Research Paper

A Nomogram Predicting Extrahepatic Metastases for Patients with Adjuvant Transarterial Chemoembolization after Hepatectomy

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Abstract

Background: Prognosis remains poor for hepatocellular carcinoma (HCC) patients with extrahepatic metastases (EHMs). This study aimed to develop a nomogram to predict EHMs in HCC patients who underwent adjuvant transarterial chemoembolization (TACE) following hepatectomy.

Methods: Data of 578 HCC patients who underwent TACE after hepatectomy at the Eastern Hepatobiliary Surgery Hospital was retrospectively reviewed. Cox regression analyses was used to select variables to construct the nomogram. Predictive accuracy and discriminative ability of the model were performed using concordance index (C-index), calibration curve and the area under time-dependent receiver operating characteristic (ROC) curve.

Results: Postoperative EHMs were detected in 89 and 31 patients in the training cohort (n = 453) and validation cohort (n = 125), respectively. Multivariate analysis showed that tumor size (HR, 1.099; 95% CI, 1.049-1.152), coarse beam type of tumor histopathological structure (HR, 2.382; 95% CI, 1.030-5.512), presence of satellite nodules (HR, 1.936; 95% CI, 1.156-3.244) and alpha-fetoprotein (AFP) (HR, 1.399; 95% CI, 1.098-1.783) were independent risk factors for EHMs (all p < 0.05). The nomogram incorporated these factors achieved good agreement between prediction and actual observation with a concordance index (C-index) of 0.73 (95% CI, 0.68 to 0.78) and 0.71 (95% CI, 0.63 to 0.79) in the training cohort and validation cohort, respectively. In addition, patients who had a nomogram score > 17 were considered to have higher risk for EHMs compared with those scored ≤ 12. Furthermore, the time-dependent area under the ROC curve indicated comparative stability and adequate discriminative ability of the model.

Conclusions: This novel nomogram can identify those with high risk of EHMs after adjuvant TACE following hepatectomy. The validation cohort showed a good performance, suggesting it could benefit surgeons on decision-making.

Key words: Hepatocellular carcinoma, Adjuvant transarterial chemoembolization, Extrahepatic metastases, Nomogram

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent malignancy and the third most frequent cause of cancer-related death worldwide [1].

Although hepatectomy and liver transplantation remain the main treatments for resectable tumors, the prognosis for HCC is still poor. HCC patients could

only achieve a 5-year survival rate nearly 33% - 50% through resection, while the 5-year recurrence rate after surgical resection is more than 75% [1]. In many randomized trials, it was reported that patients who received adjuvant transarterial chemoembolization (TACE) after hepatectomy had significantly higher survival rate [2, 3]. Nonetheless, extrahepatic metastases (EHMs) were observed more frequently because of the prolonged survival, with an incidence of 13.5% to 42% in HCC patients [4].

Therapeutic options for EHMs are comparatively limited currently, especially for diffuse EHMs [5]. HCC can metastasize to many parts of the body by way of blood circulation and direct invasion of lymphatic spread. Patients with EHMs from primary HCC are considered to be in the terminal stage of cancer; accordingly, the prognosis for them continues to be poor. Recently, the management of EHMs in the lung, bone and brain has been improved, leading to better outcomes than before [6-8]. Moreover, patients can benefit from adjuvant therapies, including surgical, adoptive immunotherapy, antiviral therapy and radiotherapy [9-12]. For example, it reported that external radiotherapy can slow tumor progression and prolong survival for patients with EHMs [13-15]. Besides, Llovet and Kudo M et al reported that sorafenib and lenvatinib could extend survival in the treatment of advanced HCC, respectively [16, 17]. In addition, oxaliplatin can benefit patients with metastatic liver cancer [18]. Furthermore, Qiu et al reported that the thymalfasin can significantly prolong remission in patients who received adjuvant TACE after tumor resection [19]. Most importantly, accumulated evidence suggests that Huaier may be associated with inhibition of cell proliferation, anti-metastasis, interference with tumor angiogenesis and tumor-specific immunomodulatory effect [20]. It may reduce metastasis and improve survival by strengthening immune function. Consequently, it makes sense to identify patients who received TACE after hepatectomy are at high risk for EHMs. Such EHMs profile would prove essential for surgeons planning potential adjuvant treatments, as noted above, and other novel therapies at an earlier stage. Furthermore, identifying patients at high risk for EHMs could concurrently support the early detection of lesions, thus maximizing the preventive benefits of treatment through early diagnosis and treatment as well as preventing unnecessary liver transplantation in these patients.

Currently, the realistic methods for reducing EHMs after resection include early detection and aggressive management of it. Although significant progress has been made in imaging technology, many deficiencies limit its use for EHMs from HCC, not to mention those patients with no early signs. EHMs from HCC are hard to predict based on routine clinical assay, but some specific and predictive method could provide early detection or even prevention of it. In this regard, the nomogram is a tool that generates the probability of an individual clinical event by integrating diverse prognostic and determinative variables [21]. Therefore, in the present research, we constructed a nomogram from a training cohort of 453 patients to predict the probability of EHMs in HCC patients who received TACE after hepatectomy. The nomogram was further validated in another independent cohort of 125 patients.

Patients and Methods

Patient inclusion and exclusion

The flowchart of enrolled patients underwent partial hepatectomy for HCC and adjuvant TACE in the Eastern Hepatobiliary Surgery Hospital (Figure 1). From March 2009 to December 2012, a cohort of 453 patients diagnosed with HCC by histopathology, according to EASL criteria [22], underwent partial hepatectomy for HCC and adjuvant TACE at Department of Hepatic Surgery of Eastern Hepatobiliary Surgery Hospital were enrolled. Inclusion criteria included the following: no history of preoperative anticancer therapy; no EHMs at the time of diagnosis; no history of other malignancies; no macrovascular invasion; R0 resection; and pathological diagnosis of HCC in all resected tumors. In addition, we checked all the patients again at our hospital 4 weeks after partial hepatectomy. Then TACE therapy was appropriately recommended according to the liver function of the patients if no recurrence was found. Patients diagnosed with recurrence at that time were excluded, and in order to avoid counting deaths due to postoperative complications, patients died within 30 days post-hepatectomy were also excluded. Besides, the study was also conducted on another separate cohort of 125 patients. These patients, who met the same inclusion and exclusion criteria mentioned above, were considered as the validation cohort.

Data collection

All patients enrolled in this study were evaluated with a baseline history and physical examination at the discretion of the treating surgeons. All laboratory tests, such as alpha-fetoprotein (AFP) as well as liver function parameters, were calculated before the hepatectomy. Besides, appropriate pre-surgical imaging, such as dynamic contrast enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) of liver,

abdominal ultrasound, chest CT were performed before hepatectomy. In addition, bone scan were performed when hepatocellular carcinoma patients with signs and symptoms of bone metastasis including: bone pain, fractures, spinal cord compression and hypercalcemia et al.

Histopathological study of the resected specimens, including tumor diameter and number, degree of cirrhosis, microvascular invasion and the status of tumor encapsulation, was carried out independently by two experienced pathologists. In the event of disagreement, deference was given to the senior pathologist, but only when consensus was reached would histopathology be decided.

Follow up

Every enrolled patient was followed up every 3 months during the first 2 years after hepatectomy and then every 3 - 6 months thereafter until death or dropout from our program. Overall survival was defined as the interval between hepatectomy and death, or the last date of follow-up program. EHMs were diagnosed based on a patient's CT/MRI scan, and time to development of EHMs was calculated as the time from hepatectomy to the date when EHMs were first confirmed. The median (interquartile range) postoperative follow-up time was 40.47 (24.03-48.93) months in all patients. The diagnostic criteria for EHMs were as follows: (1) raised AFP that had declined to normal range after hepatectomy, (2) evidence of new extrahepatic lesions not found previously, (3) histopathological study of extrahepatic lesions in patients who underwent re-resection for recurrence of HCC. Patients with intrahepatic recurrence prior to EHMs, or concurrent with EHMs, were excluded in this study. Patients diagnosed with EHMs and other malignancies were also excluded. Active treatment plans were implemented according to liver function status and tumor number when recurrence was confirmed.
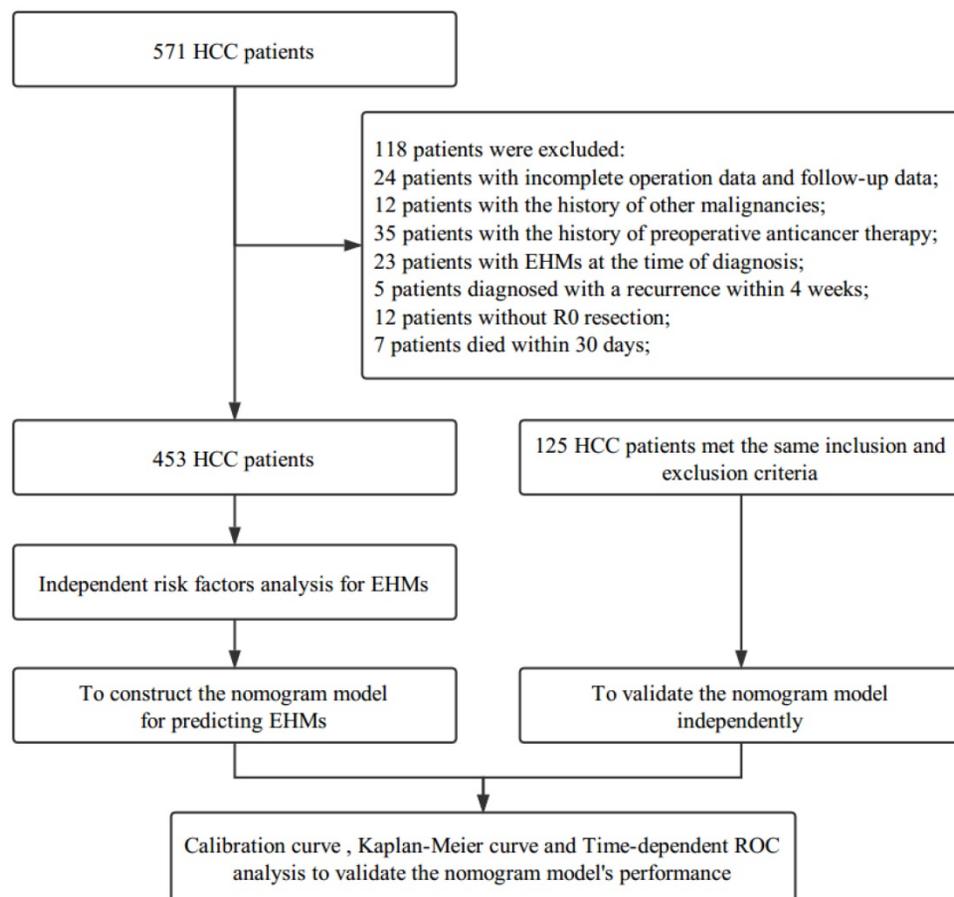
Figure 1. The flowchart of the enrolled patients

Table 1. Baseline characteristics of HCC patients in the training and validation cohorts

Variables	Training Cohort (n=453)	Validation Cohort (n=125)	P-value
Age (years)	50.81±9.77	49.37±11.39	0.160
Gender (%)			0.255
Male	384.00 (84.77)	111.00 (88.80)	
Female	69.00 (15.23)	14.00 (11.20)	
Tumor size (cm)	5.20 (3.60-8.00)	4.90 (3.40-8.15)	0.901
State of recurrence (%)			0.146
Presence	206.00 (45.47)	66.00 (52.80)	
Absence	247.00 (54.53)	59.00 (47.20)	
Extrahepatic metastases (%)			0.213
Lung	47.00 (10.38)	14.00 (11.20)	
Bone	8.00 (1.77)	3.00 (2.40)	
Lung & Bone	15.00 (3.31)	2.00 (1.60)	
Others	19.00 (4.19)	12.00 (9.60)	
Number of tumor (%)			0.675
Single	362.00 (79.91)	102.00 (81.60)	
Multiple	91.00 (20.09)	23.00 (18.40)	
Tumor encapsulation (%)			0.120
Complete	224.00 (49.45)	52.00 (41.60)	
Incomplete	229.00 (50.55)	73.00 (58.40)	
Liver cirrhosis (%)			0.793
Presence	256.00 (56.51)	69.00 (55.20)	
Absence	197.00 (43.49)	56.00 (44.80)	
Microvascular invasion (%)			0.434
Presence	171.00 (37.75)	52.00 (41.60)	
Absence	282.00 (62.25)	73.00 (58.40)	
Histopathological structure of tumor (%)			0.995
Coarse beam type	377.00 (83.22)	104.00 (83.20)	
Fine beam type	76.00 (16.78)	21.00 (16.80)	
Tumor differentiation (%)			0.950
Lower	2.00 (0.44)	1.00 (0.80)	
Low	71.00 (15.67)	19.00 (15.20)	
Moderate	359.00 (79.25)	100.00 (80.00)	
High	21.00 (4.64)	5.00 (4.00)	
Satellite nodules (%)			0.416
Presence	53.00 (11.70)	18.00 (14.40)	
Absence	400.00 (88.30)	107.00 (85.60)	
HBsAg (%)			0.955
Positive	336.00 (74.17)	92.00 (73.60)	
Negative	41.00 (9.05)	11.00 (8.80)	
HBV DNA (log IU/mL)	3.24 (3.00-5.03)	3.33 (3.00-5.22)	0.653
TP (g/L)	70.20 (65.30-74.95)	71.30 (65.70-75.75)	0.258
ALB (g/L)	40.90 (37.50-43.30)	41.00 (37.00-44.15)	0.557
TBIL (umol/L)	13.90 (10.65-18.45)	14.10 (10.75-18.30)	0.824
GGT (U/L)	63.00 (36.25-116.50)	63.00 (36.50-102.50)	0.966
AFU (U/L)	25.00 (21.00-32.50)	27.00 (21.00-33.00)	0.407
ALP (U/L)	83.00 (69.00-106.00)	83.00 (67.00-106.50)	0.450
ALT (U/L)	40.80 (27.70-90.50)	44.40 (23.55-75.50)	0.555
AST (U/L)	40.00 (28.00-86.95)	39.50 (27.35-74.10)	0.650
PT (s)	12.20 (11.50-12.80)	12.10 (11.40-12.80)	0.622
PLT (10⁹/L)	158.00 (118.00-205.00)	157.00 (127.50-208.00)	0.541
AFP (log ug/L)	2.32 (1.10-3.08)	2.23 (1.34-3.05)	0.892
CEA (ug/L)	2.20 (1.50-3.48)	2.10 (1.40-3.25)	0.389
CA19-9 (U/mL)	18.10 (10.57-30.45)	16.90 (10.35-31.10)	0.976

Categorical variables presented as number (percentage) and continuous data presented as means±standard deviations or median (interquartile range). Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the independent t-test or Mann-Whitney U test. HBsAg: hepatitis B surface antigen; TP: total protein; ALB, albumin; TBIL: total bilirubin; GGT: γ-glutamyltransferase; AFU: α-L-fucosidase; ALP: alkaline phosphates; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; PLT: platelet count; AFP: alpha-fetoprotein; CEA: carcino-embryonic antigen; CA19-9: carbohydrate antigen 19-9.

Statistical analysis

Independent samples *t*-test or Mann-Whitney U test was used to calculate the differences between different sets in continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test. Based on the results of the multivariate Cox regression analysis, we used R program packages, including "rcspline", "rms", "timeROC", "survivalROC", and "party", to construct and validate the nomogram model. The "rcspline" (restricted cubic splines) package was used to analyze the nonlinear effect among risk factors on EHMs. "rms" was used to draw the nomogram and validate

this model which predicted the probability of EHMs. The predictive performance of the model in continuous time were expressed with the area under time-dependent ROC curve (AUC) by the "timeROC" package. Decision tree analysis in the "party" package was used to better stratify HCC patients into three groups with different EHMs probabilities both in the training and validation cohorts. Furthermore, the EHMs rates were compared using the Kaplan-Meier method and log-rank test among the high, moderate and low risk groups. A two-sided p value of less than 0.05 was considered statistically significant. All statistical analyses and graphics in this study were performed in SPSS 23.0 (SPSS, Chicago, IL, USA), GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA) and R-3.3.0 for Windows (https://www.r-project.org/).

Results

Baseline characteristics of patients

Baseline characteristics of the patients are shown in Table 1. In the training cohort (n=453), the mean age of patients was 50.81 years among whom 384 (84.77%) was male. Most people 336 (74.17%) were positive for hepatitis B virus surface antigen, and 256 (56.51%) of these patients presented with liver cirrhosis. In terms of tumor factors, 362 (79.91%) of the patients had single tumor, and the median diameter of the tumors was 5.20 (interquartile range: 3.60-8.00) cm. In addition, encapsulation incomplete and microvascular invasion were documented in 229 (50.55%) and 171 (37.75%) patients, respectively. As

for postoperative prognosis, the rate of tumor recurrence was 206 (45.47%) in the training cohort. All clinical and histopathological factors of the training cohort (n=453) and validation cohort (n=125) are summarized in Table 1. No significant differences in baseline characteristics were found between the training and validation cohorts.

Independent factors associated with EHMs in the training cohort

Table 2 shows the results of the univariate and multivariate analyses with the Cox proportional hazard regression model. It showed that tumor size (HR, 1.099; 95% CI, 1.049-1.152), coarse beam type of tumor histopathological structure (HR, 2.382; 95% CI, 1.030-5.512), presence of satellite nodules (HR, 1.936; 95% CI, 1.156-3.244), and log AFP (HR, 1.399; 95% CI, 1.098-1.783) were four independent variables associated with EHMs (all p < 0.05). Histopathological structure of tumor was mainly divided into two categories: coarse beam type and fine beam type. In addition, before finally selecting variables for input, the influence of AFP and tumor size were performed by using restricted cubic splines. Both AFP and tumor size had nonlinear influence on the hazard ratio of EHMs. Using the R package "rcspline", we noted that the effect of AFP on the HR was at first linear below a threshold of almost 2 log(AFP) ug/L, but after that it then increased dramatically (Figure 2A). Similarly, the effect of tumor size on the HR was linear, just below almost 6 cm, and then grew gradually (Figure 2B).
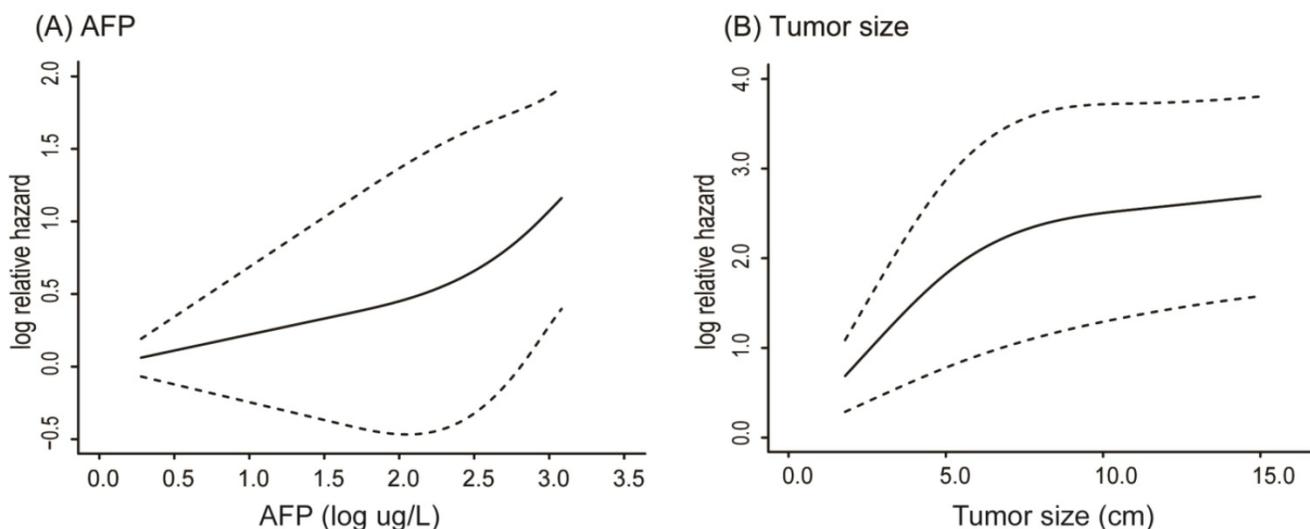
Figure 2. Nonlinear influence of AFP (A) and tumor size (B) on the hazard ratio of EHMs

Table 2. Cox proportional hazards regression model showing the factors associated with extrahepatic metastasis of HCC in the training cohort (N=453)

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	0.998	0.977-1.019	0.845			
Gender (male)	0.621	0.374-1.030	0.065			
HBsAg (positive)	1.305	0.599-2.843	0.503			
Tumor size (cm)	1.123	1.073-1.175	<0.001	1.099	1.049-1.152	<0.001
Microvascular invasion (presence)	1.854	1.223-2.810	0.004			
Tumor encapsulation (incomplete)	1.991	1.290-3.072	0.002			
Histopathological structure of tumor (coarse beam type)	3.212	1.402-7.361	0.006	2.382	1.030-5.512	0.043
Tumor differentiation (low)	1.714	1.073-2.739	0.024			
Satellite nodules (presence)	2.505	1.508-4.163	<0.001	1.936	1.156-3.244	0.012
Number of tumors (multiple)	1.611	1.009-2.575	0.046			
Liver cirrhosis (presence)	1.030	0.676-1.571	0.890			
HBV DNA (log IU/mL)	0.979	0.813-1.179	0.824			
TP (g/L)	0.991	0.964-1.017	0.483			
TBIL (umol/L)	1.009	0.983-1.036	0.489			
ALB (g/L)	0.957	0.919-0.997	0.034			
ALT (U/L)	1.000	1.000-1.001	0.415			
AST (U/L)	1.000	1.000-1.001	0.200			
GGT (U/L)	1.001	1.000-1.002	0.164			
AFU (U/L)	1.001	0.980-1.022	0.919			
ALP (U/L)	1.003	1.001-1.005	0.003			
PT (s)	0.985	0.828-1.171	0.860			
AFP (log ug/L)	1.522	1.198-1.934	0.001	1.399	1.098-1.783	0.007
CEA (ug/L)	0.994	0.956-1.032	0.742			
CA19-9 (U/mL)	1.001	0.991-1.011	0.812			
PLT (10⁹/L)	1.002	0.998-1.005	0.338			

CI: confidence interval; HR: hazard ratio; HBsAg: Hepatitis B surface antigen; TP: total protein; TBIL: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyltransferase; AFU: α-L-fucosidase; ALP: alkaline phosphates; PT: prothrombin time; AFP: a-fetoprotein; CEA: carcino-embryonic antigen; CA19-9: carbohydrate antigen 19-9; PLT: platelets.
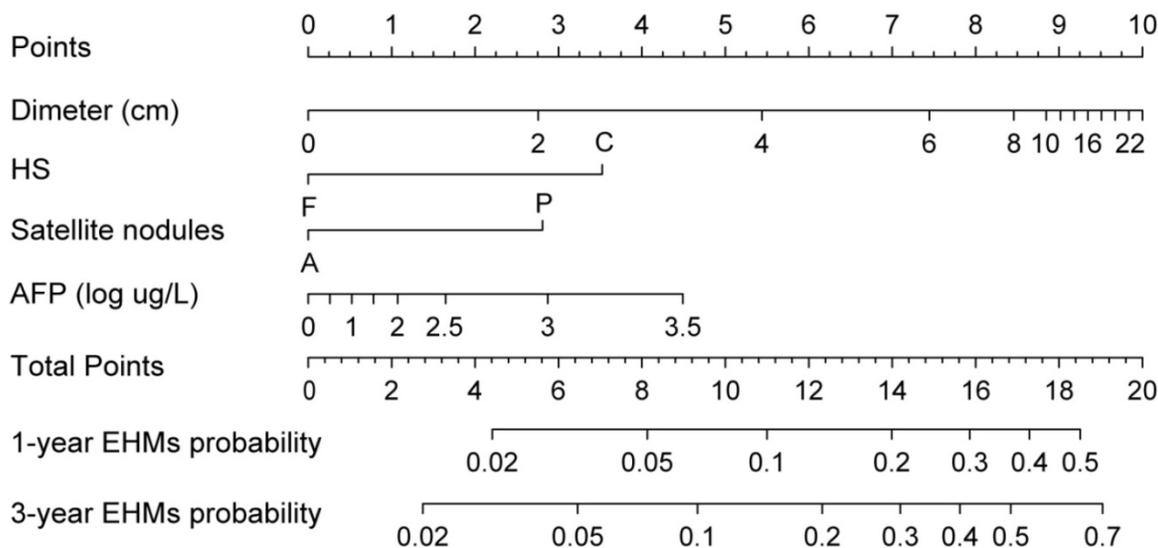
Figure 3. Nomogram predicting EHMs for HCC patients with adjuvant TACE following Hepatectomy. HS: histopathological structure of tumor; F: fine beam type; C: coarse beam type; A: absence; P: presence.

Construction of the nomogram for EHMs

A nomogram integrating these four significant independent variables to predict EHMs in the training cohort was then constructed (Figure 3). Patients who received TACE after hepatectomy had a higher score indicate a higher probability of developing EHMs. In order to calculate this score, the first step involved drawing a vertical line from the variable to the points scale in order to determine the corresponding points. This procedure was then repeated for each of the remaining risk factors. Finally, all values were summed on the total points axis, and a vertical line was drawn from the total points scale to the axis labeled "1-year EHMs probability" and "3-year EHMs probability" to calculate the probability of EHMs.
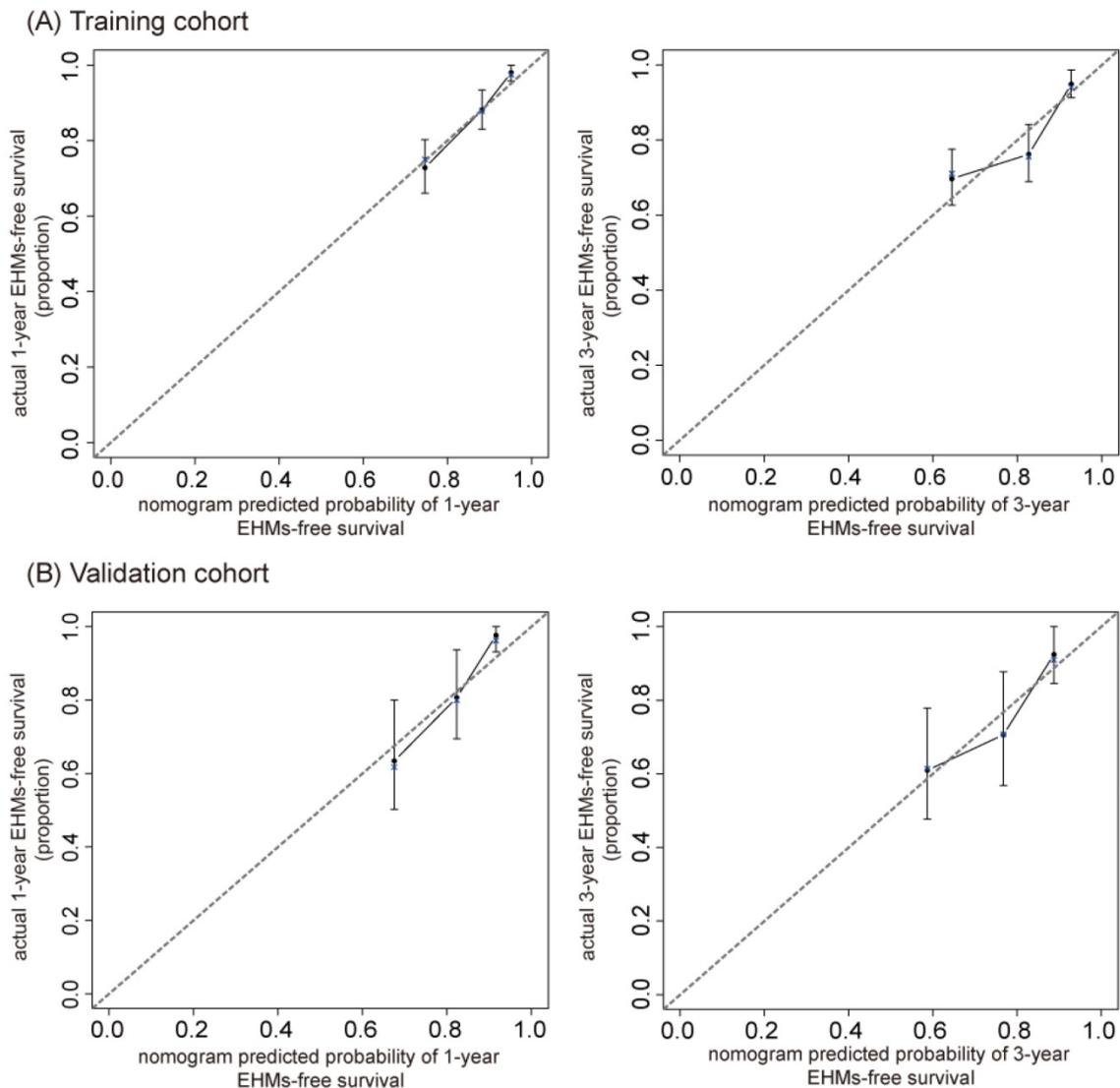
Figure 4. The calibration curve for nomogram at 1- and 3-year in the training cohort (A) and validation cohort (B). The nomogram predicted probability of EHMs-free survival is plotted on the x-axis; actual EHMs-free survival proportion is plotted on the y-axis. Thin gray dashed represents the reference line.

Validation and performance of the prediction nomogram

The C-index of our nomogram in the training cohort was 0.73 (95% CI, 0.68- 0.78), and calibration plots showed good agreement between the estimated probability by nomogram and the actual proportion (Figure 4A). For the independent validation cohort, and the nomogram displayed a C-index of 0.71 (95% CI, 0.63-0.79), which also represented a good calibration curve (Figure 4B). In addition, Figure 5 shows a plot of the time-dependent AUC, reflecting area under the ROC curve at all time points, indicating the comparative stability and adequate discriminative ability of our nomogram for predicting EHMs. It is clear that the AUC of the model is stable, which fluctuated around 0.75 both in the training and validation cohorts. Furthermore, the diagnostic capacity of the model is higher than that of any single one risk factor taken independently.

Decision tree model for predicted probabilities of EHMs based on nomogram

As noted previously, patients with higher scores had worse prognoses. Predicted probabilities of EHMs based on nomogram were divided into three groups using decision tree model by predicted risk scores. Patients who scored > 17 were determined to be in the high risk group. Scores ranging > 12 and ≤ 17 resulted in classifying patients into the moderate risk group. Patients who scored ≤ 12 were determined to be in the low risk group. We observed that 37.50% of patients in the high risk group had EHMs, while those in the moderate and low risk groups exhibited a rate of 20.11% and 5.66%, respectively, after three years of follow-up in the training cohort. Similarly, patients in

the high, moderate and low risk groups had EHMs with a rate of 38.46%, 21.43%, and 15.91%, respectively, after three years of follow-up in the validation cohort. Decision tree modeling was used to stratify probabilities of EHMs that were then used to plot Kaplan-Meier curves, both in the training and validation cohorts (all p < 0.05) (Figure 6). It is clear that those patients who scored ≤ 12 points had a much lower rate of EHMs.

Discussion

Adjuvant TACE is widely used in postoperative HCC patients with recurrence risk [23]. It was reported that patients who received adjuvant TACE after hepatectomy had significantly higher survival [2, 3]. Frequently, HCC presents as advanced disease, and despite curative-intent surgical resection, EHMs were common in HCC patients who underwent TACE after hepatectomy [6, 24]. Precise information about prognosis is essential for decision-making and patient counseling. Although some progress has been made on the management of EHMs, no good method is available for predicting EHMs, thus limiting their early detection. At present, there are some tools known as nomograms to predict disease outcomes or assess risk based on specific characteristics of a patient in the clinical practice [25-27]. In this study, we developed a nomogram, which is a kind of statistical
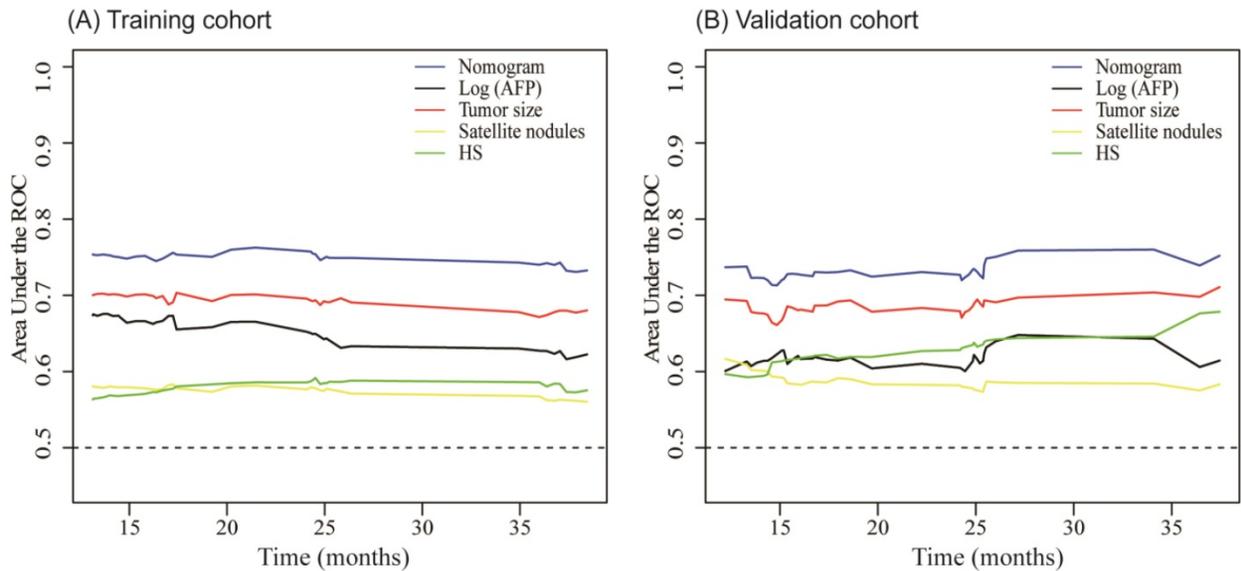
Figure 5. Time-dependent AUC plot for EHMs prediction model in the training cohort (A) and validation cohort (B). HS: histopathological structure of tumor.
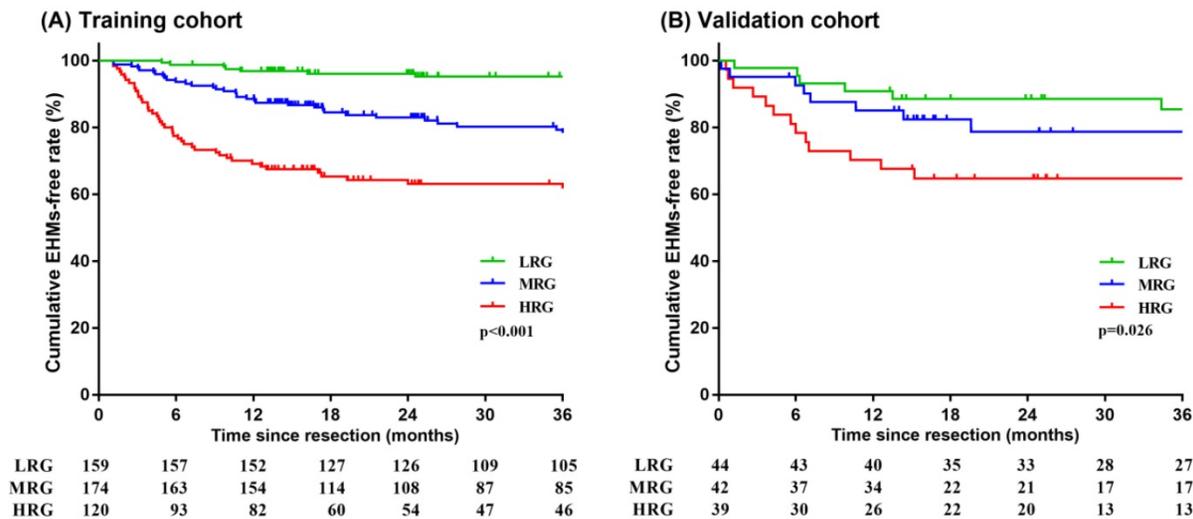
Figure 6. Kaplan–Meier survival analysis of HCC patients stratified into low-, moderate- and high-risk groups in the training cohort (A) and validation cohort **(B).** LRG: low risk group; MRG: moderate risk group; HRG: high risk group.

tool able to predict the probability of EHMs for individual patients by assessing multiple risk factors. Based on patients in the training cohort who had undergone adjuvant TACE following hepatectomy for HCC, we created a statistically predictive nomogram of EHMs probability. To the best of our knowledge, this is the first clinical scoring system for EHMs prediction in HCC patients who had undergone adjuvant TACE following hepatectomy.

In the present research, we developed a nomogram that performed well with a C-index of 0.73 (95% CI, 0.68 to 0.78) for prediction in the training cohort. Predictive performance was further certified by an external validation cohort with a C-index of 0.71 (95% CI, 0.63 to 0.79). Furthermore, by using a decision tree model, patients were divided into three groups: high risk, > 17 points; moderate risk, > 12 and ≤ 17 points; and low risk, ≤ 12 points. On the Kaplan-Meier curves, it is clear that those patients with low risk had a much lower rate of EHMs (Figure 6).

In this study, the nomogram included four variables consisting of presurgical baseline characteristics and pathological features of tumor. Our study suggests that large tumor diameter, coarse beam type of tumor histopathological structure, presence of satellite nodules and higher serum AFP level are significantly associated with an increased probability of EHMs. AFP is a routine tumor marker for HCC patients, higher AFP may suggest more advanced cancer burden and greater risk of remaining tumor and recurrence after surgery [28, 29]. In addition, many have reported that serum AFP is an important variable associated with HCC with EHMs [30, 31]. Thus, AFP was previously included as an independent risk factor for establishing a nomogram to predict metastasis of HCC [32]. It was previously modeled as having linear effect on predictive results; However, the use of a linear model alone may not accurately reflect the effect of AFP on outcome. Therefore, it is essential to take the nonlinear effect of AFP into consideration. It is clear from the graph that the influence of AFP on the HR of EHMs was linear under a threshold of almost 2 log(AFP) ug/L, after which it increased dramatically (Figure 2A).

As for tumor size which was also associated with a nonlinear effect on HR of EHMs. Studies have reported that tumor size is a vital predictive factor associated with HCC progression [33]. It also has been included in many staging systems for HCC. Overall survival among patients with a single-tumor > 5cm was significantly lower than patients with a single-tumor > 2 and ≤ 5cm (p < 0.001) [34]. Moreover, huge HCC (≥ 10 cm) is an independent risk factor owing to a high risk for initial extrahepatic

recurrence [35]. However, very few studies have reported on tumor diameter of HCC patients after partial hepatectomy and adjuvant TACE. The effect of tumor size on the risk of EHMs was linear up to approximately 6 cm diameter, after which the risk of EHMs increases more gradually (Figure 2B). The threshold effect of tumor size was also noted by Lim et al [36].

Other factors were also selected based on multivariate analyses, including the presence of satellite nodules and coarse beam type of tumor histopathological structure. Satellite nodules are an independent risk factor for tumor recurrence and patient survival [37]. The presence of satellite nodules was independently associated with the occurrence of postoperative complications [38]. In this study, tumor diameter and satellite nodules reflected the invasiveness of HCC, and they were significantly associated with EHMs. Patients who underwent TACE after curative resection with the presence of satellite nodules had a higher probability of EHMs (Figure 3). The tumor histopathological structure is mainly based on the number, arrangement and interstitial response of tumor cells, which are related to tumor differentiation, growth and dissemination. It includes fine beam type, coarse beam type, false gland tube type, compact type and hardened type. In pathological diagnosis, the histopathological structure of tumor exists interactively, so we distinguish it according to the main lesion types [39]. Fine beam type consists of 1-3 layers of cells, and the differentiation of tumor cells is better. Coarse beam type is formed by 20-30 cell layers, and the morphology of tumor cells is obviously abnormal. Also, the blood supply for coarse beam type is much more abundant; therefore, the invasiveness of this tumor type could be strengthened [40]. Thus, those patients classified as coarse beam type are at a high risk of EHMs.

In this study, we constructed a tool able to generate an individual's probability of developing EHMs by different prognostic and determinative variables. Using this model, the chance of developing EHMs based on data from individual cases could be calculated. Thus, the surgeon would be able to plan for case management early on to reduce both recurrence and EHMs after adjuvant TACE following HCC resection. The tool would also help the surgeon to determine which patients are good candidates for liver transplantation based on their risk for EHMs.

Our study does have some limitations. First, the data were acquired from a single institution, while it is generally necessary to validate such model against external centers with different geography. Second, most of our patients had a background of HBV

infection and liver cirrhosis, making it necessary to validate this model against a different disease background. Third, we also do think that it is necessary to validate our model with larger sample size in the future. Besides, many studies have demonstrated the association between circulating tumor cells (CTCs)/cancer stem cell markers and HCC postoperative metastasis. Currently we mainly aimed to use the clinical routine available detections to predict EHMs. CTCs and cancer stem cell markers might be integrated into the nomogram in the future, if the assay could be more optimized and clinical applicable as well as enough data available. However, in spite of these shortcomings, our model may offer an alternative way to monitor the risk of EHMs in postoperative HCC patients.

In conclusion, we have constructed a reliable nomogram to predict the probability of EHMs in individual HCC patients who have undergone TACE after hepatectomy. This is an easy-to-use tool for the early diagnosis and prevention of EHMs and could benefit surgeons in decision-making.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee of Eastern Hepatobiliary Surgery Hospital, Second Military Medical University.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Competing Interests

The authors have declared that no competing interest exists.

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