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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Multi-Institutional Development and External Validation of a Nomogram for Prediction of Extrahepatic Recurrence After Curative-Intent Resection for Hepatocellular Carcinoma

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ABSTRACT

Backgrounds. Extrahepatic recurrence of hepatocellular carcinoma (HCC) after surgical resection is associated with unfavorable prognosis. The objectives of the current study were to identify the risk factors and develop a nomogram for the prediction of extrahepatic recurrence after initial curative surgery.

Methods. A total of 635 patients who underwent curative-intent resection for HCC between 2000 and 2017 were identified from an international multi-institutional database. The clinicopathological characteristics, risk factors, and long-term survival of patients with extrahepatic recurrence were analyzed. A nomogram for the prediction of extrahepatic recurrence was established and validated in 144 patients from an external cohort.

Results. Among the 635 patients in the derivative cohort, 283 (44.6%) experienced recurrence. Among patients who recurred, 80 (28.3%) patients had extrahepatic ± intrahepatic recurrence, whereas 203 (71.7%) had intrahepatic recurrence only. Extrahepatic recurrence was associated with more advanced initial tumor characteristics, early recurrence, and worse prognosis versus non-extrahepatic recurrence. A nomogram for the prediction of extrahepatic recurrence was developed using the β-coefficients from the identified risk factors, including neutrophil-to-lymphocyte ratio, multiple lesions, tumor size, and microvascular invasion. The nomogram demonstrated good ability to predict extrahepatic recurrence (c-index: training cohort 0.786; validation cohort: 0.845). The calibration plots demonstrated good agreement between estimated and observed extrahepatic recurrence ($p = 0.658$).

Tao Wei and Xu-Feng Zhang Contributed equally to this work.

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Conclusions. An externally validated nomogram was developed with good accuracy to predict extrahepatic recurrence following curative-intent resection of HCC. This nomogram may help identify patients at high risk of extrahepatic recurrence and guide surveillance protocols as well as adjuvant treatments.

Hepatocellular carcinoma (HCC) is the most common liver malignancy and represents the third leading cause of cancer-related death globally with a 5-year survival of only 18%.[1] Curative treatment modalities for early-stage tumors include surgical resection, liver transplantation, and radiofrequency ablation.[2,3] Prognosis even after potentially curative treatment remains unfavorable, largely due to the high incidence of recurrence.[4,5] For example, among patients with Barcelona Clinic Liver Cancer (BCLC) stage 0-A tumors, curative resection is associated with a survival of 60% at 5 years, yet the incidence of recurrence can be as high as 65–70%.[3,6] Understanding recurrence patterns, as well as factors associated with recurrence, can be important to inform postoperative surveillance and guide emerging adjuvant treatment strategies.

HCC recurrence can occur within the liver or at distant sites outside of the liver. Intrahepatic recurrence may be a consequence of intrahepatic dissemination from the initial tumor or be due to de novo primary lesions.[7] In contrast, extrahepatic recurrence represents metastatic disease and is typically a more aggressive tumor phenotype.[8] Indeed, several studies have demonstrated that extrahepatic recurrence was associated with unfavorable clinicopathological factors, including a higher tumor burden and vascular invasion.[8,9] Although challenging, the management of extrahepatic recurrence after curative-intent resection of the primary HCC has evolved over time. In particular, well-selected patients with extrahepatic recurrence may benefit from locoregional therapies, metastasectomy, and radiotherapy, as well as molecular-targeted agents and immune checkpoint inhibitors.[10–13] As such, prediction and early detection of extrahepatic HCC recurrence after curative resection of the primary tumor is important. Specifically, identification of patients at high risk of extrahepatic recurrence may help direct adjuvant treatment strategies, as well as determine which patients may be candidates for repeat attempts at curative-intent therapy. Therefore, the objective of the current study was to define the clinical characteristics, risk factors, and outcomes associated with risk of extrahepatic recurrence of HCC after curative-intent resection using a large multi-institutional cohort. In addition, we developed and validated a nomogram to predict extrahepatic recurrence after initial curative-intent resection of HCC.

METHODS

Study Population

Patients who underwent surgical resection with curative intent of HCC between 2000 and 2017 were identified from an international multi-institutional database.[14] Patients were followed and outcomes were recorded in a multi-institutional database. A total of 837 patients were initially identified. Patients were excluded if postoperative follow-up was <12 months ($n = 125$) or if no data were available on site of recurrence ($n = 77$). In turn, 635 patients were included for analysis; patients from Curry Cabral Hospital, Lisbon, Portugal, were used as the external validation cohort to assess the nomogram ($n = 144$). The study was approved by the Institutional Review Boards of each participating institution.

Clinicopathological Variables

Clinicopathological factors included age, sex, α-fetoprotein (AFP), neutrophil-to-lymphocyte ratio (NLR), Child–Pugh classification, BCLC staging, maximum tumor diameter, tumor number and location, tumor differentiation, presence of cirrhosis and macro-/microvascular invasion, liver capsule involvement, and resection margin status.

Patients were monitored for both intra- and extrahepatic recurrence, with imaging work-up including ultrasonography, computed tomography, and/or magnetic resonance imaging. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. Recurrence-free survival (RFS) was defined as the time duration from the date of surgery to tumor recurrence, while recurrence was defined as suspicious or confirmed lesions based on imaging or histological examination. Recurrence sites were classified as intrahepatic only and extrahepatic ± intrahepatic recurrence, defined as the first recurrence site identified after the initially curative resection of the primary tumor. Timing of recurrence was defined as early (within 12 months) or late recurrence (beyond 12 months) after the initial surgery. Curative-intent treatment of recurrent disease included complete resection and/or ablation of the intra- and/or extrahepatic disease, whereas palliative treatment of recurrent disease included intra-arterial treatments (e.g. transarterial chemoembolization, transarterial embolization), target therapies, chemo- and radiotherapy, and best supportive care.

Statistical Analysis

Clinicopathological variables were summarized using frequencies/percentages for categorical variables, while median and interquartile range (IQR) were reported for continuous covariates. Categorical covariates were compared using the Chi-square or Fisher's exact tests, and continuous variables were compared using the Mann–Whitney U test. OS was calculated using the Kaplan–Meier method and differences were compared using the log-rank test. Univariate analysis was performed to identify potential risk factors of extrahepatic recurrence; factors with a p-value <0.05 were included in the multivariate Cox regression model. Variables independently associated with extrahepatic recurrence on multivariate analysis were selected to construct the prediction nomogram model.[15] Model discrimination was measured using Harrell's concordance index (c-index) and area under the curve (AUC). The performance of the nomogram was measured using the c-index and calibration with 1000 bootstrap samples to decrease the overfit bias. In addition, the performance of the nomogram was evaluated using an external validation cohort from the Curry Cabral Hospital (Lisbon, Portugal). Calibration was performed comparing the observed and predicted incidence of extrahepatic recurrence with the Hosmer and Lemeshow test. All statistical analyses were conducted using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) or R version 3.6.1 (http://www.r-project.org). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 635 patients who underwent curative-intent resection of HCC were included in the analytic cohort. The majority of patients were male ($n = 488$, 76.9%) and median patient age was 61 years (IQR 52–70); a subset of patients had hepatitis B virus (HBV; $n = 145$, 22.8%) or hepatitis C virus (HCV; $n = 134$, 21.1%) infection (Table 1). The majority of individuals had well-compensated liver function (Child–Pugh class A: $n = 474$, 74.6%) and an early-stage tumor (BCLC stage 0-A: $n = 499$, 78.6%). Median tumor size was 5.0 cm (IQR 3.0–8.0) and median AFP level was 19.0 ng/mL (IQR 4.0–240.2). At the time of surgery, approximately one-third of patients underwent a major liver resection ($n = 221$, 34.8%) and most patients ($n = 566$, 89.3%) underwent an R0 resection. On pathology, most HCC lesions were well- to moderately differentiated ($n = 516$, 81.3%); a subset of HCC tumors had associated macrovascular ($n = 33$, 5.2%) or microvascular invasion ($n = 173$, 27.2%).

Patterns of Recurrence and Prediction of Extrahepatic Recurrence

The median and 5-year RFS following curative-intent resection of HCC were 47.2 months (95% confidence interval [CI] 38.5–55.8 months) and 43.3%, respectively. At a median follow-up of 28.4 months, 166 (26.1%) patients had died, 291 (45.8%) were alive with no evidence of disease, and 178 (28.0%) patients were alive with recurrence. Overall, among all patients who experienced a recurrence ($n = 283$, 44.6%), 203 (71.7%) patients had a liver-only recurrence and 80 (28.3%) patients recurred with an extrahepatic site ± liver site as a component of the recurrence. Of the 80 patients who experienced an extrahepatic recurrence, 32 (40.0%) patients had a lung recurrence and 23 (28.8%) patients had abdominal disease, while other sites of recurrent disease included lymph nodes, bone, adrenal, brain, or pelvis ($n = 42$, 52.5%); 15 (18.8%) patients had multiple sites of extrahepatic disease.

Compared with patients who had no recurrence or liver-only recurrence, several tumor-related characteristics were associated with extrahepatic recurrence. In particular, compared with patients who did not have extrahepatic recurrence, individuals who recurred at an extrahepatic site were more likely to have larger tumors (median 9.0 vs. 4.5 cm), multiple tumors (20.0% vs. 11.4%), more advanced BCLC stage (BCLC B/C: 26.3% vs. 12.4%), higher preoperative AFP (median: 57.6 vs. 15.9 ng/mL) and NLR (median 2.9 vs. 2.3) levels, and tumors with microvascular invasion (47.5% vs. 24.3%) [all $p < 0.05$] (Table 1). In contrast, patients with extrahepatic recurrence were less likely to have underlying liver cirrhosis versus patients who had no extrahepatic recurrence (22.5% vs. 46.7%, $p < 0.001$).

On multivariable analysis, after accounting for competing risk factors, tumor size (odds ratio [OR] 1.2, 95% CI 1.1–1.2), multiple lesions (OR 3.0, 95% CI 1.3–6.6), NLR (OR 1.1, 95% CI 1.0-1.2), and microvascular invasion (OR 2.0, 95% CI 1.0–3.9) each remained independent risk factors of extrahepatic recurrence after curative resection for HCC (Table 2). In contrast, liver cirrhosis was associated with lower odds of extra- versus intrahepatic recurrence (OR 0.4, 95% CI 0.2–0.9). To estimate the risk of extrahepatic recurrence following HCC resection, a nomogram predictive model was constructed utilizing the β-coefficients of these factors (Fig. 1). The cumulative risk of extrahepatic recurrence incrementally increased among individuals with more nomogram points. For example, a patient who underwent a resection for a solitary, 3.0 cm HCC lesion who had a preoperative NLR of 3.5 and no vascular invasion on final pathology would have 20 nomogram points, which would translate into a 5-year risk of extrahepatic recurrence below 10%. In contrast, a patient

TABLE 1 Baseline demographics and clinicopathological variables of patients with extrahepatic versus non-extrahepatic recurrence

Variables	Overall [$n = 635$]	Extrahepatic recurrence [$n = 80$]	No extrahepatic recurrence [$n = 555$]	p-Value
Age, years [median (IQR)]	61 (52–70)	62 (47–71)	62 (53–70)	0.538
Sex				0.508
Male	488 (76.9)	64 (80.0)	424 (76.4)	
Female	145 (22.8)	16 (20.0)	129 (23.2)	
Missing	2 (0.3)	0 (0)	2 (0.4)	
ASA score				0.557
≤2	349 (55.0)	47 (58.8)	302 (54.4)	
>2	237 (37.3)	28 (35.0)	209 (37.7)	
Missing	49 (7.7)	5 (6.3)	44 (7.9)	
HBV infection	145 (22.8)	14 (17.5)	131 (23.6)	0.151
HCV infection	134 (21.1)	13 (16.3)	121 (21.8)	0.243
Underlying cause				0.018
Alcoholic	52 (8.2)	11 (13.8)	41 (7.4)	
Viral	279 (43.9)	27 (33.8)	252 (45.4)	
NAFLD	37 (5.8)	2 (2.5)	35 (6.3)	
Cryptogenic	245 (38.6)	40 (50.0)	205 (36.9)	
Missing	22 (3.5)	0 (0)	22 (4.0)	
AFP, ng/mL [median (IQR)]	19.0 (4.0–240.2)	57.6 (5.8–1201.5)	15.9 (4.0–144.6)	0.005
Neutrophil-to-lymphocyte ratio [median (IQR)]	2.4 (1.6–3.3)	2.9 (1.9–4.0)	2.3 (1.6–3.2)	0.006
Child–Pugh classification				0.232
A	474 (74.6)	57 (71.3)	417 (75.1)	
B	31 (4.9)	6 (7.5)	25 (4.5)	
Missing	130 (20.5)	17 (21.3)	113 (20.4)	
Tumor size, cm [median (IQR)]	5.0 (3.0–8.0)	9.0 (5.0–12.0)	4.5 (3.0–7.0)	<0.001
Multiple lesions				0.028
Yes	79 (12.4)	16 (20.0)	63 (11.4)	
No	556 (87.6)	64 (80.0)	492 (88.6)	
Bilobar tumors				0.634
Yes	39 (6.1)	4 (5.0)	35 (6.3)	
No	551 (86.8)	71 (88.8)	480 (86.5)	
Missing	45 (7.1)	5 (6.3)	40 (7.2)	
Macrovascular invasion				0.133
Yes	33 (5.2)	7 (8.8)	26 (4.7)	
No	556 (87.6)	68 (85.0)	488 87.9)	
Missing	46 (7.2)	5 (6.3)	41 (7.4)	
BCLC stage				0.001
0/A	499 (78.6)	54 (67.5)	445 (80.2)	
B/C	90 (14.2)	21 (26.3)	69 (12.4)	
Missing	46 (7.2)	5 (6.3)	41 (7.4)	
Cirrhosis				<0.001
Yes	277 (43.6)	18 (22.5)	259 (46.7)	
No	456 (56.1)	61 (76.3)	295 (53.2)	
Missing	2 (0.3)	1 (1.3)	1 (0.2)	
Grade				<0.001
Well	137 (21.6)	8 (10.0)	129 (23.2)	
Moderate	379 (59.7)	42 (52.5)	337 (60.7)	
Poor	109 (17.2)	29 (36.3)	80 (14.4)	

TABLE 1 continued

Variables	Overall [$n = 635$]	Extrahepatic recurrence [$n = 80$]	No extrahepatic recurrence [$n = 555$]	p-Value
Undifferentiated	5 (0.8)	0 (0)	5 (0.9)	
Missing	5 (0.8)	1 (1.3)	4 (0.7)	
Microvascular invasion				<0.001
Yes	173 (27.2)	38 (47.5)	135 (24.3)	
No	358 (56.4)	30 (37.5)	328 (59.1)	
Missing	104 (16.4)	12 (15.0)	91 (16.6)	
Liver capsule involvement				0.675
Yes	191 (42.9)	23 (28.7)	168 (30.3)	
No	254 (57.1)	34 (42.5)	220 (39.6)	
Missing	190 (29.9)	23 (28.7)	167 (30.1)	
Margin status				0.838
R0	566 (89.3)	70 (87.5)	496 (89.4)	
R1	68 (10.7)	9 (11.3)	59 (10.6)	
Missing	1 (0.2)	1 (1.3)	0 (0)	

Data are expressed as n (%) unless otherwise specified

ASA American Society of Anesthesiologists, HBV hepatitis B virus, HCV hepatitis C virus, NAFLD non-alcoholic fatty liver disease, AFP α-fetoprotein, BCLC Barcelona Clinic Liver Cancer

TABLE 2 Multivariate logistic regression analysis of risk factors for extrahepatic recurrence

Variables	Univariate		Multivariate	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age, years	1.0 (1.0–1.0)	0.161		
AFP, ng/mL	2.5 (1.5–4.4)	0.001	1.3 (0.6–2.8)	0.457
Child–Pugh grade, B vs. A	1.8 (0.7–4.5)	0.237		
Neutrophil-to-lymphocyte ratio	1.1 (1.0–1.2)	0.004	1.1 (1.0–1.2)	**0.025**
Multiple lesions	2.0 (1.1–3.6)	0.031	3.0 (1.3–6.6)	**0.007**
Tumor size	1.2 (1.1–1.2)	<0.001	1.2 (1.1–1.2)	**<0.001**
Cirrhosis, yes vs. no	0.3 (0.2–0.6)	<0.001	0.4 (0.2–0.9)	**0.026**
Macrovascular invasion, yes vs. no	1.9 (0.8–4.6)	0.139		
Resection margin, R1 vs. R0	1.1 (0.5–2.3)	0.838		
Liver capsule involvement, yes vs. no	0.9 (0.5–1.6)	0.675		
Microvascular invasion, yes vs. no	3.1 (1.8–5.2)	<0.001	2.0 (1.0–3.9)	**0.049**
Tumor grade	3.2 (1.9–5.3)	<0.001	1.5 (0.9–2.4)	0.129

OR odds ratio, CI confidence interval, AFP α-fetoprotein

with a preoperative NLR of 15, two HCC lesions (with the larger tumor being 8 cm) and vascular invasion would have 100 nomogram points, which would represent a 5-year risk of extrahepatic recurrence over 50%. The nomogram demonstrated good predictive performance, with an AUC of 0.786 to estimate the risk of extrahepatic recurrence after resection of HCC (Fig. 2a). The calibration plot for the probability of extrahepatic risk demonstrated good agreement between the prediction made by the nomogram and actual observation ($p = 0.658$) (Fig. 2b). The nomogram also demonstrated very good performance on both internal bootstrapping validation ($n = 1000$) [c-index 0.786, 95% CI 0.727–0.846] and external validation ($n = 144$) [c-index 0.845, 95% CI 0.765–0.925] (electronic supplementary Table 1).

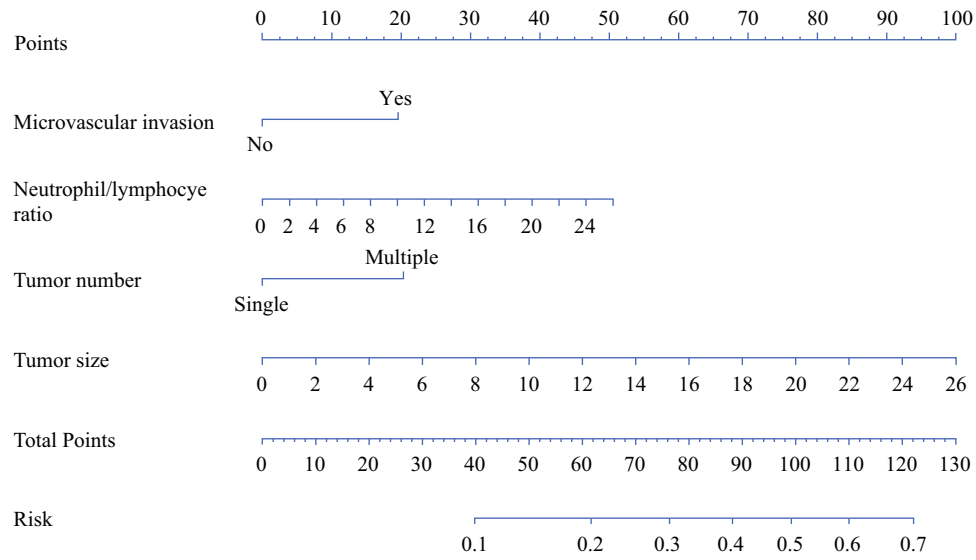

FIG. 1 Nomogram for prediction of extrahepatic recurrence after surgical resection for hepatocellular carcinoma

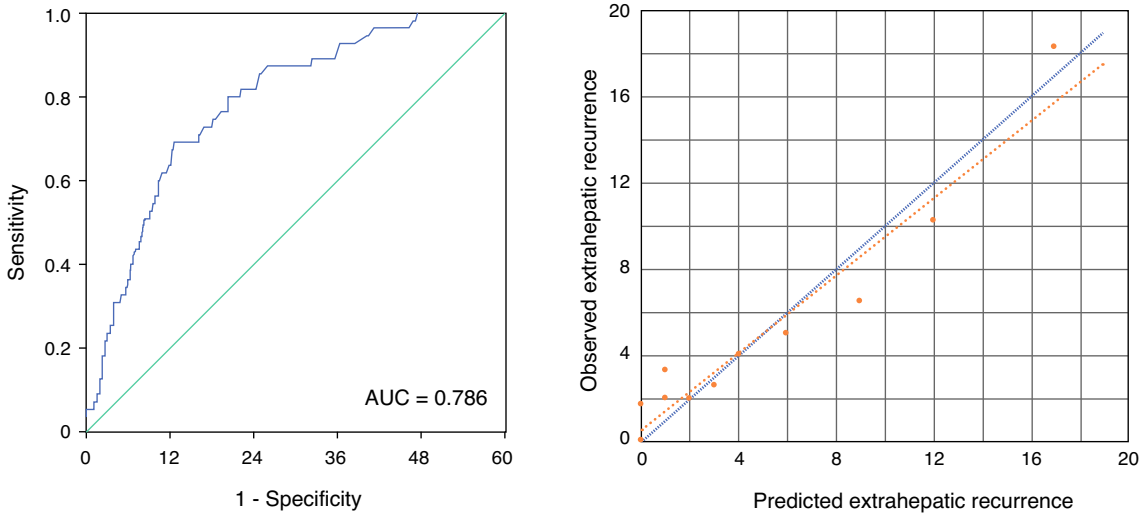

FIG. 2 **a** AUC and **b** calibration plot of the nomogram for the prediction of extrahepatic recurrence. *AUC* area under the curve

Prognostic Impact of Extrahepatic Recurrence

The median, 1-, 3- and 5-year OS among the entire cohort was 72.0 months, 89.5%, 72.0%, and 50.3%, respectively, and the median, 1-, 3-, and 5-year RFS was 47.2 months, 61.6%, 49.6%, and 39.3%, respectively. Patients who experienced extrahepatic recurrence had worse long-term OS (5-year OS: extrahepatic recurrence 39.4% vs. non-extrahepatic recurrence 66.8%; $p < 0.001$) (Fig. 3a). In fact, there was a stepwise increased risk of death among patients who had intrahepatic-only recurrence versus extrahepatic-only recurrence versus both intra- and extrahepatic recurrence (5-year OS 56.0% vs. 39.9% vs. 37.0%; $p = 0.013$) (Fig. 3b). Patients who had an extrahepatic site as a component of recurrence were more likely to recur within 12 months after surgery compared with individuals who had an intrahepatic-only recurrence (extrahepatic recurrence: 70.4% vs. intra- and extrahepatic recurrence 69.2% vs. intrahepatic-only recurrence 43.5%; $p < 0.001$) (Fig. 4).

Among patients with an extrahepatic recurrence ($n = 80$), curative-intent resection ± ablation of the extrahepatic disease was performed in a small subset of 14 (17.5%) patients (electronic supplementary Table 2). Patients who underwent resection ± ablation of the extrahepatic recurrence site had a 5-year survival of 66.9% versus 37.1% among patients with extrahepatic disease treated with best-supportive care ($p = 0.037$) (Fig. 5). Of note, patients who underwent curative-intent resection ± ablation of extrahepatic recurrence had comparable survival as patients with intrahepatic-only recurrence (5-year

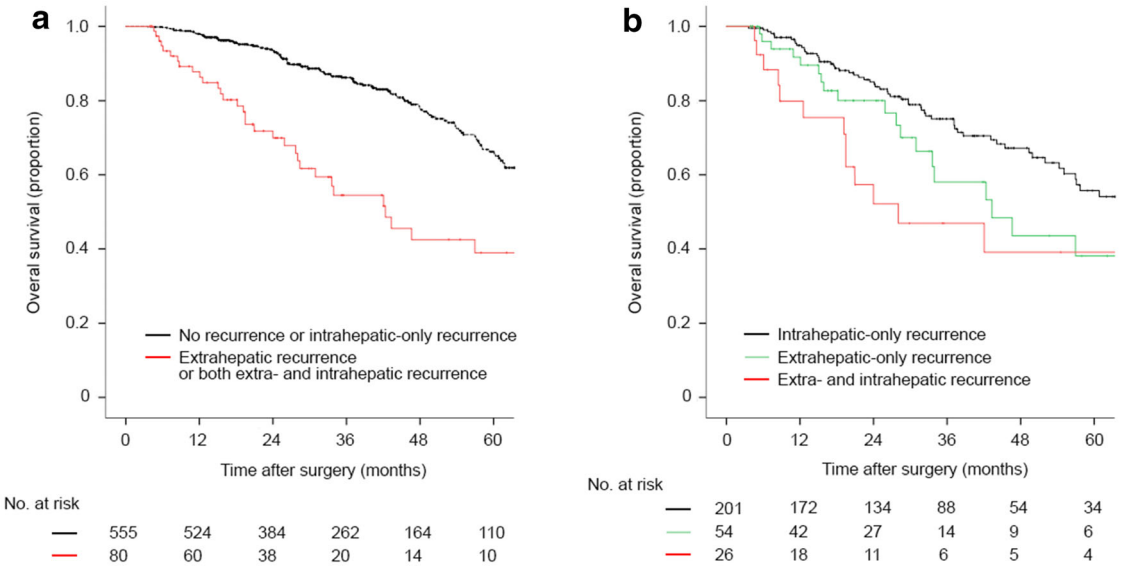

FIG. 3 Overall survival of patients with **a** extrahepatic ± intrahepatic recurrence versus non-extrahepatic recurrence, and **b** intrahepatic-only, extrahepatic-only, versus both intra- and extrahepatic recurrence

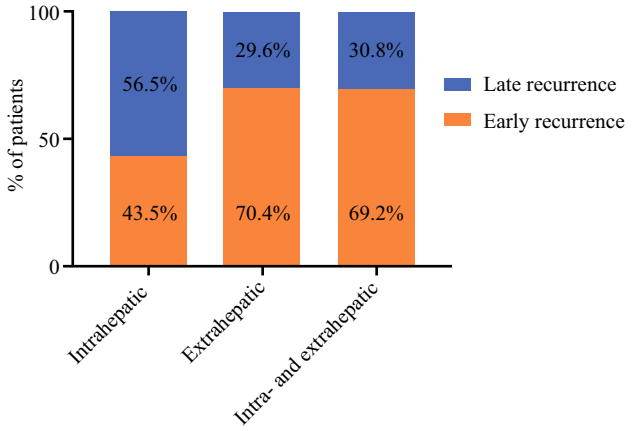

FIG. 4 Recurrence within 1 year (early) and beyond 1 year (late) following the initial resection for hepatocellular carcinoma among patients who developed intrahepatic-only, extrahepatic-only, versus intra- and extrahepatic recurrence

OS: extrahepatic recurrence 66.9% vs. intrahepatic-only recurrence 59.8%; $p = 0.998$).

DISCUSSION

While hepatic resection is a cornerstone of curative-intent treatment of HCC, 5-year survival following surgery remains only 40–60% at 5 years.[16] Survival can be adversely impacted by both progression of any underlying liver process (e.g. worsening hepatic function, progression of cirrhosis) and tumor biology (e.g. recurrence). In particular, recurrence following resection of HCC has been reported to be as high as 50–70%.[17] In fact, in the current study, we noted that almost one in two patients experienced a recurrence. Given that the underlying liver often suffers from a 'field defect', most attention has typically focused on the risk of intrahepatic recurrence, with data on extrahepatic recurrence after resection of the primary HCC being scarce. The current study was therefore important as we specifically focused on defining the clinical characteristics, risk factors, and outcomes associated with risk of extrahepatic HCC recurrence after curative-intent resection. Of note, among patients who did recur ($n = 281$), approximately 28.4% (80/281) had an extrahepatic site as a component of the recurrence. Identification of patients at high risk of extrahepatic recurrence may assist in planning postoperative surveillance, as well as direct considerations around adjuvant therapies, such as postoperative transcatheter arterial chemoembolization (TACE) or tyrosine kinase inhibitors.[18] Perhaps more importantly, using a large international multi-institutional database, we identified several factors that were associated with risk of extrahepatic recurrence to create a nomogram. The nomogram performed very well to predict extrahepatic recurrence in both the derivative (c-index 0.786) and external validation (c-index 0.845) cohorts. In particular, the calibration plots demonstrated good agreement between the estimated and observed extrahepatic recurrence. As such, the proposed nomogram may be a helpful clinical tool to stratify patients relative to risk of extrahepatic recurrence following resection of HCC.

Unlike intrahepatic recurrence, which can represent intrahepatic spread or *de novo* tumor formation, extrahepatic disease is indicative of hematogenous dissemination of

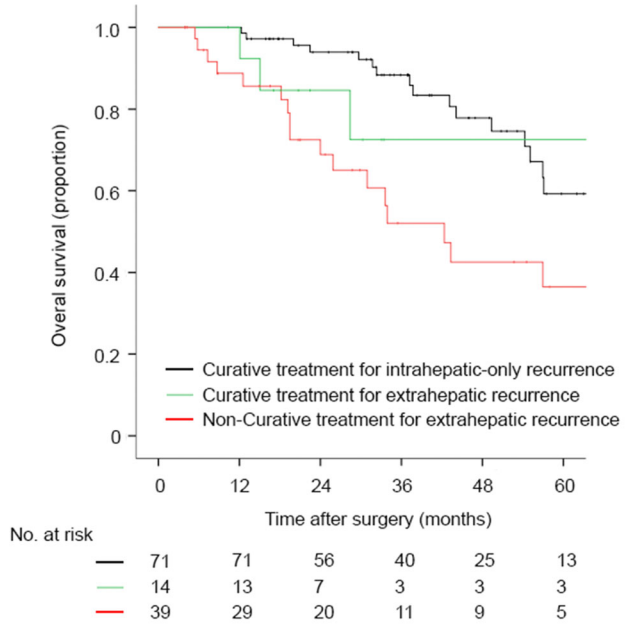

FIG. 5 Overall survival of patients who underwent curative treatments for intrahepatic-only recurrence or extrahepatic recurrence versus patients who underwent non-curative treatments for extrahepatic recurrence

HCC.[19] In the current study, several factors were associated with increased risk of systemic disease manifested as an extrahepatic recurrence. Specifically, tumor size and number, as well as microvascular invasion were associated with extrahepatic recurrence after curative resection of HCC. Tumor size and number have been strongly associated with the presence of vascular invasion. Pawlik et al. previously reported that the incidence of microscopic vascular invasion increased with tumor size (≤3 cm: 25%; 3.1–5 cm: 40%; 5.1–6.5 cm: 55%; >6.5 cm: 63%).[20] In turn, vascular involvement can lead to increased dissemination of HCC through hematogenous spread of circulating tumor cells that contribute to tumor metastasis through the epithelial-to-mesenchymal transition.[21] As such, increased tumor number and size, as well as microvascular invasion, can increase the risk of extrahepatic recurrence.[9,19,22,23] In addition, NLR strongly correlated with risk of extrahepatic recurrence. An increased NLR may be an indicator of local and systemic inflammatory status, as well as indicate infiltration of anti-immune cells such as tumor-associated macrophages that can facilitate tumor growth and metastasis.[24–26] In turn, NLR has been noted to be an important marker of inflammation linked to the prognosis of patients with HCC and other tumors.[25,27,28] Interestingly, the presence of liver cirrhosis was inversely associated with the risk of extrahepatic recurrence. While the reasons for this were undoubtedly multifactorial, liver cirrhosis is a well-known driver of intrahepatic recurrence, and different molecular signatures of the non-tumorous liver may predict carcinogenesis and patterns of recurrence [29,30].

While knowledge of various risk factors associated with recurrence or survival may be helpful, the practical utilization of this information can be challenging in the clinical setting. In turn, prognostic nomograms have gained popularity as they are relatively easy to use with a simple graphic that enables the incorporation of multiple relevant clinical predictors that can be applied to individual patients. In addition, in an era of personalized medicine, nomograms directly quantify individual patient risk based on statistically derived prognostic variables rather than placing patients into prognostic groups.[31–33] The variables used in our predictive nomogram included tumor size and number, as well as NLR and the presence of microvascular invasion, all of which are readily and routinely available. Importantly, the proposed nomogram to predict extrahepatic recurrence after resection of HCC performed very well, with a c-index of 0.786 in the training cohort and 0.845 in the validation cohort, as well as excellent calibration. Given that surveillance strategies vary and adjuvant therapy for HCC is not routinely utilized, the proposed nomogram may help identify patients at high risk of extrahepatic recurrence to inform postoperative surveillance and treatment.

Perhaps not surprisingly, patients who experienced extrahepatic recurrence had worse long-term OS (5-year OS: extrahepatic recurrence 39.4% vs. non-extrahepatic recurrence 66.8%; $p < 0.001$). Taketomi et al. similarly reported a worse survival among patients with extrahepatic recurrence versus patients with intrahepatic recurrence (5-year OS: 24.0% vs. 54.7%).[19] Interestingly, we also noted a stepwise increased risk of death among patients who had intrahepatic-only recurrence versus extrahepatic-only recurrence versus both intra- and extrahepatic recurrence (5-year OS: 56.0% vs. 39.9% vs. 37.0%; $p = 0.013$). Yang et al. have previously suggested categorizing patients with recurrence into three groups: liver-first recurrence versus simultaneous intra- and extrahepatic recurrence versus extrahepatic-only recurrence.[8] In the current study, no difference in survival was noted among patients with different patterns of extrahepatic recurrence, suggesting that the presence, rather than actual site, of extrahepatic disease is what drives prognosis. Among patients who experienced an extrahepatic recurrence, a small subset underwent a secondary curative-intent treatment, with a 5-year OS of 66.9%. Yoon et al. reported similarly favorable long-term survival after resection of the solitary lung metastasis from HCC.[34] In a separate study, Hirokawa and colleagues reported on 32 patients who underwent resection of extrahepatic HCC recurrence and noted an improved survival compared with patients offered best supportive care

(median OS: 539 vs. 133 days).[22] While these data were subject to selection bias due to the retrospective nature of the studies, the data collectively suggest that re-resection or ablation of extrahepatic disease should be entrained in very well-selected patients.

The proposed nomogram may help predict progression and recurrence of HCC after resection to guide postoperative surveillance. In addition, the nomogram may inform the selection of patients at high risk of postoperative extrahepatic recurrence who may benefit from adjuvant therapy. Currently, there is no standard of care regarding adjuvant therapy for surgically treated HCC patients. The STORM trial, which randomized patients to sorafenib versus placebo after surgery, demonstrated no benefit in RFS.[35] However, several retrospective reports have suggested that postoperative use of sorafenib may reduce recurrence; importantly, these studies only included patients with high risk of recurrence, such as patients who had HCC with microvascular invasion.[36,37] More recently, several clinical trials are currently evaluating the efficacy of emerging therapies such as levatinib and immune checkpoint inhibitors in the adjuvant setting.[38] The nomogram for prediction of extrahepatic recurrence of HCC after surgical resection may therefore help in identifying high-risk patients who may benefit from such adjuvant therapy in the future.

The current study should be interpreted in light of several limitations. While the international multi-institutional-based cohort increased sample size and generalizability, patient selection, surgical procedures, and follow-up strategies varied among the different centers. The cohort included only patients treated at major tertiary hepatobiliary centers, which are more likely to follow standardized treatment guidelines.[39] Furthermore, given the retrospective nature of this study, selection bias was possible relative to which patients were chosen for primary HCC resection, as well as which individuals with extrahepatic recurrence were offered secondary curative-intent treatment. Furthermore, the work-up to detect extrahepatic diseases might have evolved over time, which may have impacted the findings given the long time interval included in the current study. While no patient received adjuvant therapy following index resection of the primary HCC, data of systemic therapies, including sorafenib, lenvatinib, and immune checkpoint inhibitors, that may have been used to treat recurrence were not available.

CONCLUSION

Approximately one-half of patients experienced tumor recurrence following curative resection of HCC. Among patients who recurred, nearly 30% of postoperative recurrence occurred at an extrahepatic site. Compared with intrahepatic recurrence, extrahepatic recurrence was more likely to occur early and was associated with worse prognosis. Several factors associated with the risk of extrahepatic recurrence were identified and were used to develop a nomogram. The nomogram to predict extrahepatic recurrence performed very well on internal and external validation, with very good calibration and accuracy. As such, the proposed nomogram may help predict extrahepatic recurrence following curative resection for HCC, which, in turn, may inform surveillance strategies and consideration of postoperative targeted treatments.

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