nomogram, the previous nomogram and the BCLC staging system were carried out by rcorrp.cens in Hmisc R package. During these activities, bootstraps with 1000 resample were used [26, 27]. All statistical analyses were carried out with R software (version 4.0.3, http://cran.r-project.org/). For all statistical tests, P less than 0.05 was regarded as with statistical significance.

Results

Basic characteristics

The clinicopathologic features of patients in the three cohorts are presented in **Table 1**. In patients from SYSUCC, this study enrolled 805 patients who accepted curative thermal ablation for primary HCC. For these patients, the median follow-up time was 50.6 months. All 805 patients were stochastically separated into a training cohort (n=565) and an internal validation cohort (n=240), with a ratio of 7:3. For the training cohort, the median follow-up time was 40.7 months, and it was 56.0 months for the internal validation cohort. The 3-, and 5-year overall survival rates were 82.2% and 68.3%, respectively, for the training cohort and 97.5% and 80.7% for the internal validation cohort. Finally, 154 out of 227 patients from TAHSYSU were identified as an independent external validation cohort, with a median follow-up time of 72.2 months. The 3-, and 5-year overall survival rates of the external validation cohort were 94.1% and 89.8%, respectively.

Development of the prognostic nomogram

First of all, we made univariate analyses in the training cohort. After univariate analyses, fourteen factors including age, operation method, tumor number, tumor size, Hb, PLT, RBC, WBC, ALB, AST, PT, risk area, early recurrence and liver function were selected to construct the initial model (all P<0.1) (**Table 2**). After selected by multivariate analyses, six factors with *P* value less than 0.1 including age, ALB, operation method, risk area, tumor number and early recurrence entered the final model (**Table 2**). We also plotted OS curves of patients in training cohort according to the six factors respectively and the results are presented in **Figure 2**. Finally, the six factors that entered the final model were used to construct a nomogram for predicting 3- and 5-year OS (**Figure 3**). The nomogram presents the predicted probabilities of each factor with points on a scale, the total points summed by all factors indicates the predicted OS of 3 years and 5 years for a patient.

The prognostic nomogram validation

In the training, internal validation, and external validation cohorts, the C-indexes of the nomogram for OS prediction were 0.736 (95% CI, 0.689 to 0.783), 0.763 (95% CI, 0.702 to 0.824), and 0.825 (95% CI, 0.735 to 0.915), respectively, which were superior to that of the BCLC staging system, the previous nomogram (Prenomogram) [28] and the nomogram without operation factor (Nomogram_op) (**Table 3**). The calibration plots for 3- and 5-year OS after thermal ablation demonstrated the best consistency between nomogram prediction and observation in the training cohort (**Figure 4A**, **4B**). The calibration plots for 5-year OS also presented optimal consistency between nomogram prediction and the actual observation in the two validation cohorts (**Figure 4C**, **4D**).

Decision curve analysis (DCA)

We analyzed the clinical usefulness of this nomogram by DCA. **Figure 5** presents the DCA for all 4 models including this nomogram, BCLC system, Prenomogram and Nomogram_op. As shown by the DCA, the net benefit of the nomogram was higher than that of treat none or treat all strategies for the threshold probability within a range of 0.1-0.5. Furthermore, when com-

Table 1. Clinicopathologic characteristics of patients in three cohorts

Variables*	Training cohort (N=565)	Internal validation cohort (N=240)	External validation cohort (N=154)
Age, y median (IQR)	56 (48, 64)	56 (47, 64)	54 (46, 59.8)
Gender, cases (%)			
female	65 (11.5)	18 (7.5)	27 (17.5)
male	500 (88.5)	222 (92.5)	127 (82.5)
PreTACE, cases (%)			
no	422 (74.7)	176 (73.3)	113 (73.4)
yes	143 (25.3)	64 (26.7)	41 (26.6)
Operation, cases (%)			
MWA	151 (26.7)	55 (22.9)	40 (26)
RFA	414 (73.3)	185 (77.1)	114 (74)
Tumor number, cases (%)			
solitary	448 (79.3)	190 (79.2)	117 (76)
mutiple	117 (20.7)	50 (20.8)	37 (24)
Tumor size, cm median (IQR)	2.4 (1.8, 3.2)	2.5 (1.9, 3.2)	2.2 (1.6, 2.8)
Tumor location, cases (%)[a]			
central	277 (49)	134 (55.8)	64 (41.6)
non-central	288 (51)	106 (44.2)	90 (58.4)
AFP, ng/mL median (IQR)	43.2 (5.6, 321.8)	39.2 (5.1, 406.4)	20.2 (4.3, 165.2)
Hb, g/L median (IQR)	140 (127, 150)	143 (130, 152.5)	134.5 (122.2, 147)
PLT, 10^9/L median (IQR)	118.3 (74, 167)	116 (75, 161.1)	106 (76.2, 151.8)
RBC, 10^{12}/L median (IQR)	4.5 (4.1, 5)	4.6 (4.1, 5)	4.3 (3.8, 4.8)
WBC, 10^9/L median (IQR)	5.1 (4, 6.3)	5.4 (4.2, 6.7)	4.7 (3.7, 6)
ALB, g/L median (IQR)	41.1 (38, 44)	40.8 (37.3, 44.6)	37.2 (34.6, 41.4)
ALT, IU/L median (IQR)	37.1 (25.4, 55)	36 (25.8, 52.6)	32 (23, 43)
AST, IU/L median (IQR)	35 (27.3, 52)	36.7 (27, 56.5)	33 (26, 43)
TBIL, μmol/L median (IQR)	14.8 (11.4, 21.2)	16 (11.6, 21.9)	16.4 (11.6, 23.4)
ALBI, cases (%)			
grade 1	347 (61.4)	139 (57.9)	53 (34.4)
grade 2	215 (38.1)	100 (41.7)	101 (65.6)
grade3	3 (0.5)	1 (0.4)	0 (0)
Child-Pugh, cases (%)			
grade A	542 (95.9)	227 (94.6)	136 (88.3)
grade B	23 (4.1)	13 (5.4)	18 (11.7)
PT, s median (IQR)	12.3 (11.6, 13.4)	12.5 (11.7, 13.6)	14.2 (13.2, 15.3)
Hepatitis, cases (%)[b]			
no	38 (6.7)	16 (6.7)	0 (0)
yes	527 (93.3)	224 (93.3)	154 (100)
Cirrhosis, cases (%)			
no	109 (19.3)	32 (13.3)	36 (23.4)
yes	456 (80.7)	208 (86.7)	118 (76.6)
Risk area, cases (%)[c]			
no	400 (70.8)	179 (74.6)	112 (72.7)
yes	165 (29.2)	61 (25.4)	42 (27.3)
BCLC stage, cases (%)			
0	167 (29.6)	71 (29.6)	53 (34.4)
A	338 (59.8)	144 (60)	99 (64.3)

B	60 (10.6)	25 (10.4)	2 (1.3)
Early recurrence, case (%)[d]			
no	290 (51.3)	129 (53.8)	130 (84.4)
yes	275 (48.7)	111 (46.2)	24 (15.6)
Liver function, case (%)[e]			
0	347 (61.4)	139 (57.9)	53 (34.4)
1	195 (34.5)	88 (36.7)	83 (53.9)
2	23 (4.1)	13 (5.4)	18 (11.7)

[*]Values are presented as the median [interquartile range] or n (%). PreTACE, preoperative transcatheter arterial chemoembolization; MWA, microwave ablation; RFA, radiofrequency ablation; AFP, alpha-fetoprotein; Hb, hemoglobin; PLT, platelet count; RBC, red blood cell; WBC, white blood cell; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALBI, albumin-bilirubin; PT, prothrombin time; BCLC stage, Barcelona Clinic Liver Cancer stage. [a]Central means section 1, 5, 8; non-central means section 2, 3, 6, 7. [b]Hepatitis B virus or hepatitis C virus. [c]Tumor adjacent to the cavity viscera, hepatic capsule, right or left bile duct or large vessels less than 1 cm. [d]Early recurrence means time from ablation to recurrence less than 12 months. [e]0, ALBI grade 1 and Child-Pugh A; 1, ALBI grade 1 or Child-Pugh A; 2, ALBI grade 2 or 3 and Child-Pugh B.

Table 2. Univariate and multivariate analysis of OS in the training cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y >60: ≤60	1.556 (1.095-2.210)	0.014	1.424 (0.981-2.066)	0.063
Gender, male: female	1.193 (0.625-2.276)	0.592		
PreTACE, yes: no	0.876 (0.582-1.319)	0.527		
Operation, RFA: MWA	1.501 (0.976-2.310)	0.064	1.979 (1.241-3.159)	0.004
Tumor number, multiple: solitary	1.592 (1.071-2.367)	0.022	1.438 (0.940-2.200)	0.094
Tumor size, cm >3: ≤3	1.478 (1.035-2.111)	0.032	1.286 (0.890-1.858)	0.181
Tumor location[a], non-central: central	0.947 (0.670-1.339)	0.758		
AFP, ng/mL ≥400: <400	0.960 (0.635-1.452)	0.848		
Hb, g/L ≥120: <120	0.646 (0.420-0.993)	0.046	0.873 (0.531-1.435)	0.593
PLT, 10^9/L ≥100: <100	0.543 (0.384-0.767)	0.001	0.882 (0.572-1.362)	0.572
RBC, 10^{12}/L ≥4.3: <4.3	0.595 (0.421-0.841)	0.003	0.947 (0.622-1.441)	0.799
WBC, 10^9/L ≥4.0: <4.0	0.621 (0.424-0.908)	0.014	1.000 (0.627-1.595)	0.999
ALB, g/L ≥35: <35	0.297 (0.201-0.438)	<0.001	0.395 (0.236-0.661)	<0.001
ALT, IU/L ≥50: <50	1.256 (0.869-1.816)	0.226		
AST, IU/L ≥40: <40	1.812 (1.282-2.562)	0.001	1.304 (0.887-1.916)	0.177
TBIL, μmol/L ≥17.1: <17.1	1.216 (0.858-1.724)	0.271		
PT prolongation, s ≥3: <3	2.063 (0.907-4.693)	0.084	2.051 (0.832-5.053)	0.118
Hepatitis[b], yes: no	1.638 (0.722-3.719)	0.238		
Cirrhosis, yes: no	1.416 (0.901-2.226)	0.132		
Risk area[c], yes: no	1.525 (1.073-2.168)	0.019	1.675 (1.166-2.408)	0.005
Early recurrence[d], yes: no	2.419 (1.698-3.447)	<0.001	2.060 (1.414-3.002)	<0.001
Liver fucntion[e]				
1:0	2.523 (1.758-3.621)	<0.001	1.559 (0.997-2.439)	0.051
2:0	2.503 (1.187-5.277)	0.016	0.876 (0.361-2.124)	0.77

PreTACE, preoperative transcatheter arterial chemoembolization; MWA, microwave ablation; RFA, radiofrequency ablation; AFP, alpha-fetoprotein; Hb, hemoglobin; PLT, platelet count; RBC, red blood cell; WBC, white blood cell; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALBI, albumin-bilirubin; PT, prothrombin time; HR, hazard ratio. [a]Central means section 1, 5, 8; non-central means section 2, 3, 6, 7. [b]Hepatitis B virus or hepatitis C virus. [c]Tumor adjacent to the cavity viscera, hepatic capsule, right or left bile duct or large vessels less than 1 cm. [d]Early recurrence means time from ablation to recurrence less than 12 months. [e]0, ALBI grade 1 and Child-Pugh A; 1, ALBI grade 1 or Child-Pugh A; 2, ALBI grade 2 or 3 and Child-Pugh B.

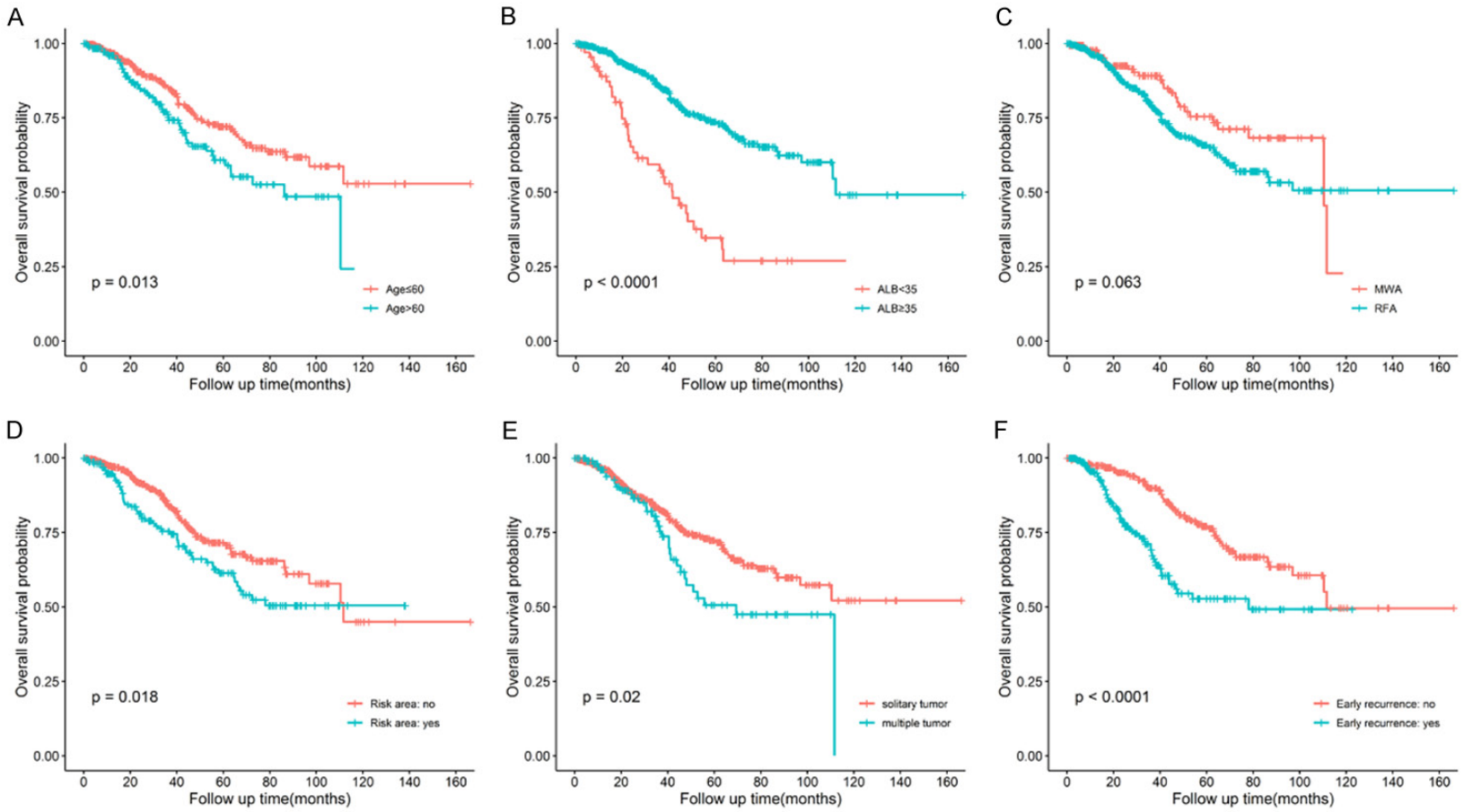

Figure 2. Kaplan-Meier OS curves for patients in training cohort stratified by factors included in the nomogram.

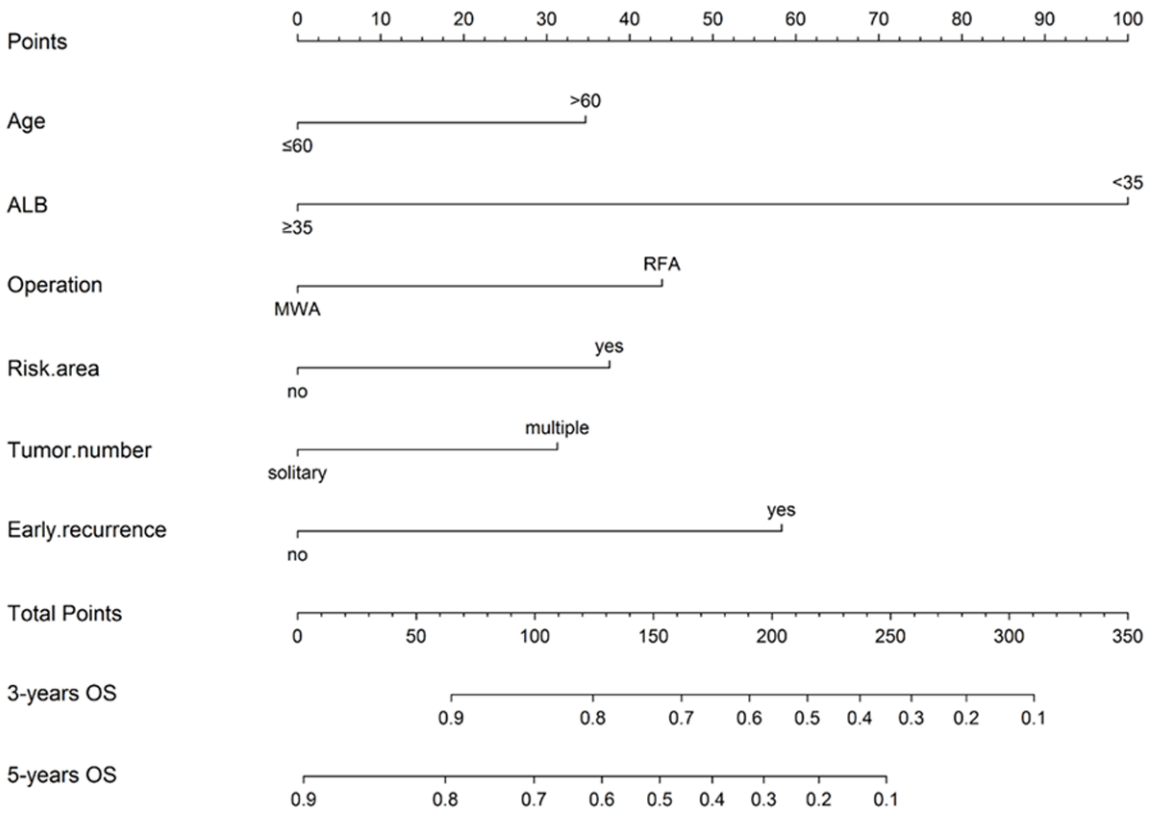

Figure 3. Nomogram for predicting the 3- and 5-year OS rates in patients with HCC receiving thermal ablation.

Table 3. C-index of models in three cohorts

Model	Training cohort		Internal validation cohort		External validation cohort	
	C-index	95% CI	C-index	95% CI	C-index	95% CI
Nomogram	0.736	0.689, 0.783	0.763	0.702, 0.824	0.825	0.735, 0.915
BCLC stage	0.558	0.515, 0.601	0.621	0.543, 0.699	0.551	0.445, 0.657
Prenomogram	0.698	0.655, 0.741	0.740	0.666, 0.814	0.737	0.610, 0.864
Nomogram_op	0.713	0.664, 0.762	0.739	0.674, 0.804	0.819	0.721, 0.917

BCLC stage, Barcelona Clinic Liver Cancer stage; Prenomogram, the previous nomogram; Nomogram_op, the nomogram without operation factor.

paring the net benefit of the nomogram with that of the other three models, the nomogram also had the highest net benefit in the same range.

Comparison of discrimination abilities between the nomogram and BCLC staging system

According to the prediction probabilities of OS rates, patients were separated into three groups for investigating the discrimination performance of our developed nomogram in OS prediction through drawing Kaplan-Meier curves (**Figure 6A-C**). Based on the nomogram, patients were stratified into low-risk, medium-risk and high-risk groups (n=279, n=257, and n=29, respectively) on the basis of prediction probabilities of OS, which presented good prognostic classification of OS for patients in the training cohort. For the low-, medium-, and high-risk group in the training cohort, the 3-year OS rates were 91.3%, 76.4%, and 28.7% respectively, and the 5-year OS rates were 81.9%, 52.8%, and 19.1% (both P<0.0001). Patients in the internal validation cohort were also well classified into low-risk, medium-risk and high-risk groups (n=102, n=118, and n=20, respectively), and the 5-year OS rates were

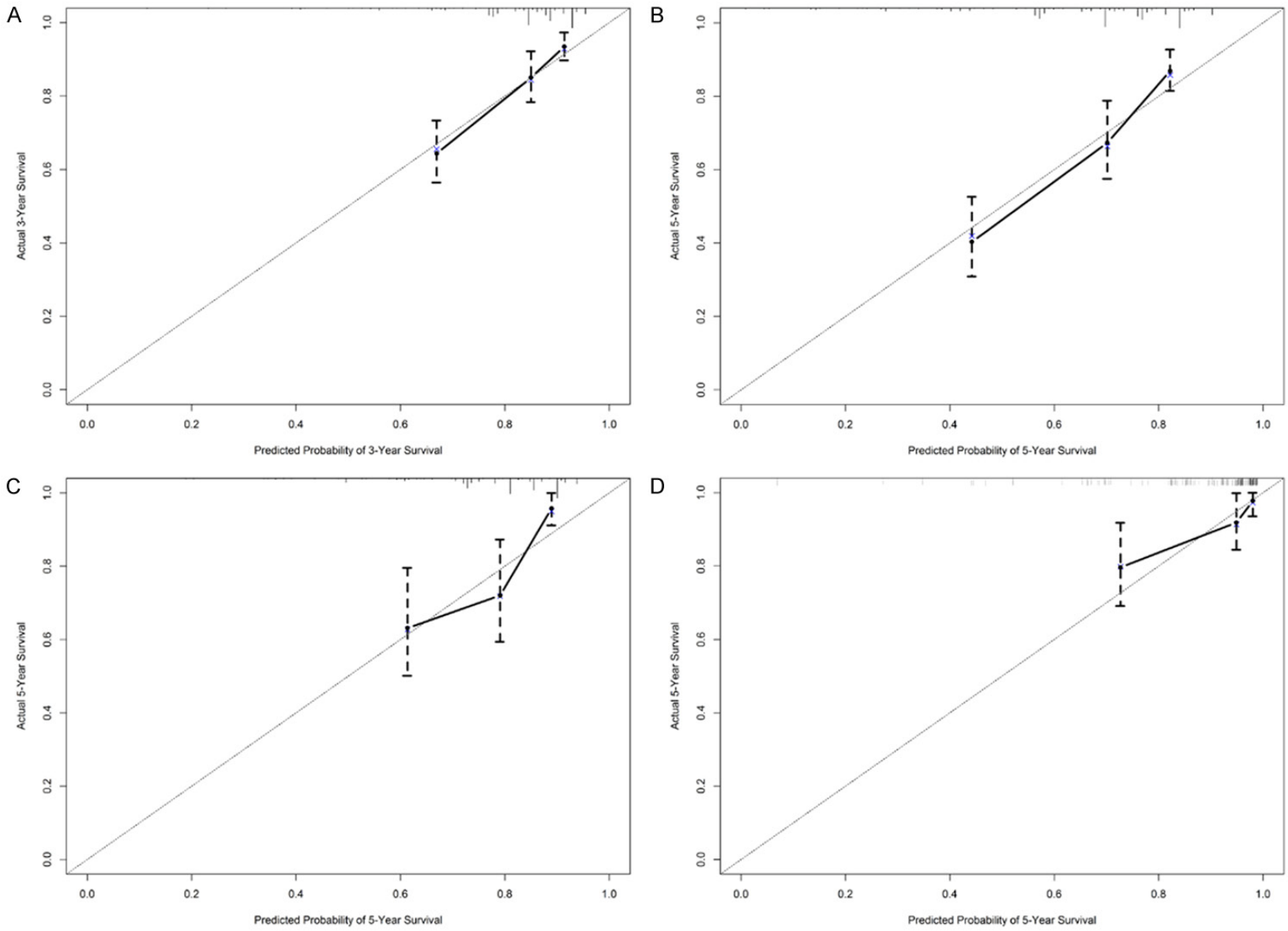

Figure 4. The calibration plot for predicting patient survival at (A) 3 years and (B) 5 years in the training cohort and at 5 years in the (C) internal validation cohort and (D) external validation cohort.

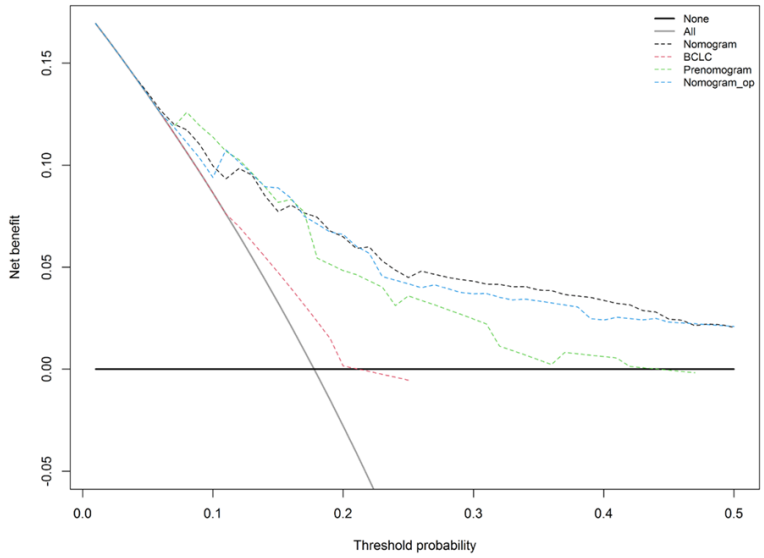

Figure 5. Decision curve for models predicting the OS rates in the training cohort.

93.6%, 72.4%, and 36.2%, respectively. As for the external validation cohort, patients were also well stratified into low-risk, medium-risk and high-risk groups (n=89, n=53, and n=12, respectively) with 5-year OS rates of 97.6%, 87.7%, and 32.4%, respectively. Furthermore, we also drew Kaplan-Meier curves of patients in these three cohorts according to the BCLC staging system to compare the discrimination abilities between the nomogram and BCLC staging system (**Figure 6D-F**). In the training cohort, at the early stage of follow-up, the survival curves of patients with BCLC stage B overlapped with those of the other two stages. However, for patients in the internal validation cohort, BCLC staging system could differentiate them well based on prognosis. As for patients in the external validation cohort, they were well distinguished based on prognosis by the nomogram rather than the BCLC staging system.

Discussion

Due to regular surveillance of patients at risk for HCC, more patients have improved prognosis by receiving curative therapies [29]. As a form of curative therapy, thermal ablation is widely used in patients who are unable or unwilling to undergo liver resection or liver transplantation [4]. Therefore, it is important to clarify the accurate prognosis of HCC after thermal ablation. Previous studies have developed nomogram which predicted prognosis more accurately compared to traditional staging systems in several types of cancers [9, 30, 31]. In our present study, with a multi-center and large sample data, a novel prognostic nomogram was established and validated for patients with HCC after thermal ablation based on tumor and patient characteristics, liver function, operation method and recurrence time that performed well in predicting survival.

The BCLC staging system is a common HCC staging system. It integrates several factors including liver function preservation, tumor extension, cancer-associated symptoms, and physical status, and could serve as the practice guideline for HCC [32-34]. The BCLC staging system provides treatment suggestions for each stage according to the currently available options, which are the most different from other staging systems [35]. However, the BCLC staging system is unable to distinguish patients receiving different treatments for the same stage as well as patients receiving the same treatment for different stages, resulting in poor predicting efficacy. Furthermore, the BCLC staging system was not specially constructed to predict the survival of HCC patients after thermal ablation. The above problems might affect the predictive accuracy of the BCLC staging system for patients with HCC receiving thermal ablation. In the present study, compared with the developed nomogram, the BCLC staging system showed less effective for OS prediction in all of training, internal and external validation cohorts (C-index, 0.736 vs. 0.558, 0.763 vs. 0.621, and 0.825 vs. 0.551, respectively), and in terms of discrimination ability, it was also less useful to stratify patients based on prognosis. The DCA analysis showed that the nomogram was superior to the BCLC staging system within most of the reasonable threshold probability range, and indicated that it added incremental value to the BCLC staging system in terms of individual evaluation.

Previous study has developed a nomogram to predict prognostic of HCC after thermal ablation [28]. However, the following defects might

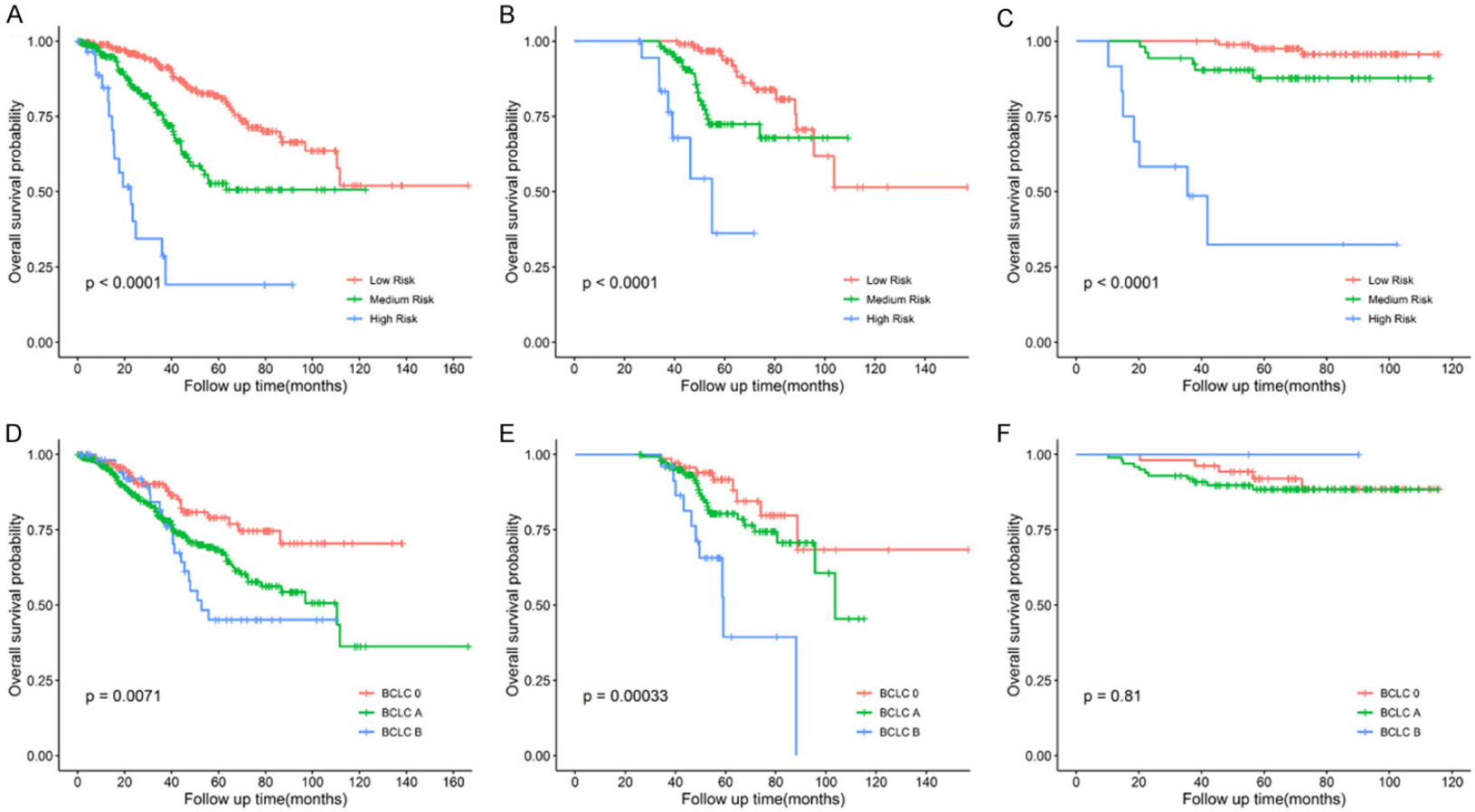

Figure 6. Kaplan-Meier OS curves for subgroups of patients. Patients were stratified by the nomogram in the training cohort (A), internal validation cohort (B), and external validatio cohort (C). Patients were stratified by the BCLC staging system in the training cohort (D), internal validation cohort (E), and external validation cohort (F).

affect the accuracy and reliability of this previous nomogram in predicting prognosis. Firstly, the sample size of the previous study is smaller than that of the present study. Secondly, the previous study did not validate the established nomogram by validation cohort after it was established, which is necessary for developing a nomogram. Thirdly, the previous nomogram was not compared with conventional staging systems, so the superiority and necessity of the model cannot be reflected. In our study, the nomogram we established integrated 6 factors affecting survival, including age, tumor number, risk area location, ALB level, early recurrence and operation method, which overcame the above defects. The results of C-index comparison and DCA analysis also revealed the superiority of our nomogram than the previous nomogram.

At present, RFA and MWA are two commonly used thermal ablation methods in clinical practice. Previous study demonstrated that MWA was superior to RFA in both 5-year OS and RFS among HCC patients within Milan criteria [19]. Santambrogio et al. compared the outcome of HCC patients with 1 to 3 tumors and tumor diameter ≤3 cm after laparoscopic MWA and RFA, and found that the MWA group had a lower tumor progression rate and a better 5-year local tumor progression rate compared with the RFA group [36]. However, a previous study also showed that the OS of patients who were treated with RFA and MWA was almost identical, although there was a possibility that MWA is superior to RFA in terms of local tumor control [37]. In our present study, we found that MWA was associated with better survival rate than RFA. The significant difference in heat generation between the two ablation methods might lead to different therapeutic effects on HCC [19]. Additionally, tumor number was identified to be factors predicted prognostic in this study, which was consistent with previous studies [12, 38, 39]. Tumors located in risk areas might resulted in difficulty in the procedure of ablation and more complications, which can affect the prognosis of patients with HCC [16, 17]. Our present study also identified tumor located in risk areas to be a factor leading to poor prognosis. The prognosis of patients with early recurrence after radical therapy is generally poor, because it is often accompanied by invasive tumor features such as high AFP, large tumor size and MWI [14, 15]. Like previous studies, our study found that patients with early recurrence after ablation had poor prognosis, which was included in the prognostic nomogram. Other variables entering our prediction model are ALB and age, which can reflect the condition of liver function and patient and have sufficient scientific basis in determining the prognosis of patients. AFP level was demonstrated as a prognostic factor of HCC in previous studies [40, 41]. However, this study and other studies failed to find it to be a prognostic factor of HCC [24, 42]. AFP level may not be powerful enough to predict the survival of HCC after ablation compared with other factors included in our nomogram.

There are some limitations in our study. First, despite a multi-center and large number of patients, this is a retrospective study. Thus, prospective randomized controlled trials will be necessary to validate our conclusions. Second, most HCC patients enrolled our study were infected by hepatitis B virus. Therefore, our present nomogram needs to be further validated in areas where hepatitis C or alcoholic hepatitis is the main risk factors.

In conclusion, based on several clinical factors, we put forward a nomogram for predicting the OS of HCC patients receiving thermal ablation, which can be used to assist prognosis prediction and individual monitoring.

Acknowledgements

This work was funded by grants from the Science and Technology Program of Guangzhou, China (No. 201803010071) and the Rural Science and Technology Commissioner Program of Guangdong Province, China (KTP-2020342). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Disclosure of conflict of interest

None.

Abbreviations

HCC, hepatocellular carcinoma; C-index, concordance index; BCLC, Barcelona Clinic Liver Cancer; OS, overall survival rates; RFA, radiofrequency ablation; MWA, microwave ablation;

PreTACE, preoperative transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; Hb, hemoglobin; PLT, platelet count; RBC, red blood cell; WBC, white blood cell; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALBI, albumin-bilirubin; PT, prothrombin time; HR, hazard ratio; AASLD, American Association for the Study of Liver Diseases; CT, computed tomography; MRI, magnetic resonance imaging; DCA, decision curve analysis.

Address correspondence to: Yun Zheng, Department of Liver Surgery, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, China. Tel: +86-13711660795; Fax: +86-20-8734-3585; E-mail: zhengyun@sysucc.org.cn; Dr. Qilin Xu, The Second Department of General Surgery, The First People's Hospital of Kashi Prefecture, Kashi 844000, The Xinjiang Uygur Autonomous Region, China. Tel: +86-15276026792; E-mail: 50879846@qq.com; Dr. Liang Wang, The First Department of General Surgery, The First People's Hospital of Kashi Prefecture, Kashi 844000, The Xinjiang Uygur Autonomous Region, China. Tel: +86-13565652885; E-mail: 49414300@qq.com

References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.

[2] Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, Ferlay J, Valery PC, Bray F and McGlynn KA. International trends in hepatocellular carcinoma incidence, 1978-2012. Int J Cancer 2020; 147: 317-330.

[3] Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault JC, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D and Martinelli E. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30: 871-873.

[4] Benson AB, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Anaya DA, Anders R, Are C, Brown D, Chang DT, Cloyd J, Covey AM, Hawkins W, Iyer R, Jacob R, Karachristos A, Kelley RK, Kim R, Palta M, Park JO, Sahai V, Schefter T, Sicklick JK, Singh G, Sohal D, Stein S, Tian GG, Vauthey JN, Venook AP, Hammond LJ and Darlow SD. Guidelines insights: hepatobiliary cancers, version 2.2019. J Natl Compr Canc Netw 2019; 17: 302-310.

[5] Nault JC, Sutter O, Nahon P, Ganne-Carrie N and Seror O. Percutaneous treatment of hepatocellular carcinoma: state of the art and innovations. J Hepatol 2018; 68: 783-797.

[6] Bruix J and Sherman M; American Association for the Study of Liver Disease. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.

[7] Jeong WK, Jamshidi N, Felker ER, Raman SS and Lu DS. Radiomics and radiogenomics of primary liver cancers. Clin Mol Hepatol 2019; 25: 21-29.

[8] Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, Cindolo L, De la Taille A, Tostain J, Mulders PF, Salomon L, Zigeuner R, Prayer-Galetti T, Chautard D, Valeri A, Lechevallier E, Descotes JL, Lang H, Mejean A and Patard JJ. Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol 2007; 25: 1316-1322.

[9] Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, Wan X, Liu G, Wu D, Shi L, Lau W, Wu M and Shen F. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013; 31: 1188-1195.

[10] Han G, Berhane S, Toyoda H, Bettinger D, Elshaarawy O, Chan AWH, Kirstein M, Mosconi C, Hucke F, Palmer D, Pinato DJ, Sharma R, Ottaviani D, Jang JW, Labeur TA, van Delden OM, Pirisi M, Stern N, Sangro B, Meyer T, Fateen W, Garcia-Finana M, Gomaa A, Waked I, Rewisha E, Aithal GP, Travis S, Kudo M, Cucchetti A, Peck-Radosavljevic M, Takkenberg RB, Chan SL, Vogel A and Johnson PJ. Prediction of survival among patients receiving transarterial chemoembolization for hepatocellular carcinoma: a response-based approach. Hepatology 2020; 72: 198-212.

[11] He W, Peng B, Tang Y, Yang J, Zheng Y, Qiu J, Zou R, Shen J, Li B and Yuan Y. Nomogram to predict survival of patients with recurrence of hepatocellular carcinoma after surgery. Clin Gastroenterol Hepatol 2018; 16: 756-764 e710.

[12] Kim CG, Lee HW, Choi HJ, Lee JI, Lee HW, Kim SU, Park JY, Kim DY, Ahn SH, Han KH, Kim HS, Kim KH, Choi SJ, Kim Y, Lee KS, Kim GM, Kim MD, Won JY, Lee DY and Kim BK. Development and validation of a prognostic model for patients with hepatocellular carcinoma undergoing radiofrequency ablation. Cancer Med 2019; 8: 5023-5032.

[13] Lu Z, Sun Z, Liu C, Shi X, Li R, Shao W, Zheng Y, Li Y and Song J. Prognostic nomogram for hepatocellular carcinoma with radiofrequency ablation: a retrospective cohort study. BMC Cancer 2021; 21: 751.

[14] Xing H, Zhang WG, Cescon M, Liang L, Li C, Wang MD, Wu H, Lau WY, Zhou YH, Gu WM, Wang H, Chen TH, Zeng YY, Schwartz M, Pawlik TM, Serenari M, Shen F, Wu MC and Yang T.

Defining and predicting early recurrence after liver resection of hepatocellular carcinoma: a multi-institutional study. HPB (Oxford) 2020; 22: 677-689.
[15] Xu XF, Xing H, Han J, Li ZL, Lau WY, Zhou YH, Gu WM, Wang H, Chen TH, Zeng YY, Li C, Wu MC, Shen F and Yang T. Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. JAMA Surg 2019; 154: 209-217.
[16] Komorizono Y, Oketani M, Sako K, Yamasaki N, Shibatou T, Maeda M, Kohara K, Shigenobu S, Ishibashi K and Arima T. Risk factors for local recurrence of small hepatocellular carcinoma tumors after a single session, single application of percutaneous radiofrequency ablation. Cancer 2003; 97: 1253-1262.
[17] Lu DS, Raman SS, Limanond P, Aziz D, Economou J, Busuttil R and Sayre J. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. J Vasc Interv Radiol 2003; 14: 1267-1274.
[18] Balachandran VP, Gonen M, Smith JJ and DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015; 16: e173-180.
[19] Liu W, Zheng Y, He W, Zou R, Qiu J, Shen J, Yang Z, Zhang Y, Wang C, Wang Y, Zuo D, Li B and Yuan Y. Microwave vs radiofrequency ablation for hepatocellular carcinoma within the Milan criteria: a propensity score analysis. Aliment Pharmacol Ther 2018; 48: 671-681.
[20] Wells SA, Hinshaw JL, Lubner MG, Ziemlewicz TJ, Brace CL and Lee FT Jr. Liver ablation: best practice. Radiol Clin North Am 2015; 53: 933-971.
[21] Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, Mine N, Kondo Y, Kawabe T and Omata M. Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. Hepatology 2006; 43: 1101-1108.
[22] Bruix J and Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.
[23] Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ and Lau WY. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013; 31: 426-432.
[24] He W, Li B, Zheng Y, Zou R, Shen J, Cheng D, Tao Q, Liu W, Li Q, Chen G and Yuan Y. Resection vs. ablation for alpha-fetoprotein positive hepatocellular carcinoma within the Milan criteria: a propensity score analysis. Liver Int 2016; 36: 1677-1687.
[25] Liu Y, Li S, Wan X, Li Y, Li B, Zhang Y, Yuan Y and Zheng Y. Efficacy and safety of thermal ablation in patients with liver metastases. Eur J Gastroenterol Hepatol 2013; 25: 442-446.
[26] Iasonos A, Schrag D, Raj GV and Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008; 26: 1364-1370.
[27] van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. Stat Med 2000; 19: 3401-3415.
[28] Zhou Y, Ding J, Qin Z, Wang Y, Zhang J, Jia K, Wang Y, Zhou H, Wang F and Jing X. Predicting the survival rate of patients with hepatocellular carcinoma after thermal ablation by nomograms. Ann Transl Med 2020; 8: 1159.
[29] Kim HY, Nam JY, Lee JH, Lee HA, Chang Y, Lee HY, Cho H, Lee DH, Cho YY, Cho EJ, Yu SJ, Lee JM, Kim YJ and Yoon JH. Intensity of surveillance for hepatocellular carcinoma determines survival in patients at risk in a hepatitis B-endemic area. Aliment Pharmacol Ther 2018; 47: 1490-1501.
[30] Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, Lai XP, He Y, Xu YX, Hu DP, Wen SH, Peng YT, Zhang L, Guo SS, Liu LT, Guo L, Wu YS, Luo DH, Huang PY, Mo HY, Xiang YQ, Sun R, Chen MY, Hua YJ, Lv X, Wang L, Zhao C, Cao KJ, Qian CN, Guo X, Zeng YX, Mai HQ and Zeng MS. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J Natl Cancer Inst 2015; 108: djv291.
[31] Huang YQ, Liang CH, He L, Tian J, Liang CS, Chen X, Ma ZL and Liu ZY. Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer. J Clin Oncol 2016; 34: 2157-2164.
[32] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.
[33] Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019; 380: 1450-1462.
[34] Llovet JM, Bru C and Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338.
[35] Marrero JA, Kudo M and Bronowicki JP. The challenge of prognosis and staging for hepatocellular carcinoma. Oncologist 2010; 15 Suppl 4: 23-33.
[36] Santambrogio R, Chiang J, Barabino M, Meloni FM, Bertolini E, Melchiorre F and Opocher E. Comparison of laparoscopic microwave to radiofrequency ablation of small hepatocellular

carcinoma (≤3 cm). Ann Surg Oncol 2017; 24: 257-263.
[37] Chong CCN, Lee KF, Cheung SYS, Chu CCM, Fong AKW, Wong J, Hui JWY, Fung AKY, Lok HT, Lo EYJ, Chan SL, Yu SCH, Ng KKC and Lai PBS. Prospective double-blinded randomized controlled trial of microwave versus radiofrequency ablation for hepatocellular carcinoma (McRFA trial). HPB (Oxford) 2020; 22: 1121-1127.
[38] An C, Wu S, Huang Z, Ni J, Zuo M, Gu Y, Zhang T and Huang J. A novel nomogram to predict the local tumor progression after microwave ablation in patients with early-stage hepatocellular carcinoma: a tool in prediction of successful ablation. Cancer Med 2020; 9: 104-115.
[39] Ding M, Zhao X, Zhao M, Shi Y, Wang T, Cui D, Shi D and Zhai B. Prognostic nomogram for patients with hepatocellular carcinoma after thermal ablation. Cardiovasc Intervent Radiol 2020; 43: 1621-1630.
[40] Fu YP, Yi Y, Huang JL, Jing CY, Sun J, Ni XC, Lu ZF, Cao Y, Zhou J, Fan J and Qiu SJ. Prognostic nomograms stratify survival of patients with hepatocellular carcinoma without portal vein tumor thrombosis after curative resection. Oncologist 2017; 22: 561-569.
[41] Xu L, Peng ZW, Chen MS, Shi M, Zhang YJ, Guo RP, Lin XJ and Lau WY. Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. J Hepatol 2015; 63: 122-130.
[42] Tao Q, He W, Li B, Zheng Y, Zou R, Shen J, Liu W, Zhang Y and Yuan Y. Resection versus resection with preoperative transcatheter arterial chemoembolization for resectable hepatocellular carcinoma recurrence. J Cancer 2018; 9: 2778-2785.