Original Article

DOI: 10.5582/bst.2024.01387

Risk stratification model for predicting distant metastasis after hepatectomy for hepatocellular carcinoma: A multi-institutional analysis

Mingda Wang[1,2,§,*], Shaodong Lv[1,§], Yongkang Diao[1,2,§], Jiahao Xu[1,2], Fujie Chen[3], Yuchen Li[3], Weimin Gu[4], Hong Wang[5], Yuze Yang[6], Yongyi Zeng[7], Yahao Zhou[8], Xianming Wang[9], Jie Li[10], Tinghao Chen[11], Yingjian Liang[12], Lanqing Yao[1,2], Lihui Gu[1,2], Han Wu[1,2], Xinfei Xu[1,2], Chao Li[1,2], Feng Shen[1,2], Tian Yang[1,2,3,*]

[1] Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Naval Medical University), Shanghai, China;
[2] Eastern Hepatobiliary Clinical Research Institute, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Naval Medical University), Shanghai, China;
[3] Department of Graduate, Bengbu Medical College, Bengbu, China;
[4] The First Department of General Surgery, the Fourth Hospital of Harbin, Heilongjiang, China;
[5] Department of General Surgery, Liuyang People's Hospital, Hunan, China;
[6] Department of Hepatobiliary and Pancreatic Surgery, General Surgery Centre, First Hospital of Jilin University, Changchun, China;
[7] Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital, Fujian Medical University, Fujian, China;
[8] Department of Hepatobiliary Surgery, Pu'er People's Hospital, Yunnan, China;
[9] Department of General Surgery, First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong, China;
[10] Department of Hepatobiliary Surgery, Fuyang People's Hospital, Anhui, China;
[11] Department of General Surgery, Ziyang First People's Hospital, Sichuan, China;
[12] Department of Hepatobiliary Surgery, First Affiliated Hospital of Harbin Medical University, Heilongjiang, China.

SUMMARY: Distant metastasis after hepatectomy for hepatocellular carcinoma (HCC) significantly impairs long-term outcome. This study aimed to identify patterns, risk factors, and develop a prediction model for distant metastasis at first recurrence following HCC resection. This multi-center retrospective study included patients undergoing curative hepatectomy for HCC. Risk factors for distant metastasis were identified using Cox regression. A nomogram was constructed and validated using the concordance index (C-index) and calibration curves. Among 2,705 patients, 1,507 experienced recurrence, with 342 (22.7 per cent) developing distant metastasis. Common metastatic sites included extrahepatic vessels (36.2 per cent), lungs (26.0 per cent), and lymph nodes (20.8 per cent). Patients with distant metastasis had significantly worse 5-year overall survival compared to those with intrahepatic recurrence (9.1 versus 41.1 per cent, $p < 0.001$). Independent risk factors included preoperative tumor rupture, tumor size over 5.0 cm, multiple tumors, satellite nodules, macro- and microvascular invasion, narrow resection margin, and intraoperative blood transfusion. The nomogram demonstrated excellent discrimination (C-index > 0.85) and accurately stratified patients into three risk categories. In conclusion, distant metastasis at first recurrence following HCC resection was associated with poor prognosis. The proposed nomogram facilitates accurate prediction of distant metastasis, potentially informing personalized postoperative monitoring and interventions for high-risk patients.

Keywords: hepatocellular carcinoma, hepatectomy, distant metastasis, survival, recurrence

1. Introduction

Hepatocellular carcinoma (HCC) remains a formidable global health challenge, ranking as the 6th most common cancer and the 3rd leading cause of cancer-related mortality worldwide (*1,2*). Despite advancements in treatment modalities, hepatectomy persists as the primary curative option for a significant proportion of HCC patients. However, postoperative recurrence poses a substantial obstacle to long-term survival, with up to 70% of patients experiencing recurrence within 5 years (*3-8*). This high recurrence rate underscores critical need for a comprehensive understanding of recurrence patterns and associated risk factors to guide

postoperative surveillance and adjuvant treatment strategies (*9,10*).

Recurrence patterns in HCC can be broadly categorized as intrahepatic or extrahepatic (distant metastasis) (*11,12*). While intrahepatic recurrence is more common and often attributed to residual microscopic lesions or *de novo* tumors, distant metastasis represents a particularly aggressive form of disease progression (*13,14*). Distant metastasis not only signifies a more malignant tumor phenotype but also portends a markedly adverse prognosis, especially when occurring at the initial diagnosis of recurrence (*15*). Patients with distant metastasis face limited effective therapeutic options compared to those with isolated intrahepatic recurrence, who may benefit from curative treatments such as repeat hepatectomy or local ablation (*11*). Recent studies have identified various risk factors for HCC recurrence, including tumor-related factors (*e.g.*, tumor size, tumor number, microsatellite nodules, vascular invasion) and treatment-related factors (*e.g.*, narrow surgical margin, intraoperative blood transfusion) (*4,6,7,15-22*). However, the comprehensive landscape of risk factors specifically for distant metastasis at first recurrence remains sparsely documented. Moreover, existing prediction models for HCC recurrence often lack specificity for distant metastasis and have not been widely validated across diverse patient populations (*23-26*).

Recent advancements in understanding distant metastasis have led to potential long-term survival benefits through re-resection for oligometastases or systemic treatments for unresectable multiple metastases (*27,28*). However, standardized protocols and optimized treatment strategies for managing distant metastasis at first recurrence after HCC resection are still lacking, necessitating further in-depth exploration. Given the significant impact of distant metastasis on patient outcomes and potential for targeted interventions in high-risk individuals, there is an urgent need for accurate risk stratification tools. Early identification of patients at elevated risk for distant metastasis could inform more intensive surveillance protocols and guide application of adjuvant therapies, potentially improving long-term outcomes (*29,30*).

As such, this large-scale, multi-institutional study aimed at elucidating patterns and risk factors of distant metastasis at first recurrence following curative-intent hepatic resection for HCC. Furthermore, this study sought to develop and validate a predictive nomogram to stratify patients according to their risk of distant metastasis. This tool could potentially enable clinicians to tailor postoperative management strategies and optimize allocation of healthcare resources during postoperative follow-up for HCC patients.

2. Patients and Methods

2.1. Study design and patient population

This retrospective cohort study encompassed patients who underwent curative-intent hepatic resection for initially diagnosed HCC from January 2013 to December 2020 at 11 tertiary hospitals across China (Eastern Hepatobiliary Surgery Hospital, Fourth Hospital of Harbin, Liuyang People's Hospital, First Hospital of Jilin University, Mengchao Hepatobiliary Hospital, Pu'er People's Hospital, Shandong Provincial Qianfoshan Hospital, Fuyang People's Hospital, Ziyang First People's Hospital, First Affiliated Hospital of Harbin Medical University, and Affiliated Hospital of Nantong University). Each participating center contributed more than 100 cases (ranging from 118 to 1,053 cases). The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013) and was approved by the Institutional Review Boards of all participating centers. Informed consent for data use in clinical research was obtained from all patients at the time of surgery. Inclusion criteria were: *i*) age ≥ 18 years, *ii*) histologically confirmed HCC, iii) no prior anti-tumor treatments, and *iv*) curative hepatectomy (R0 resection) performed. Exclusion criteria included: *i*) palliative hepatectomy (R1 or R2 resection), *ii*) early death within 90 days after surgery or loss to follow-up at 6 months after surgery, and *iii*) missing critical prognostic data.

2.2. Data collection

Detailed baseline information on clinicopathological characteristics and operative variables was obtained from prospectively maintained databases at each institution. Patient-related factors included age, sex, etiology of liver disease, Child-Pugh grade, preoperative serum alpha-fetoprotein (AFP) level, and presence of cirrhosis or portal hypertension. Tumor and surgery-related variables consisted of largest tumor size, tumor number, vascular invasion status (microscopic or macroscopic), satellite nodules, tumor differentiation, preoperative tumor rupture, width of resection margin, intraoperative blood loss and transfusion, surgical approach (open or laparoscopic), type (anatomical or non-anatomical) and extent (minor or major) of hepatectomy. Preoperative tumor rupture was documented based on clinical presentations and imaging findings. For patients with controlled rupture and no evidence of peritoneal seeding on intraoperative exploration, surgical resection was considered feasible since rupture typically occurs on tumor surface rather than affecting intrahepatic boundaries. Cirrhosis was confirmed by postoperative histopathological findings. Portal hypertension was determined based on endoscopic evidence of esophageal varices or splenomegaly with platelet count less than 100 $\times 10^9$/L. Major hepatectomy was defined as removal of ≥ 3 Couinaud liver segments (*31*). Anatomical hepatectomy was characterized as complete anatomical removal of hepatic segments based on Couinaud's classification according to the Brisbane 2000 system (*31*).

2.3. Follow-up and study endpoints

After hepatectomy, a relatively uniform and standardized surveillance strategy for recurrence was implemented across all participating centers. This protocol involved regular monitoring of serum AFP level, abdominal ultrasonography, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) every 2-3 months for the first two years, then every 3-6 months thereafter.

The diagnosis of HCC recurrence primarily relied on the identification of new lesions showing consistent radiological manifestations with the primary tumors, with or without a continuous increase of serum AFP level. Generally, intrahepatic recurrence was confirmed by abdominal CT or MRI scan, while suspicion of extrahepatic recurrence was confirmed by performing additional examinations, including brain and chest CT, bone scintigraphy, or positron emission tomography when necessary. A variety of treatment modalities ranging from curative to palliative approaches were implemented upon the confirmation of HCC recurrence, taking into consideration the type, location, and extent of the recurrent disease. Specifically, patients with only intrahepatic recurrence may undergo curative treatment options such as repeat hepatectomy, local ablation, or liver transplantation, as well as non-curative treatments including transarterial chemoembolization, systemic therapy, or best supportive care.

The primary outcome was the occurrence of distant metastasis at first recurrence following hepatectomy, which was defined as a recurrence site outside the liver, with or without concomitant intrahepatic lesions. Secondary outcomes included overall survival (OS), calculated from initial hepatectomy to the date of death or last follow-up, and post-recurrence survival (PRS), measured from the diagnosis of first recurrence to death or last follow-up. Early recurrence was defined as occurring within 12 months post-hepatectomy, while late recurrence occurred beyond 12 months. Detailed information regarding the patterns of recurrence, treatment modality, and post-recurrence follow-up data is documented.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies (n) or percentages (%). Comparisons between groups were performed using the Student's *t*-test or Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher's exact test for categorical variables.

Survival outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were conducted to identify risk factors associated with distant metastasis. Variables with a p-value < 0.10 in univariate analysis were included in the multivariate model. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI). A nomogram for predicting distant metastasis was constructed based on the independent risk factors identified in the multivariate analysis. The model's discriminative capability was assessed using Harrell's concordance index (C-index) and the area under the receiver operating characteristic curve (AUC). Calibration was evaluated using calibration curves. The nomogram was subjected to internal validation using bootstrap resampling (1,000 resamples). Based on the nomogram scores, patients were stratified into low-, intermediate-, and high-risk groups using cut-off values setting at the 50th and 85th percentiles. Kaplan-Meier curves were used to compare distant metastasis-free survival among the risk groups. All statistical analyses were performed using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and recurrence patterns

Of 2,902 HCC patients who underwent curative-intent hepatectomy, 2,705 met the inclusion criteria and constituted the final analytic cohort (Supplemental Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=246*). At a median follow-up of 62.0 months, 1,507 patients (55.7%) experienced postoperative recurrence. Among these, 342 patients (22.7% of overall recurrences, 12.6% of the entire cohort) presented with distant metastasis at first recurrence.

Comparisons of clinicopathological characteristics among patients with intrahepatic recurrence only, distant metastasis at first recurrence, and patients without recurrence are summarized in Table 1. Compared to patients without recurrence or with only intrahepatic recurrence, those with distant metastasis were significantly younger, had higher rates of preoperative tumor rupture, larger tumor size, multiple tumors, satellite nodules, poor tumor differentiation, and increased likelihood of microvascular and macrovascular invasion (all p < 0.001). Additionally, patients with distant metastasis more frequently underwent major hepatectomy, had narrow surgical margin (< 1.0 cm), experienced massive intraoperative blood loss, and received intraoperative blood transfusion.

3.2. Patterns of distant metastasis

Table 2 details the clinical characteristics of patients with

Table 1. Clinicopathologic and operative characteristics of patients undergoing hepatectomy for hepatocellular carcinoma

n (%)	Total (*n* = 2,705)	No Recurrence (*n* = 1,198)	Only Intrahepatic Recurrence (*n* = 1,165)	Distant Metastasis (*n* = 342)	p^a	p^b	p^C
Age, years*	53 ± 12	54 ± 11	53 ± 12	50 ± 11	0.001	< 0.001	0.001
> 65 years	421 (15.6)	203 (16.9)	182 (15.6)	36 (10.5)	0.077	0.006	0.015
Male sex	2,364 (87.4)	1,033 (86.2)	1,030 (88.4)	301 (88.0)	0.103	0.729	0.260
ASA score > 2	351 (13.0)	183 (15.3)	140 (12.0)	28 (8.2)	0.002	0.004	0.001
HBV (+)	2,314 (85.5)	981 (81.9)	1,040 (89.3)	293 (85.7)	< 0.001	0.962	< 0.001
HCV (+)	71 (2.6)	23 (1.9)	40 (3.4)	8 (2.3)	0.052	0.857	0.067
Cirrhosis	1,918 (70.9)	807 (67.4)	879 (75.5)	232 (67.8)	< 0.001	0.169	< 0.001
Portal hypertension	625 (23.1)	260 (21.7)	286 (24.5)	79 (23.1)	0.123	0.914	0.260
Preoperative Child-Pugh grade B	224 (8.3)	73 (6.1)	120 (10.3)	31 (9.1)	< 0.001	0.530	0.001
Preoperative BCLC stage B/C	1,184 (48.3)	312 (26.0)	599 (51.4)	273 (79.8)	< 0.001	< 0.001	< 0.001
Preoperative AFP level > 400 ng/mL	768 (32.9)	231 (26.5)	379 (33.0)	158 (50.8)	< 0.001	< 0.001	< 0.001
Preoperative tumor rupture	100 (3.7)	20 (1.7)	40 (3.4)	40 (11.7)	< 0.001	< 0.001	< 0.001
Largest tumor size, cm*	5.9 ± 3.9	4.7 ± 3.1	6.2 ± 4.0	8.7 ± 4.3	< 0.001	< 0.001	< 0.001
> 5.0 cm	1,315 (48.6)	449 (37.5)	601 (51.5)	265 (77.7)	< 0.001	< 0.001	< 0.001
Multiple tumors	520 (19.2)	120 (10.0)	280 (24.1)	120 (35.2)	< 0.001	< 0.001	< 0.001
Macrovascular invasion	255 (9.4)	31 (2.6)	121 (10.4)	103 (30.1)	< 0.001	< 0.001	< 0.001
Microvascular invasion	1,195 (44.2)	343 (28.6)	607 (52.1)	245 (71.8)	< 0.001	< 0.001	< 0.001
Satellite nodules	516 (19.1)	103 (8.6)	276 (23.7)	137 (40.2)	< 0.001	< 0.001	< 0.001
Poor tumor differentiation	2,296 (84.9)	947 (79.0)	1,039 (89.2)	310 (90.6)	< 0.001	0.002	< 0.001
Laparoscopic approach	1,051 (38.9)	432 (36.1)	555 (47.6)	64 (18.7)	0.008	< 0.001	< 0.001
Narrow resection margin (< 1.0 cm)	1,428 (52.8)	518 (43.2)	698 (59.9)	212 (62.0)	< 0.001	< 0.001	< 0.001
Major hepatectomy	626 (23.1)	175 (14.6)	298 (25.6)	153 (44.7)	< 0.001	< 0.001	< 0.001
Intraoperative blood loss > 600 mL	485 (17.9)	157 (13.1)	208 (17.9)	120 (35.2)	< 0.001	< 0.001	< 0.001
Intraoperative blood transfusion	401 (14.8)	127 (10.6)	162 (13.9)	112 (32.8)	< 0.001	< 0.001	< 0.001

AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer. *Values are mean ± standard deviation or median (interquartile range). [a]Compared between patients with recurrence (distant metastasis with/without intrahepatic recurrence) *vs.* patients without recurrence. [b]Compared between patients with distant metastasis *vs.* patients without distant metastasis (only intrahepatic recurrence or no recurrence). [C]Compared among the three groups.

distant metastasis at first recurrence. The most common sites were extrahepatic gross vessels (*n* = 124, 36.2%), lungs (*n* = 89, 26.0%), lymph nodes (*n* = 71, 20.8%), peritoneal seeding (*n* = 48, 14.0%), adrenal glands (*n* = 26, 7.6%), bones (*n* = 10, 2.9%), and brain (*n* = 4, 1.2%). Notably, 230 patients (67.3%) experienced distant metastasis within the first year after surgery, and 255 (74.6%) had multiple metastatic lesions.

3.3. Survival outcomes

Table 2. Clinical characteristics of patients with distant metastasis at first recurrence after hepatectomy for hepatocellular carcinoma

n (%)	Distant Metastasis (*n* = 342)
Male sex	301 (88.0)
Age at the diagnosis of distant metastasis, years*	51 ± 11
Child-Pugh grade at the diagnosis of distant metastasis (*n* = 302)	
A	254 (84.1)
B/C	48 (15.9)
Interval to first recurrence, months*	
Early recurrence (within 1 year after surgery)	230 (67.3)
Late recurrence (beyond 1 year after surgery)	112 (32.7)
Lesion numbers of distant metastasis	
Single metastatic lesion	87 (25.4)
Multiple metastatic lesions	255 (74.6)
Metastatic site of distant metastasis	
Extrahepatic gross vascular metastasis	124 (36.2)
Lung metastasis	89 (26.0)
Lymph node metastasis	71 (20.8)
Peritoneal seeding metastasis	48 (14.0)
Adrenal metastasis	26 (7.6)
Bone metastasis	10 (2.9)
Brain metastasis	4 (1.2)

*Values are mean ± standard deviation.

As shown in Table 3 and Figure 1, patients with distant metastasis had significantly poorer survival outcomes. The 5-year OS rates were 9.1%, 41.1%, and 90.8% for patients with distant metastasis, only intrahepatic recurrence, and no recurrence, respectively ($p < 0.001$). The median PRS for patients with distant metastasis was significantly shorter than for those with only intrahepatic recurrence (7.0 *vs.* 24.6 months, $p < 0.001$). With regard to the treatment modalities, the proportion of patients undergoing potentially curative treatment for recurrent lesions among patients with distant metastasis was significantly lower than among patients with only intrahepatic recurrence (14.0% *vs.* 47.1%, $p < 0.001$).

3.4. Risk factors of distant metastasis

Supplemental Table S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=246*) and Table 4 summarize the independent risk factors associated with overall recurrence and distant metastasis at first recurrence after surgery, as identified through univariate and multivariate Cox-regression analyses. Several variables, including preoperative AFP level > 400 ng/mL, preoperative tumor rupture, largest tumor size > 5.0 cm, multiple tumors, microvascular and macrovascular invasion, satellite nodules, narrow surgical margin, and intraoperative blood transfusion, were identified as independent risk factors of distant metastasis at the first recurrence after HCC resection.

Further analysis of predictors for worse PRS was conducted among patients who experienced distant metastasis at first recurrence. As noted in Table 5, independent risk factors associated with PRS included short time interval to recurrence (within 1 year after hepatectomy), concurrent intrahepatic recurrence, and

Table 3. Comparison of recurrent patterns, treatment modalities and post-recurrence survival between patients with intrahepatic recurrence only and patients with distant metastasis at first recurrenc

n (%)	Overall Recurrence (*n* = 1,507)	Only Intrahepatic Recurrence (*n* = 1,165)	Distant Metastasis (*n* = 342)	*p*
Male sex	1,331 (88.3)	1,030 (88.4)	301 (88.0)	0.867
Age at first recurrence, years*	54 ± 12	55 ± 12	51 ± 12	< 0.001
Child-Pugh grade B/C at the diagnosis of recurrence	181/1,334 (13.6)	133/1,032 (12.9)	48/302 (15.9)	< 0.001
Interval to recurrence				
Early recurrence (within 1 year after surgery)	791 (52.5)	561 (48.2)	230 (67.3)	< 0.001
Late recurrence (beyond 1 year after surgery)	716 (47.5)	604 (51.8)	112 (32.7)	
Treatment modality for the recurrent tumor				
Potentially curative treatments	597 (39.6)	549 (47.1)	48 (14.0)	< 0.001
Non-curative treatments	910 (60.4)	616 (62.9)	294 (86.0)	
Deaths during the follow-up	1,118 (74.2)	792 (68.0)	326 (95.3)	< 0.001
Median OS (95% CI), months	37.8 (34.5, 41.0)	49.6 (45.9, 53.2)	17.6 (15.4, 19.7)	< 0.001
1-year OS rate, %	81.2	86.6	62.9	
3-year OS rate, %	51.1	59.8	21.6	
5-year OS rate, %	33.8	41.1	9.1	
Median PRS (95% CI), months	18.2 (16.6, 19.9)	24.6 (22.3, 26.9)	7.0 (6.1, 7.9)	< 0.001
1-year PRS rate, %	62.0	70.9	32.5	
3-year PRS rate, %	32.4	39.7	8.4	
5-year PRS rate, %	19.7	25.1	2.7	

*Values are mean ± standard deviation; CI, confidence interval; OS, overall survival; PRS, post-recurrence survival.

receiving non-curative treatment modalities for recurrent tumors. Furthermore, survival curves also demonstrated that patients who experienced early recurrence or had concurrent intrahepatic recurrence had worse PRS rates in comparison to those who experienced late recurrence (beyond 1 year after surgery) or did not have concurrent intrahepatic recurrence (Supplemental Figure S2-S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=246*).

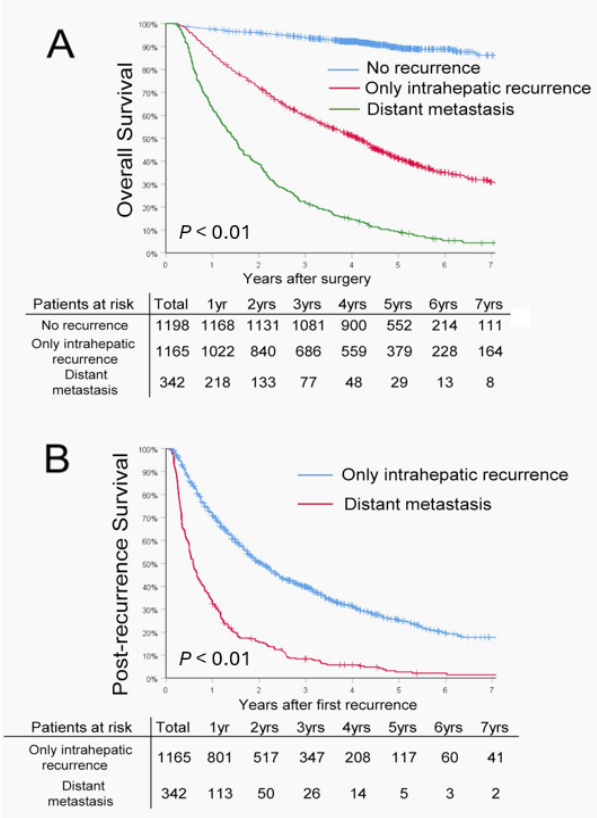

Figure 1. Kaplan-Meier survival curves comparing (A) overall survival and (B) post-recurrence survival among patients with no recurrence, only intrahepatic recurrence, and distant metastasis at first recurrence after hepatectomy for hepatocellular carcinoma.

3.5. Prediction model for distant metastasis

Based on the independent risk factors of distant metastasis, a novel nomogram for predicting 1-year and 3-year distant metastasis at first recurrence following HCC resection has been constructed (Figure 2A). Each predictive variable in the nomogram was assigned a weighted score, which was determined by its regression coefficient in the multivariable analysis (Supplemental Table S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=246*). These scores were then summed for each patient, representing their total scores and corresponding to the predicted probabilities of developing distant metastasis. The nomograms exhibited excellent discriminatory and calibration abilities across the entire cohort, with C-indices of 0.875, 0.865, and 0.871 for predicting distant metastasis at 1-year, 2-year, and 3-year intervals, respectively (Figure 2B). The calibration curves further demonstrated a robust alignment between the predicted probabilities and the observed occurrences of distant metastasis (Figure 2, C-D).

3.6. Risk stratification of distant metastasis

Based on the nomogram scores, patients were stratified

Table 4. Univariate and multivariate Cox-regression analyses predicting distant metastasis at first recurrence after hepatectomy for hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV *p*	MV HR (95% CI)	MV *p*
Age	> 65 *vs.* ≤ 65 years	0.622 (0.441-0.879)	0.007	NS	0.383
Sex	Male *vs.* female	0.936 (0.676-1.298)	0.692		
ASA score	> 2 *vs.* ≤ 2	0.871 (0.688-1.096)	0.164		
HBV (+)	Yes *vs.* no	1.093 (0.808-1.480)	0.564		
HCV (+)	Yes *vs.* no	0.881 (0.437-1.776)	0.723		
Cirrhosis	Yes *vs.* no	0.900 (0.717-1.130)	0.364		
Portal hypertension	Yes *vs.* no	1.017 (0.790-1.309)	0.896		
Preoperative Child-Pugh grade	B *vs.* A	1.293 (0.894-1.872)	0.172		
Preoperative AFP level > 400 ng/mL	Yes *vs.* no	2.766 (2.213-3.456)	< 0.001	1.687 (1.344-2.117)	< 0.001
Preoperative tumor rupture	Yes *vs.* no	5.133 (3.687-7.145)	< 0.001	2.558 (1.808-3.617)	< 0.001
Largest tumor size	> 5.0 *vs.* ≤ 5.0 cm	4.946 (3.830-6.389)	< 0.001	2.430 (1.845-3.202)	< 0.001
Multiple tumors	Yes *vs.* no	3.255 (2.603-4.071)	< 0.001	1.388 (1.013-1.902)	0.042
Macrovascular invasion	Yes *vs.* no	9.703 (7.640-12.323)	< 0.001	3.442 (2.639-4.489)	< 0.001
Microvascular invasion	Yes *vs.* no	4.420 (3.488-5.601)	< 0.001	2.079 (1.597-2.706)	< 0.001
Satellite nodules	Yes *vs.* no	4.615 (3.707-5.746)	< 0.001	1.716 (1.246-2.364)	0.001
Poor tumor differentiation	Yes *vs.* no	2.114 (1.469-3.044)	< 0.001	NS	0.792
Surgical approach	Open *vs.* laparoscopic	1.170 (0.882-1.486)	0.451		
Narrow resection margin	Yes *vs.* no	1.761 (1.414-2.193)	< 0.001	1.653 (1.325-2.063)	< 0.001
Major hepatectomy	Yes *vs.* no	3.816 (3.078-4.730)	< 0.001	NS	0.563
Intraoperative blood loss > 600 mL	Yes *vs.* no	3.159 (2.528-3.947)	< 0.001	NS	0.534
Intraoperative blood transfusion	Yes *vs.* no	3.670 (2.925-4.604)	< 0.001	1.486 (1.157-1.910)	0.002

AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; NS, not significant; UV, univariate.

Table 5. Univariate and multivariate Cox-regression analyses predicting post-recurrence survival among patients who developed distant metastasis at first recurrence after hepatectomy for hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV *p*	MV HR (95% CI)	MV *p*
Sex	Male *vs.* female	1.693 (0.839-3.414)	0.141		
Age at first recurrence	> 65 *vs.* ≤ 65 years	0.406 (0.673-2.940)	0.365		
HBV (+)	Yes *vs.* no	0.972 (0.561-1.685)	0.920		
Cirrhosis at first recurrence	Yes *vs.* no	1.004 (0.631-1.596)	0.987		
Portal hypertension at first recurrence	Yes *vs.* no	1.902 (0.753-4.805)	0.174		
Child-Pugh grade at first recurrence	B/C *vs.* A	1.677 (1.015-2.771)	0.044	NS	0.213
Interval to recurrence	<1 *vs.* ≥ 1 year	1.433 (0.935-2.196)	0.099	2.340 (1.477-3.706)	< 0.001
Largest recurrent tumor size	> 5.0 *vs.* ≤ 5.0 cm	1.671 (0.947-2.948)	0.076	NS	0.356
Multiple metastatic lesions	Yes *vs.* no	2.322 (0.918-5.872)	0.075	NS	0.546
Metastatic site	Others *vs.* lung	1.285 (0.831-1.986)	0.259		
Concurrent intrahepatic recurrence	Yes *vs.* no	1.575 (1.175-2.111)	0.002	3.169 (1.303-7.706)	0.011
Treatment modality for recurrent tumor	Curative *vs.* non-curative	0.556 (0.279-0.782)	0.001	0.423 (0.268-0.669)	< 0.001

AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MV, multivariate; NS, not significant; UV, univariate.

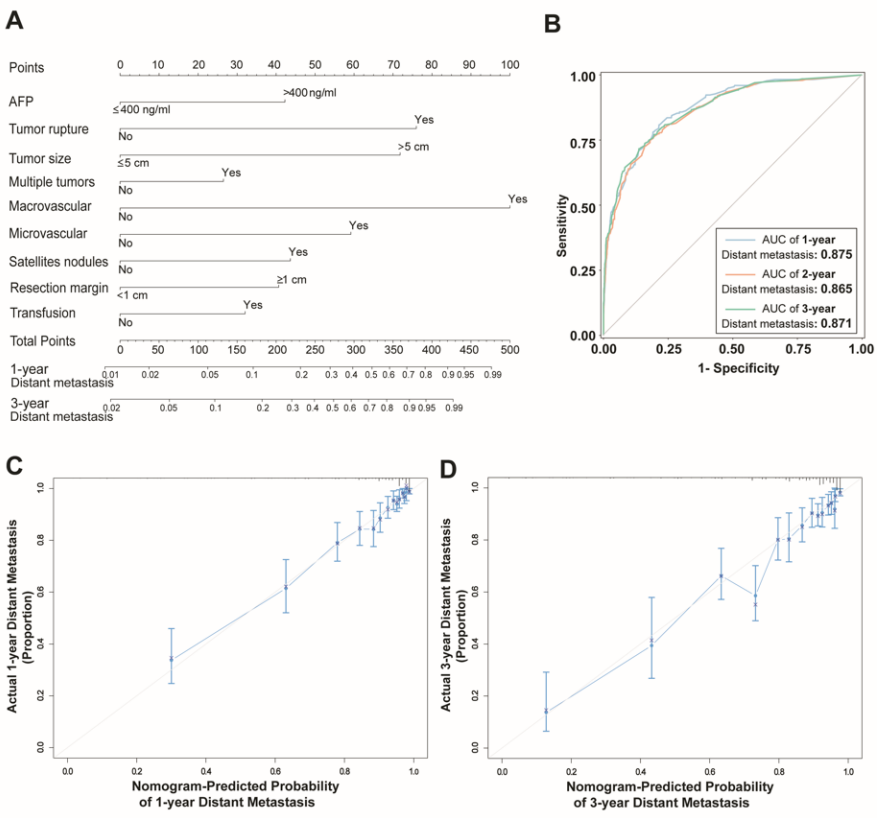

Figure 2. Nomogram for predicting distant metastasis at first recurrence after hepatectomy for hepatocellular carcinoma. **(A)** The nomogram incorporating independent risk factors. **(B)** Receiver operating characteristic curves for predicting 1-, 2-, and 3-year distant metastasis. **(C)** Calibration curve for 1-year distant metastasis prediction. **(D)** Calibration curve for 3-year distant metastasis prediction. The nomogram-predicted probability of distant metastasis is plotted on the X axis, and the actual distant metastasis is plotted on the Y axis. AUC, Area under the curve.

into low, intermediate, and high-risk groups, with cut-off values setting at the 50th and 85th percentiles. The high-risk group had a 2.98-fold higher probability of developing distant metastasis compared to the low-risk group (HR: 2.981, 95% CI: 2.639-3.268, $p < 0.001$), while the intermediate-risk group had a 1.54-fold higher probability (HR: 1.544, 95% CI: 1.253-1.845, $p < 0.001$) (Supplemental Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=246*). Kaplan-Meier survival curves for the low, intermediate, and high-risk groups stratified by the nomograms for distant metastasis are depicted in Figure 3. The cumulative rate of distant metastasis at first recurrence after hepatectomy for HCC is significantly higher in the high-risk group compared to the low-risk and moderate-risk groups ($p < 0.001$).

4. Discussion

This large-scale, multi-institutional study comprehensively

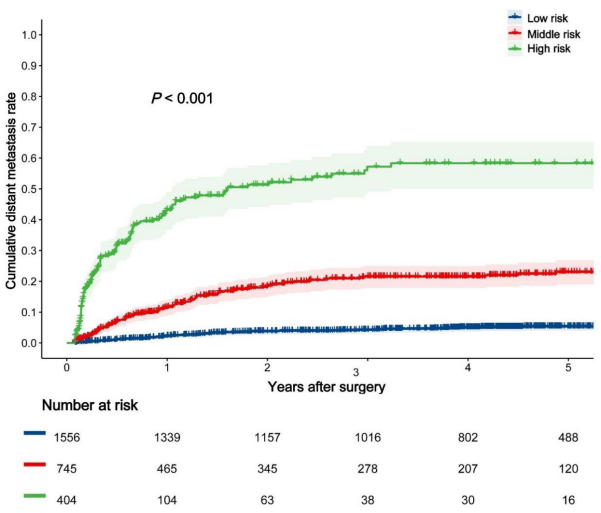

Figure 3. Kaplan-Meier curves showing cumulative rate of distant metastasis for low-, intermediate-, and high-risk groups stratified by the nomogram.

analyzed the patterns, risk factors, and outcomes of distant metastasis at first recurrence following curative hepatectomy for HCC. The findings of the present study reveal that distant metastasis occurs in a substantial proportion of patients with postoperative recurrence (22.7%) and is associated with dismal long-term outcomes. We have developed and internally validated a novel nomogram that accurately predicts the risk of distant metastasis, potentially enabling more personalized postoperative management strategies. Meanwhile, the observed patterns of distant metastasis in our cohort provide important insights into the biological behavior of recurrent HCC. The predominance of extrahepatic vascular and pulmonary metastases underscores the hematogenous spread as a key mechanism of distant dissemination. This finding is consistent with previous studies highlighting the role of circulating tumor cells in HCC metastasis (*32-35*) and suggests potential targets for future interventions aimed at preventing distant spread.

Our study identified several independent risk factors for distant metastasis, many of which reflect aggressive tumor biology. Among these factors, preoperative tumor rupture warrants particular attention. Through stringent inclusion criteria, we selected only patients whose preoperative rupture was promptly controlled and showed no evidence of peritoneal seeding upon intraoperative exploration. Since tumor rupture typically occurs on the diaphragmatic or visceral surface rather than affecting intrahepatic tumor boundaries, surgical resection with adequate margins was technically feasible following careful evaluation of tumor size and location, as confirmed by negative surgical margins on postoperative pathological examination. Notably, among the 100 patients with tumor rupture, 40% developed distant metastasis, a significantly higher rate compared to the non-rupture group, indicating that tumor rupture remains a crucial risk factor for distant dissemination even when R0 resection is achieved. Other risk factors, including vascular invasion, tumor size, and multiplicity, further emphasize the importance of early detection and timely intervention.

Our study on predicting post-hepatectomy distant metastasis demonstrates several distinctive features. First, unlike most existing models in previous studies that predict overall recurrence or survival (*23-26*), this work represents the first large-scale investigation specifically addressing distant metastasis, the recurrence pattern associated with the poorest prognosis. Then, we observed that 36.2% (124 cases) of distant metastases occurred in extrahepatic vessels, a critical pattern not well documented in current literature. More importantly, 67.3% of distant metastases developed within the first postoperative year, identifying a crucial temporal window for clinical intervention. Lastly, our prediction model achieved superior discriminative ability, with C-indices exceeding 0.85, surpassing most existing models, thus enabling more precise risk stratification and individualized surveillance protocols.

Our findings have important clinical implications, particularly in the context of regional differences in HCC management. While there are notable variations in disease etiology and treatment paradigms between Eastern and Western countries, especially regarding surgical intervention for intermediate/advanced HCC, carefully selected patients with high-risk features can achieve survival benefits through hepatectomy. The proposed nomogram effectively stratifies these patients into distinct risk groups, enabling adaptation of post-resection management strategies. Unlike intrahepatic recurrence where curative local treatments remain viable options, patients with distant metastasis primarily rely on systemic therapies. For those identified as high-risk, our prediction model supports administration of intensified surveillance protocols, including earlier and more frequent imaging examinations to detect metastatic lesions at a treatable stage. This risk-stratified approach proves particularly valuable as it guides both personalized monitoring schedules and the timing of systemic therapy initiation, with high-risk patients being potential candidates for adjuvant treatment or enrollment in clinical trials evaluating novel therapeutic strategies (*29,30*).

Our study has several limitations. First, despite the multi-institutional nature of our cohort, all participating centers were in China, potentially limiting the generalizability of our findings to other populations with different HCC etiologies. Second, our model is based solely on clinicopathological factors and does not incorporate molecular markers, which could potentially enhance its predictive accuracy. Future studies integrating genomic and proteomic data may further refine risk stratification for distant metastasis in HCC. Third, as a real-world retrospective study, standardization

of adjuvant therapy was challenging due to multiple factors, including evolving evidence for adjuvant treatment efficacy and varying institutional protocols. Current clinical trials have yielded conflicting results regarding the effectiveness of postoperative adjuvant therapy in reducing HCC recurrence, underscoring the need for large-scale prospective studies to establish optimal adjuvant treatment strategies, particularly for patients identified as high-risk for distant metastasis.

In conclusion, this study provides a comprehensive analysis of distant metastasis patterns following HCC resection and presents a novel, internally validated nomogram for predicting this adverse outcome. The ability to accurately stratify patients according to their risk of distant metastasis may inform personalized postoperative surveillance strategies and guide early intervention in high-risk individuals. Future prospective studies are warranted to evaluate the clinical impact of risk-adapted management based on our prediction model and to explore targeted approaches for preventing distant metastasis in HCC.

Acknowledgements

We would like to express our gratitude to Prof. Chen Zhong and his team from the Department of Hepatobiliary Surgery, Affiliated Hospital of Nantong University, for their participation in this multicenter retrospective study and their valuable contribution of HCC patient data.

Funding: This study was supported by the National Natural Science Foundation of China (No. 82273074, 82425049 for Yang T; 82372813 for Wang MD), Shanghai Health and Hygiene Discipline Leader Project (No. 2022XD001 for Yang T), Shanghai Outstanding Academic Leader Program (No. 23XD1424900 for Yang T), Natural Science Foundation of Shanghai (No. 22ZR1477900 for Wang MD), and Shanghai Science and Technology Committee Rising-Star Program (No. 22QA1411600 for Wang MD; 24YF2758600 for Diao YK).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022; 400:1345-1362.
2. Wang MD, Diao YK, Yao LQ, Fan ZQ, Wang KC, Wu H, Gu LH, Xu JH, Li C, Lv GY, Yang T. Emerging role of molecular diagnosis and personalized therapy for hepatocellular carcinoma. *iLIVER.* 2024; 3:100083.
3. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: Trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019; 16:589-604.
4. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018; 68:723-750.
5. Yao LQ, Chen ZL, Feng ZH, *et al.* Clinical features of recurrence after hepatic resection for early-stage hepatocellular carcinoma and long-term survival outcomes of patients with recurrence: A multi-institutional analysis. Ann Surg Oncol. 2022; 29:4291-4303.
6. Yan WT, Li C, Yao LQ, *et al.* Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: A large-scale multicenter study. Hepatobiliary Surg Nutr. 2023; 12:155-168.
7. Wang MD, Li C, Liang L, Xing H, Sun LY, Quan B, Wu H, Xu XF, Wu MC, Pawlik TM, Lau WY, Shen F, Yang T. Early and late recurrence of hepatitis B virus-associated hepatocellular carcinoma. Oncologist. 2020; 25:e1541-e1551.
8. Chen WY, Li C, Liu ZP, *et al.* Novel online calculator to predict reduced risk of early recurrence from adjuvant transarterial chemoembolisation for patients with hepatocellular carcinoma. eGastroenterology. 2023; 1:e100008.
9. Xu X, Wang MD, Xu JH, *et al.* Adjuvant immunotherapy improves recurrence-free and overall survival following surgical resection for intermediate/advanced hepatocellular carcinoma a multicenter propensity matching analysis. Front Immunol. 2023; 14:1322233.
10. Gou XX, Shi HY, Li C, Chen ZL, Ouyang W, Sun LY, Diao YK, Wang MD, Yao LQ, Gu LH, Pawlik TM, Lau WY, Shen F, Xue J, Yang T. Association of adjuvant radiation therapy with long-term overall and recurrence-free survival after hepatectomy for hepatocellular carcinoma: A multicenter propensity-matched study. Int J Radiat Oncol Biol Phys. 2022; 114:238-249.
11. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015; 261:947-955.
12. Tsilimigras DI, Bagante F, Moris D, *et al.* Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer Criteria. Ann Surg Oncol. 2020; 27:2321-2331.
13. Ivanics T, Murillo Perez CF, Claasen M, Claasen MPAW, Patel MS, Morgenshtern G, Erdman L, Shwaartz C, Rajendran L, O'Kane GM, Hansen BE, Cleary SP, Sapisochin G. Dynamic risk profiling of HCC recurrence after curative intent liver resection. Hepatology. 2022; 76:1291-1301.
14. Papaconstantinou D, Tsilimigras DI, Pawlik TM. Recurrent hepatocellular carcinoma: Patterns, detection, staging and treatment. J Hepatocell Carcinoma. 2022; 9:947-957.
15. Yoon JH, Choi SK, Cho SB, Kim HJ, Ko YS, Jun CH. Early extrahepatic recurrence as a pivotal factor for survival after hepatocellular carcinoma resection: A 15-year observational study. World J Gastroenterol. 2022; 28:5351-5363.
16. Hong SK, Jin XL, Suh S, Hong SY, Hong K, Han ES, Lee JM, Choi Y, Yi NJ, Lee KW, Suh KS. Different risk factors for early and late recurrence after curative resection of hepatocellular carcinoma. World J Surg. 2022; 46:197-206.
17. 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, 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.
18. Xing H, Zhang WG, Cescon M, *et al.* Defining and predicting early recurrence after liver resection of hepatocellular carcinoma: A multi-institutional study. HPB (Oxford). 2020; 22:677-689.
19. Tang SC, Diao YK, Lin KY, *et al.* Association of Pringle maneuver with postoperative recurrence and survival following hepatectomy for hepatocellular carcinoma: A multicenter propensity score and competing-risks regression analysis. Hepatobiliary Surg Nutr. 2024; 13:412-424.
20. Feng ZH, Wang MD, Chen Z, *et al.* Risk factors and long-term prognosis of beyond-Milan recurrence after hepatectomy for BCLC stage 0/A hepatocellular carcinoma: A large-scale multicenter study. Surgery. 2022; 172:1147-1155.
21. Zhang H, Han J, Xing H, Li ZL, Schwartz ME, Zhou YH, Chen TH, Wang H, Gu WM, Lau WY, Wu H, Wu MC, Shen F, Yang T. Sex difference in recurrence and survival after liver resection for hepatocellular carcinoma: A multicenter study. Surgery. 2019; 165:516-524.
22. Wang MD, Sun LY, Qian GJ, Li C, Gu LH, Yao LQ, Diao YK, Pawlik TM, Lau WY, Huang DS, Shen F, Yang T. Prothrombin induced by vitamin K Absence-II versus alpha-fetoprotein in detection of both resectable hepatocellular carcinoma and early recurrence after curative liver resection: A retrospective cohort study. Int J Surg. 2022; 105:106843.
23. Liang L, Quan B, Wu H, *et al.* Development and validation of an individualized prediction calculator of postoperative mortality within 6 months after surgical resection for hepatocellular carcinoma: an international multicenter study. Hepatol Int. 2021; 15:459-471.
24. Ni X, Li D, Dai S, Pan H, Sun H, Ao J, Chen L, Kong H. Development and evaluation of nomograms to predict the cancer-specific mortality and overall mortality of patients with hepatocellular carcinoma. Biomed Res Int. 2021; 2021:1658403.
25. Lu Y, Ren S, Jiang J. Development and validation of a nomogram for survival prediction in hepatocellular carcinoma after partial hepatectomy. BMC Surg. 2023; 23:27.
26. Diao YK, Sun L, Wang MD, *et al.* Development and validation of nomograms to predict survival and recurrence after hepatectomy for intermediate/advanced (BCLC stage B/C) hepatocellular carcinoma. Surgery. 2024; 176:137-147.
27. Yoh T, Seo S, Taura K, Iguchi K, Ogiso S, Fukumitsu K, Ishii T, Kaido T, Uemoto S. Surgery for recurrent hepatocellular carcinoma: Achieving long-term survival. *Ann Surg.* 2021; 273:792-799.
28. Midorikawa Y, Takayama T, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Teramoto K, Yoshida N, Kobayashi N, Tsuji S, Higaki T. Favorable outcomes of surgical resection for extrahepatic recurrent hepatocellular carcinoma. Hepatol Res. 2020; 50:978-984.
29. Mo A, Lin B, Chen D. Efficacy of sequential TACE on primary hepatocellular carcinoma with microvascular invasion after radical resection: a systematic review and meta-analysis. World J Surg Oncol. 2023; 21:277.
30. Feng X, Feng GY, Tao J, Ao YP, Wu XH, Qi SG, Shi ZR. Comparison of different adjuvant therapy regimen efficacies in patients with high risk of recurrence after radical resection of hepatocellular carcinoma. J Cancer Res Clin Oncol. 2023; 149:10505-10518.
31. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg. 2013; 257:377-382.
32. Lu M, Zhu WW, Wang X, *et al.* ACOT12-dependent alteration of acetyl-CoA drives hepatocellular carcinoma metastasis by epigenetic induction of epithelial-mesenchymal transition. Cell Metab. 2019; 29:886-900. e5.
33. Sun YF, Xu Y, Yang XR, Guo W, Zhang X, Qiu SJ, Shi RY, Hu B, Zhou J, Fan J. Circulating stem cell-like epithelial cell adhesion molecule-positive tumor cells indicate poor prognosis of hepatocellular carcinoma after curative resection. Hepatology. 2013; 57:1458-1468.
34. Hu ZQ, Zhou SL, Li J, Zhou ZJ, Wang PC, Xin HY, Mao L, Luo CB, Yu SY, Huang XW, Cao Y, Fan J, Zhou J. Circular RNA sequencing identifies CircASAP1 as a key regulator in hepatocellular carcinoma metastasis. Hepatology. 2020; 72:906-922.
35. Guo W, Sun YF, Shen MN, *et al.* Circulating tumor cells with stem-like phenotypes for diagnosis, prognosis, and therapeutic response evaluation in hepatocellular carcinoma. Clin Cancer Res. 2018; 24:2203-2213.

Received December 6, 2024; Revised January 26, 2025; Accepted February 21, 2025.

[§]These authors contributed equally to this work.
**Address correspondence to:*
Ming-Da Wang and Tian Yang, Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Naval Medical University), No. 225, Changhai Road, Shanghai 200438, China.
E-mail: wangmingda1987@163.com (MW); or yangtianehbh@smmu.edu.cn (TY)

Released online in J-STAGE as advance publication March 4, 2025.