


ORIGINAL ARTICLE

Nomogram predicting extrahepatic metastasis of hepatocellular carcinoma based on commonly available clinical data

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Key words

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the second leading cause of cancer mortality worldwide.^{1,2} Extrahepatic metastasis (EHM), which is present in 13.5–42% of patients with HCC,^{3,4} leads to a very poor prognosis. The median survival time after diagnosis of EHM is

as low as 4.9 months (range 1–59 months),^{5,6} and the 1-year survival rate is 24.9%.⁶ Similarly, the 5-year survival rate was lower in the HCC patients with extrahepatic recurrence (21.5%) than those with only intrahepatic recurrence (36.3%; $P < 0.001$).⁷ In addition, the median survival time of HCC patients with EHM was also much shorter than that in those with only intrahepatic

Abstract

Background and Aim: Extrahepatic metastasis (EHM) of hepatocellular carcinoma (HCC) leads to a worse prognosis. We aimed to develop a nomogram based on noninvasive pretreatment clinical data to predict EHM of HCC sooner.

Methods: Three cohorts containing 1820, 479, and 988 HCC patients were enrolled from three hospitals in different regions in Taiwan and served as the training and validation cohorts. Pretreatment clinical data were analyzed by Cox regression modeling for independent risk factors of EHM.

Results: Platelet count $\geq 200 \times 10^3/\mu\text{L}$, serum alpha-fetoprotein $\geq 100 \text{ ng/dL}$, tumor size $\geq 3 \text{ cm}$, tumor number > 1 , and macrovascular invasion were independent risk factors for EHM and were used to develop a nomogram. This nomogram had concordance indices of 0.733 (95% confidence interval [CI]: 0.688–0.778) and 0.739 (95% CI: 0.692–0.787) for the prediction of EHM during a 5-year follow-up duration in the training and validation cohorts, respectively. A nomogram score > 61 implied a high risk of EHM (hazard ratio [HR] = 3.83; 95% CI: 2.77–5.31, $P < 0.001$).

Conclusion: We have developed a nomogram that could accurately predict EHM of HCC and be readily available for formulating individualized treatment for all individual HCC patients to improve therapeutic efficacy.

recurrence.⁸ Therefore, EHM greatly changes the patients' outcomes and should be crucially considered regarding the selection of initial treatment strategies, particularly for those preparing for curative hepatectomy and liver transplantation.⁹

Many parameters or models have been developed to predict EHM of HCC. Multivariate analyses have demonstrated many clinicopathological and serological factors that are predictive of EHM of HCC, including microscopic vascular invasion, serum vascular endothelial growth factor level,¹⁰ platelet-derived factors, P-selectin, serum soluble ERBB3 (a member of EGFR subfamily of receptor tyrosine kinases),¹¹ epidermal growth factor, platelet-derived growth factor receptor α , platelet-derived endothelial cell growth factor, hepatic growth factor, microRNA 214 and hepatoma-derived growth factor,¹² insulin-like growth factor, transforming growth factor β , interleukin (IL)-1 β , IL-8, CXC (Cys-X-Cys) motif containing ligand 12 (CXCL 12), sphingosine 1-phosphate (S1P), and lysophosphatidic acid.^{11,13–15} However, these are either pathological factors, which are dependent on tissue sampling, or molecular biomarkers, which are not available in most hospitals in the world. Therefore, the development of a new nomogram that is based on noninvasively clinically readily available data for all patients of HCC with an accuracy in predicting EHM of HCC before treatment is urgently demanded.

In this study, we enrolled three cohorts containing 1820, 479, and 988 HCC patients from three hospitals in different regions of Taiwan for developing and validating a nomogram that accurately predicts EHM of HCC. As this nomogram is based on pre-treatment, noninvasive clinical data, it is applicable to all patients to evaluate the potential risk of EHM as early as at the initial diagnosis. It will be also helpful for designing the best therapeutic strategy for individual HCC patients, particularly those preparing for curative hepatectomy or orthotopic liver transplantation.

Methods

Ethical statement. This retrospective, cohort, observational study complied with the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospitals in Taiwan (No.105-6012C). All patient-identifying information was securely protected by delinking from the main dataset and was available only to the investigators.

Study subjects. All data were collected from retrospective databases. Consecutive inpatients diagnosed with HCC from 2000 to 2009 at the Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan (LK); Chang Gung Memorial Hospital at Keelung (KL); and Chang Gung Memorial Hospital at Chiayi (CY), Chang Gung Memorial Hospitals, were evaluated for inclusion in the training (LK) and validation (KL and CY) cohorts, respectively (Fig. 1). The inclusion criteria were clinical and/or pathological diagnosis of HCC and a complete medical record, which was defined as inclusion of all of the following information: patient age and gender, alcohol usage, alpha-fetoprotein (AFP) level, complete blood count, albumin level, bilirubin level, prothrombin time, creatinine (Cr) level, aspartate aminotransferase level, alanine aminotransferase level, serum hepatitis B virus surface antigen and antibodies to hepatitis C virus (anti-HCV), pathological diagnosis if available, Edmondson's histological grade, ultrasonography or other imaging studies for tumor staging, computed tomography scan for determination of Barcelona Clinic Liver Cancer (BCLC) stage, tumor metastasis location, number of tumors, largest tumor size, the presence of liver cirrhosis, macrovascular invasion, ascites,

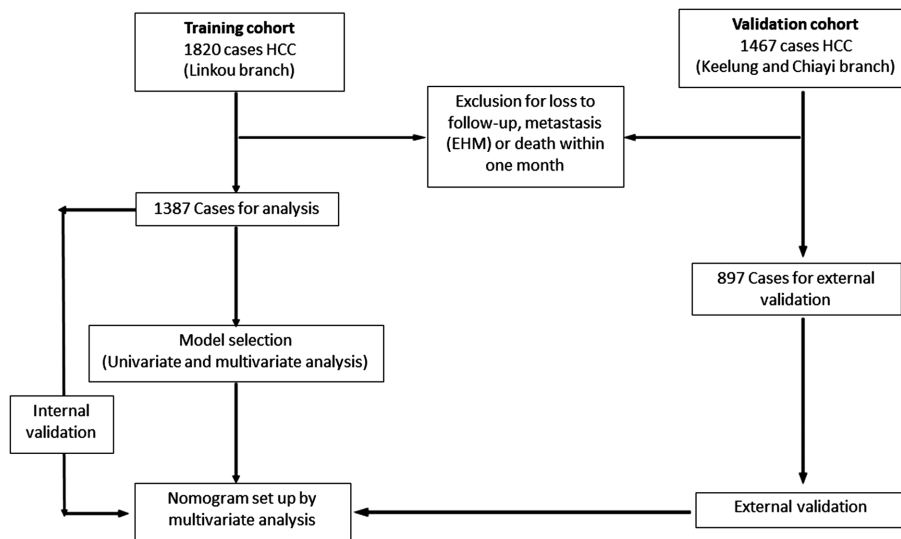


Figure 1 Patient study algorithm: Three cohorts from different regions in Taiwan were enrolled in this study. Patients with loss to follow-up or extrahepatic metastasis (EHM) or mortality within 1 month of primary treatment were excluded from the subsequent analyses. The first cohort (Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan) was used to identify factors that were able to predict EHM, thereby establishing a nomogram for this study. This nomogram was then validated regarding its accuracy in the evaluation of EHM risk by using both the training (internal validation) and validation (Chang Gung Memorial Hospital at Keelung and Chang Gung Memorial Hospital at Chiayi, external validation) cohorts. HCC, hepatocellular carcinoma.

date of surgical resection, date of diagnosis of EHM, and date of last follow-up or HCC-related death.

Macrovascular invasion, including tumor thrombosis inside a major branch of the portal vein, hepatic vein, and inferior vena cava, was diagnosed radiographically.^{16,17}

Table 1 Univariate analysis on the clinical characteristics for predicting extrahepatic metastasis of hepatocellular carcinoma patients in the training cohort[†].

Variable	Levels	HR	95% [CI]	P-value
AST (IU/L)		1.00	1.00–1.00	0.450
ALT (IU/L)		1.00	1.00–1.00	0.954
Total bilirubin (mg/dL)		0.95	0.83–1.09	0.460
Albumin (g/dL)		0.99	0.89–1.10	0.825
GGT (IU/L)		1.00	1.00–1.00	0.980
BUN (mg/dL)		1.01	1.00–1.02	0.105
Cr (mg/dL)		1.01	0.90–1.12	0.908
WBC (μ L)		1.00	1.00–1.00	0.000
Hgb (mg/dL)		0.99	0.95–1.03	0.574
Lymphocyte (%)		1.00	0.98–1.01	0.690
Neutrophil (%)		1.00	0.99–1.01	0.941
Prolong PT, s		1.01	0.95–1.06	0.776
Neutrophil/lymphocyte ratio		1.01	1.00–1.02	0.169
Gender	F	1.00		
	M	1.04	0.77–1.41	0.797
Age (year)	<65	1.00		
	\geq 65	0.91	0.69–1.19	0.471
ALK-P (IU/L)	<98	1.00		
	\geq 98	1.30	0.96–1.75	0.094
HBsAg	No	1.00		
	Yes	1.32	1.00–1.73	0.051
Anti-HCV	No	1.00		
	Yes	0.63	0.48–0.83	0.001
Alcoholism	No	1.00		
	Yes	1.04	0.57–1.92	0.896
Diabetes mellitus	No	1.00		
	Yes	0.67	0.46–0.97	0.034
Hypertension	No	1.00		
	Yes	0.77	0.55–1.07	0.122
Cirrhosis	No	1.00		
	Yes	0.82	0.59–1.14	0.236
Child-Pugh	0	1.00		
	A	0.99	0.70–1.40	0.940
	B	0.96	0.60–1.54	0.872
	C	0.61	0.24–1.55	0.299
Vascular invasion	No	1.00		
	Yes	4.40	3.15–6.15	0.000
AFP (ng/mL)	<100	1.00		
	\geq 100	1.64	1.22–2.19	0.001
Tumor size (cm)	<3	1.00		
	\geq 3	2.41	1.80–3.23	0.000
Tumor number	1	1.00		
	>1	2.21	1.69–2.89	0.000
BCLC stage	0	1.00		
	A	1.39	0.83–2.33	0.212
	B	2.96	1.81–4.85	0.000
	C	7.80	4.57–13.3	0.000
	D	1.54	0.61–3.85	0.359

Table 1 (Continued)

Variable	Levels	HR	95% [CI]	P-value
Platelet ($10^4/\mu$ L)	<10	1.00		
	10–20	1.64	1.17–2.31	0.004
	\geq 20	3.13	2.19–4.47	0.000

[†]Cases with extrahepatic metastasis on initial diagnosis or within 1 month after initial treatment have been excluded from the analysis.

AFP, alpha fetoprotein; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; anti-HCV, antibodies to hepatitis C virus; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; BUN, blood urea nitrogen; CI, confidence interval; Cr, creatinine; GGT, gamma glutamyl transpeptidase; HBsAg, hepatitis B virus surface antigen; Hgb, hemoglobin; HR, hazard ratio; PT, prothrombin time; WBC, white blood cells.

All patients were followed up for up to 5 years. Patients with less than 1 month of follow-up, who died within 1 month of diagnosis, and who developed EHM within 1 month of diagnosis were excluded (Fig. 1).

Tumor staging system. We stratified HCC stages in accordance with the BCLC staging system.¹⁸

Statistical methods. We used the statistical software R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria) to conduct the following analyses. Univariate and multivariate Cox regression analysis were used to examine the independent risk factors for predicting HCC EHM. The nomogram or discriminate functional analysis was used for the prediction of EHM, and the predictive performance was evaluated by the concordance index (C-index) and calibration curve. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics. We enrolled three cohorts of HCC patients from three hospitals in different regions of Taiwan to serve as the training (1820 cases from LK) and validation (479 cases from KL and 988 cases from CY) groups. After exclusion of those with a loss to follow-up, EHM, or mortality within 1 month after the initial treatment, 1387 and 897 eligible HCC patients were subjected to the subsequent analyses (Fig. 1). The clinical characteristics of the patients of the training and validation cohorts are not consistent (Table S1, Supporting information). The clinical characteristics of the HCC patients with *versus* without EHM in the training cohorts are shown in Table S2.

In our study, 228 patients had EHM in the training cohort. EHM mean times were 4.17 (4.01–4.29) years in the training cohort and 4.01 (3.89–4.14) years in the validation group. EHM incidence rates were 8, 20, and 29% and 10, 23, and 36% at 1 year, 3 years, and 5 years in the training and validation cohorts, respectively.

Risk factors associated with EHM during the subsequent follow-up. Univariate analysis of the 1387 cases in the training cohort indicated that anti-HCV (hazard ratio [HR] = 0.63; $P = 0.001$), WBC (HR = 1.00; $P = 0.000$), AFP ≥ 100 ng/mL (HR = 1.64; $P = 0.001$), pretreatment platelet

count $\geq 20 \times 10^4/\mu\text{L}$ ($P = 0.000$), macroscopic vascular invasion (HR 4.40; $P = 0.000$), tumor size ≥ 3 cm (HR = 2.41; $P = 0.000$), and tumor number > 1 (HR = 2.21; $P = 0.000$) at the initial diagnosis were significant factors associated with EHM (Table 1).

We also analyzed the effects of different therapies as the initial treatments on EHM as shown in Supplemental Table S3. Initial treatment with transcatheter arterial chemoembolization (HR = 0.56; $P = 0.029$), surgical resection or transplantation therapy (HR = 0.71; $P = 0.204$), and local tumor ablation (HR = 0.24; $P < 0.001$) had lower rates of EHM, whereas radiotherapy (HR = 3.29; $P = 0.006$) was associated with a higher incidence of EHM. However, because the selection of initial therapies was strictly based on the consensus guideline, which is primarily according to tumor stages, we excluded it from the subsequent multivariate analyses and nomogram establishment.

In the same cohort, multivariate Cox regression analysis indicated that pretreatment platelet count $\geq 20 \times 10^4/\mu\text{L}$ ($P = 0.002$), macroscopic vascular invasion (HR = 4.14; $P = <0.001$), tumor size ≥ 3 cm ($P = 0.003$), tumor number > 1

($P = 0.001$), and AFP ≥ 100 ng/mL ($P = 0.032$) were major independent risk factors (Table 2).

Development and validation of a nomogram predictive of EHM of HCC. We used the independent risk factors to build the nomogram for evaluation of EHM risk on the basis of macrovascular invasion, pretreatment platelet count $\geq 20 \times 10^4/\mu\text{L}$, tumor size of ≥ 3 cm, tumor number > 1 , and AFP ≥ 100 ng/mL (Fig. 2). It demonstrated good accuracy for predicting EHM with a C-index of 0.733 (95% confidence interval [CI]: 0.688–0.778) for the subsequent 5-year follow-up (Table 2). More specifically, calibration plots showed a good agreement in the presence of EHM between the risk estimation by the nomogram and clinical data at year(s) 1, 3, and 5 after the initial diagnosis (Fig. 3a).

To validate the accuracy of this nomogram in the prediction of EHM, we combined the other two cohorts (KL and CY cohorts) as the validation set, and multivariate Cox regression analysis demonstrated consistent results with those derived from the training cohort (Table 2). This nomogram model also showed

Table 2 Multivariate Cox regression analysis on the five independent factors related to extrahepatic metastasis (EHM) of the hepatocellular carcinoma (HCC) patients in both the training and validation cohorts.

Cohort	Training, $n = 872$			Validation, $n = 897$			
		0.733			0.739		
C-index							
Variable		HR	95% [CI]	P -value	HR	95% [CI]	P -value
Macrovascular invasion	Yes vs. No	4.14	2.76–6.22	<0.001	3.15	2.02–4.90	0.000
Tumor size (cm)	≥ 3 vs. <3	1.69	1.19–2.40	0.003	1.88	1.36–2.59	0.000
Tumor number	>1 vs. 1	1.70	1.25–2.31	0.001	1.39	1.03–1.88	0.030
AFP (ng/mL)	≥ 100 vs. <100	1.40	1.03–1.92	0.032	1.67	1.22–2.27	0.001
Pretreated platelet count ($10^4/\mu\text{L}$)	>20	1.97	1.28–3.04	0.002	2.56	1.72–3.81	0.000

C-index, concordance index in measuring the goodness of fit in prediction of EHM of HCC. AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio.

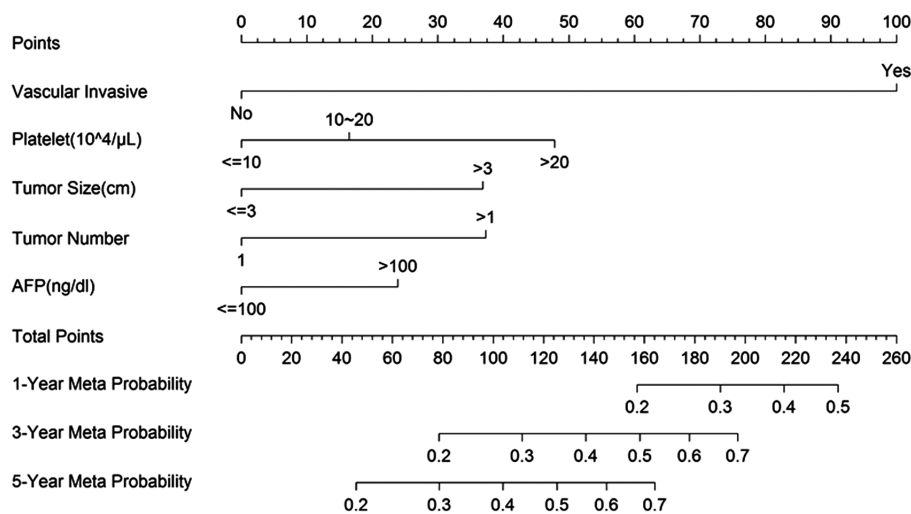


Figure 2 Nomogram predicting extrahepatic metastasis (EHM) of hepatocellular carcinoma based on the training cohort. The nomogram is used by adding the scores identified on the scale for the five parameters. The total nomogram scores of each patient can be used to predict EHM at 1, 3, and 5 year during subsequent follow-up.

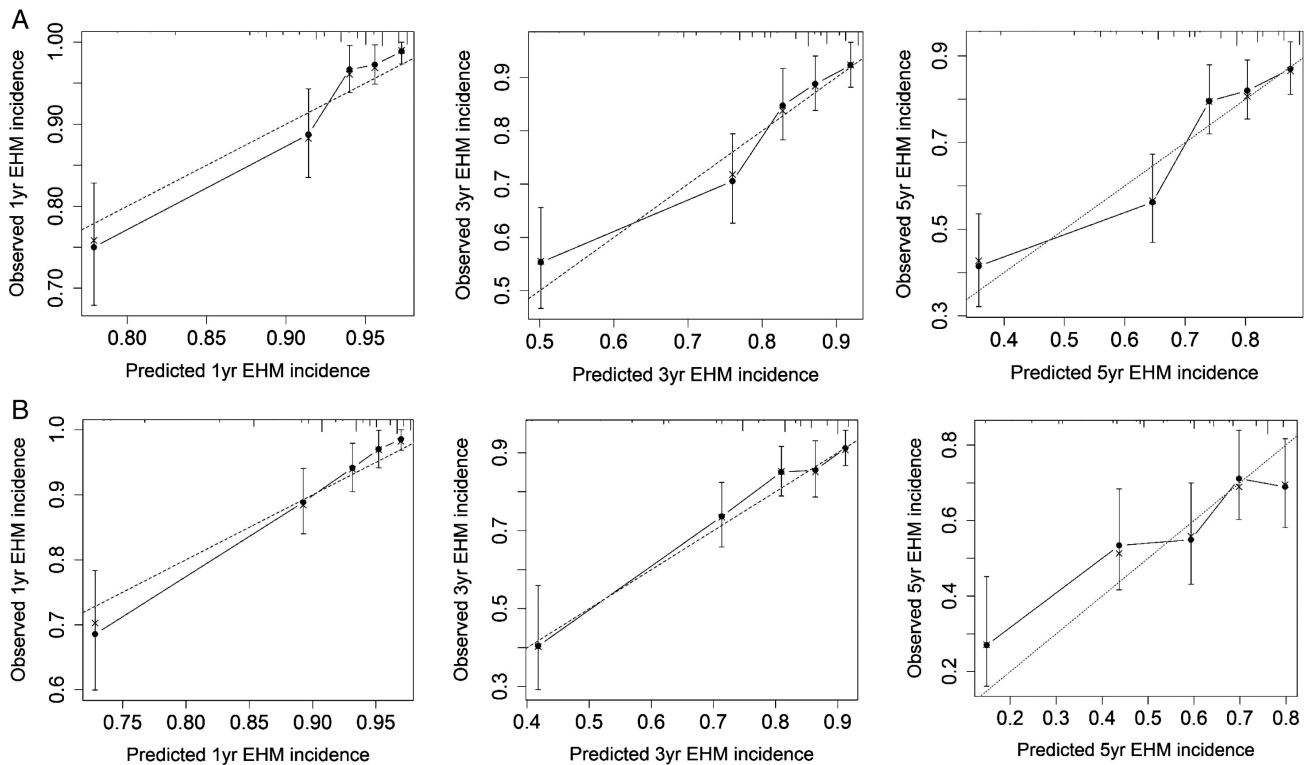


Figure 3 The calibration plots of the nomogram in the training and validation cohorts for extrahepatic metastasis (EHM) prediction. The X-axis represents the nomogram-predicted EHM, and the Y-axis shows the fraction of observed EHM and 95% CI observed by the Kaplan–Meier method. For patients with hepatocellular carcinoma, the calibration line fits along with the reference for EHM. (a) The results based on the training cohort. C index = 0.733 for 5-year follow-up. (b) The results derived from the validation cohort. C index = 0.739 for 5-year follow-up.

satisfactory goodness-of-fit and discrimination abilities with an overall C-index = 0.739 (95% CI: 0.692–0.787) in the prediction of EHM during the 5-year follow-up (Table 2). There were also good calibration curves for risk estimation at year(s) 1, 3, and 5 after the initial diagnosis in the validation set (Fig. 3b).

We further used receiver operating characteristic (ROC) to examine the performance of this nomogram in the discrimination of HCC patients with EHM from those without EHM and found that area ROC curves were 0.84, 0.79, 0.75, 0.75, and 0.74 and 0.83, 0.81, 0.78, 0.73, and 0.68 at the end of years 1, 2, 3, 4, and 5 in the training and validation cohorts, respectively (Fig. 4a and b).

A nomogram score stratified HCC patients into high and low risk for EHM. Based on the training cohort, we selected a median nomogram score of 61 as the cut-off score to examine its performance in identifying a subgroup of HCC patients with high risk of EHM. We found that it successfully categorized HCC patients into high and low risk of EHM during the subsequent 5-year follow-up in both the training (HR = 3.83; 95% CI: 2.77–5.31; $P < 0.001$; Fig. 4c) and validation (HR = 2.88; 95% CI: 2.13–3.90; $P < 0.001$; Fig. 4d) cohorts.

Discussion

Based on pretreatment, noninvasive clinical data on two sizable HCC cohorts (namely, 1820 and 1467 cases for the discovery

and validation, respectively), we have developed a nomogram that contains five independent risk factors for EHM: macrovascular invasion, pretreatment platelet count $\geq 20 \times 10^4/\mu\text{L}$, AFP $\geq 100 \text{ ng/mL}$, tumor number > 1 , and tumor size $\geq 3 \text{ cm}$. This nomogram demonstrated high accuracy in the prediction of EHM of HCC even up to 5 years after the initial treatment (C indices: 0.733 and 0.739 for the training and validation cohorts, respectively). Notably, the nomogram reported in this study can be used to predict all the HCCs as early as the initial diagnosis regardless of whether they are at an early or advanced stage. For those with AJCC (American Joint Committee on Cancer, seventh version) T1 HCC, tumor size $\geq 3 \text{ cm}$, AFP $\geq 100 \text{ ng/mL}$, and platelet count $\geq 20 \times 10^4/\mu\text{L}$ would be critically related to EHM. This is of crucial importance, particularly for HCC patients preparing for curative hepatectomy and liver transplantation.

Association of serum AFP level with HCC metastasis has been reported before by us¹⁹ and others.²⁰ Byeon *et al.* reported that the preoperative AFP level was an independent risk factor for EHM ($P = 0.014$) after a curative resection of HCC.⁷ Biologically, AFP has been reported to promote liver cancer growth and progression.²¹ Overexpression of AFP facilitates invasion and distant metastasis of HCC by upregulating the expression of metastasis-related proteins and activating the PI3K/AKT signaling pathway.^{22,23}

Thrombocytopenia is a hallmark of cirrhosis and a poor prognostic marker for patients with cirrhosis.¹⁹ Recently, we

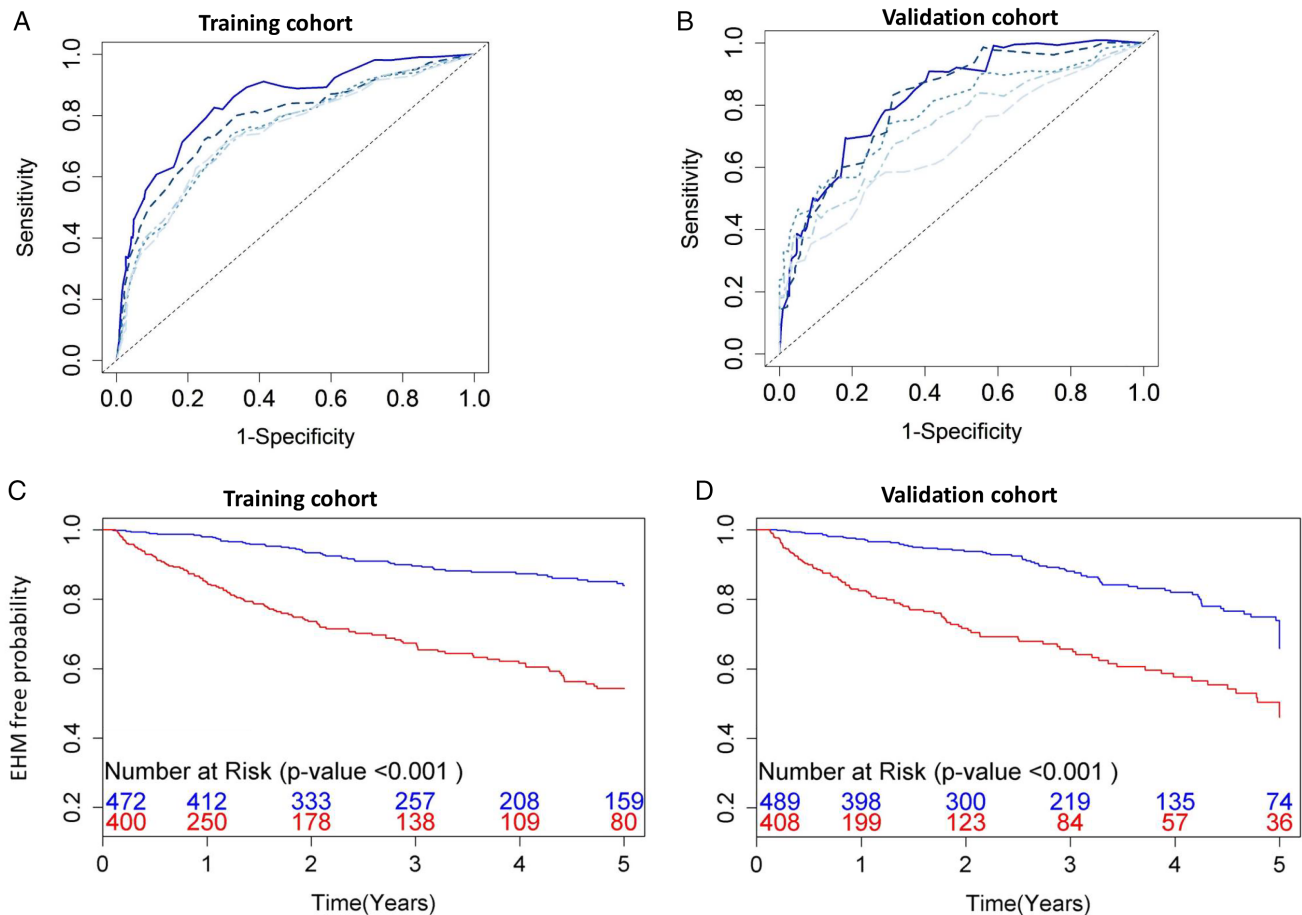


Figure 4 Performance of the nomogram in discrimination of hepatocellular carcinoma (HCC) patients with extrahepatic metastasis (EHM). (a & b) Receiver operating characteristic curves for EHM of the patients in the training cohort and the validation cohort. The receiver operating characteristic curves at the ends of year 1, 2, 3, 4, and 5 after the initial diagnosis are shown, and their areas under the curves are provided. (c & d) Kaplan–Meier cumulative survival analyses. (c) In the training cohort, the median of the nomogram score (61 points) was selected as the cut-off score to categorize the HCC patients into high- and low-risk subgroups ($P < 0.001$, log-rank tests). (d) The nomogram score of 61 divided the HCC patients of the validation cohort into high and low risk for EHM in the subsequent 5 years of follow-up. (a): (—), 1-year 0.84; (----), 2-year 0.79; (— · — ·), 3-year 0.75; (— · — ·), 4-year 0.75; (— · — ·), 5-year 0.74. (b): (—), 1-year 0.83; (----), 2-year 0.81; (— · — ·), 3-year 0.78; (— · — ·), 4-year 0.73; (— · — ·), 5-year 0.68. (c): (—), <score 61; (—), >score 61. (d): (—), <score 61; (—), >score 61.

reported that pretreatment platelet count predicts EHM of HCC.¹⁹ Indeed, it has been reported that a high platelet count is associated with systemic metastasis of other human cancers.^{24–29} Mechanistically, platelets have been shown to functionally promote the invasion and metastasis of cancer cells through a variety of molecular mechanisms.^{30–38} On the other hand, thrombocytopenia in cirrhotic patients with HCC suggests a relatively advanced stage of cirrhosis but represents protection from EHM of HCC.^{39,40}

It has been known that large tumor size is predictive of tumor metastasis, which is attributable to an actin cytoskeleton remodeling-induced epithelial–mesenchymal transition of tumor cells in a cell density-dependent manner.⁴¹ Carr *et al.* reported a relationship between increasing HCC size and the percentage of patients with EHM.⁴² In the current study, tumor size was an independent predictor of EHM ($P = 0.004$). We used a tumor size of ≥ 3 cm in the current study because a tumor size cut-off value of 3 cm or 5 cm has a similar HR for EHM. Indeed, it has

been reported that tumor size of ≥ 3 cm is an important turning point in the transformation of a tumor from having relatively benign features to a more aggressive behavior.⁴³

The association of multiple liver tumors and EHM may be related to either high invasiveness of tumor cells per se (intrahepatic metastasis) or a microenvironment favoring and facilitating tumor invasion and metastasis. Indeed, inflammatory and/or hypoxic microenvironments usually provide a niche for the epithelial–mesenchymal transition of tumor cells for invasion and metastasis.⁴⁴

Microscopic vascular invasion has been known as a major factor associated with EHM of HCC.^{45–47} Here, we further found that large vascular invasion at initial diagnosis is strongly associated with EHM during follow-up for up to 5 years.

Neoadjuvant therapies have been developed as a downstaging treatment for the tumors to meet the transplant criteria or as a bridging therapy to control the tumor growth in patients who

are waitlisted for a transplant.¹⁷ The nomogram model developed in this study could be used to identify HCC patients who meet the criteria for liver transplantation therapy but have a high risk for EHM and will benefit from neoadjuvant therapies before undergoing liver transplantation or to avoid an unnecessary main surgery.

Conclusions

We have developed a reliable nomogram that is based on readily available clinical data to predict EHM. This is a useful tool for the early prediction and primary prevention of EHM. It is also helpful for designing the best treatment strategies for each individual HCC patient as early as at the initial diagnosis.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Comparison of clinical characteristics between the patients in the training and validation cohorts.

Table S2 Comparison of the initial clinical manifestations between patients with and without EHM.

Table S3 Comparison of the selection of initial treatment between patients with and without EHM during the subsequent 5-year follow-up.