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ORIGINAL RESEARCH

Prognostic Nomograms for Patients with Hepatocellular Carcinoma After Curative Hepatectomy, with a Focus on Recurrence Timing and Post-Recurrence Management

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Background: Prognoses of patients with hepatocellular carcinoma (HCC) after curative hepatectomy remain unsatisfactory because of the high incidence of postoperative recurrence. Published predictive systems focus on pre-resection oncological characteristics, ignoring post-recurrence factors.

Purpose: This study aimed to develop prognostic nomograms for 3- and 5-year overall survival (OS) of patients with HCC after curative hepatectomy, focusing on potentially influential post-recurrence factors.

Patients and Methods: Clinicopathological and postoperative follow-up data were extracted from 494 patients with HCC who underwent curative hepatectomy between January 2012 and June 2019. Early recurrence (ER) and late recurrence (LR) were defined as recurrence at ≤2 and >2 years, respectively, after curative hepatectomy. Nomograms for the prediction of 3- and 5-year OS were established based on multivariate analysis. The areas under time-dependent receiver operating characteristic curves (AUCs) for the nomograms were calculated independently to verify predictive accuracy. The nomograms were internally validated based on 2000 bootstrap resampling of 75% of the original data.

Results: In total, 494 patients with HCC who underwent curative hepatectomy met the eligibility criteria. Cox proportional hazard regression analysis identified factors potentially influencing 3- and 5-year OS. Multivariate analysis indicated that patient age, Hong Kong Liver Cancer stage, γ-glutamyl transferase (γ-GGT) level, METAVIR inflammation activity grade, ER and post-recurrence treatment modality were influencing factors for 3-year OS (AUC, 0.891; 95% CI, 0.8364–0.9447). γ-GGT > 60 U/L, hepatectomy extent, LR and post-recurrence treatment modality were influencing factors for 5-year OS (AUC, 0.864; 95% CI, 0.8041–0.9237). Calibration plots showed satisfactory concordance between the predicted and actual observation cohorts.

Conclusion: We propose new prognostic nomograms for OS prediction with a focus on the differentiation of recurrence timing and post-recurrence management. These nomograms overcome the shortcomings of previous predictive nomograms and significantly improve predictive accuracy.

Keywords: hepatocellular carcinoma, hepatectomy, post-recurrence management, overall survival, nomogram

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Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy, accounting for 85–90% of all liver cancer cases. Most HCC cases are associated with chronic hepatitis B virus (HBV) infection, especially in the Asia-Pacific region.[1] Newly

diagnosed Chinese patients account for more than 50% of global cases.[2] Despite emerging treatment modalities, the long-term prognosis of patients with HCC remains unsatisfactory. High HBV infection rates and poor prognosis of HCC lead to high HCC incidence and mortality in China, which will pose intractable national challenges in the future.[3]

Liver resection is the most common curative approach in the Asia-Pacific region, especially in China.[2] Unfortunately, the prognosis after curative hepatectomy remains unsatisfactory because of the high incidence of postoperative recurrence.[3] Many nomograms and risk score systems have been established for post-hepatectomy overall survival (OS) prediction.[4–30] These systems focus on initial pre-resection oncological characteristics, but not on factors significantly affecting OS after curative hepatectomy in patients with HCC, such as the recurrence type and site, time to recurrence (TTR), and post-recurrence treatment modality.[31–38] Predictive nomograms and scoring systems that ignore such influencing factors are somewhat controversial. Effective treatments for HCC recurrence based on recurrence type, recurrence site, and TTR may prolong post-recurrence survival (PRS) and OS.

The purpose of this study was to provide a satisfactory interpretation of factors that may influence OS after curative hepatectomy for HCC (eg, TTR, recurrence type and site, and post-recurrence treatment modality). Novel prognostic nomograms for 3- and 5-year OS in this context are proposed based on retrospective analyses of data from a Chinese cohort.

Patients and Methods

In total, 494 patients with HCC undergoing curative hepatectomy at Hunan Provincial People's Hospital (The First Hospital Affiliated with Hunan Normal University; 165 cases recruited retrospectively between January 2012 and December 2014, and 329 cases recruited prospectively between January 2015 and June 2019) were included in this study.

The inclusion criteria were: a) Eastern Cooperative Oncology Group Performance Status score of 0 or 1, absence of a macroscopic portal- or hepatic-vein or bile-duct tumor thrombus, and absence of extrahepatic spread or distant metastasis; b) Child-Pugh class A, B, or C that could be improved to A or B; c) exact pathology of HCC; and d) complete liver tumor removal (R0 resection).

The exclusion criteria were: a) concomitant presence of another cancer; b) cardiovascular-pulmonary disease, or poor liver reserve preventing surgery; c) positive incisional margin; d) incomplete clinicopathological or follow-up data; and e) death within 90 days postoperatively.

Clinicopathological data and follow-up information (including postoperative recurrence time, post-recurrence treatment modality, and survival outcomes) were collected every 3–6 months. All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the Institutional Review Board of Hunan Provincial People's Hospital (The First Hospital Affiliated with Hunan Normal University; no. 2015-01). For patients recruited retrospectively between January 2012 and December 2014, ethical approval was waived due to the retrospective nature of the study; patients' privacy was ensured and the data were anonymized or maintained with confidentiality. Patients recruited prospectively between January 2015 and June 2019 provided written informed consent prior to study inclusion.

Preoperative Assessment

Patients' demographic and clinicopathological data were collected routinely at admission. The latest preoperative laboratory and imaging examination results were used in this study. Preoperative diagnoses of HCC were confirmed by at least two types of imaging examination [eg, four-phase multidetector contrast-enhanced dynamic computed tomography (CT) and magnetic resonance imaging (MRI)], or by a single imaging examination accompanied by alpha fetoprotein (AFP) level >400 μg/L, or by histopathological assessment.[39] When necessary, positron emission tomography (PET) was performed to rule out suspected distant metastasis before confirming the possibility of curative hepatectomy. Child-Turcotte-Pugh (CTP) scores were used to assess liver function and reserve. Portal hypertension (PH) was diagnosed by endoscopic findings of esophageal or gastric varices, or clinical signs of splenomegaly with platelet count < 10^4/mm^3.[39] PH was classified as mild (slight esophagogastric varices), moderate (obvious esophagogastric varices with no visible "red wale" sign), and severe (obvious esophagogastric varices with visible "red wale" signs). Values for indicators of liver fibrosis and cirrhosis were calculated using the following formulae: the aspartate aminotransferase/platelet ratio index (APRI) = [(AST (IU/L)/ULN of AST) × 100]/(platelet count × 10^9/L),[40] fibrosis index based on four factors (FIB-4) = [age (years) × AST (IU/L)]/[platelet

count (10^9/L) × ALT (IU/L)$^{1/2}$)],[41] albumin-bilirubin (ALBI) score = –0.085 × [albumin (g/L) + $\log_{10}$ bilirubin (mmol/L) × 0.66], ALBI grade 1 = ALBI < –2.60, ALBI grade 2 = –2.60 < ALBI = –1.39, ALBI grade 3 = ALBI > –1.39,[42] and γ-glutamyl transpeptidase/platelet ratio (GPR) = {[GGT (IU/L)/ULN of GGT] × 100}/[platelet count (10^9/L)].[43]

Assessment of Tumor Staging, Characteristics and Pathological Evaluation

The American Joint Committee on Cancer's TNM staging system (8th edition),[44] the Barcelona Clinic Liver Cancer system,[45] and the Hong Kong Liver Cancer (HKLC) system[46] were adopted for tumor staging. Data on tumor characteristics, such as tumor size and number, differentiation, encapsulation, incisional margin status, microvascular invasion (MVI), and immunohistochemical markers, were recorded from pathological reports. Tumor size was defined as the maximum diameter of the specimen on pathological examination. Tumor number was classified as 1, 2, 3, and ≥4 (with satellite nodules). Tumor encapsulation was classified as presence/absence. Tumor cell differentiation was classified according to the Edmondson-Steiner system.[47] The shortest distance from the microscopic edge of the tumor to the liver transection plane was also measured. Microvascular invasion (MVI) was defined as the presence of a cancer cell nest in vessels lined with endothelial cells on microscopy, and was classified as absent (M0), M1 (MVI < 5 and ≤1 cm from adjacent liver tissue), and M2 (MVI > 5 or >1 cm from adjacent liver tissue).[48] Liver tissue inflammation and fibrosis in the non-tumor area were graded according to the METAVIR scoring system.[49] Inflammatory activity was graded as absent (A0), mild (A1), moderate (A2), and severe (A3). Liver fibrosis was classified as absent (F0), portal fibrosis (F1), periportal fibrosis (F2), septal fibrosis (F3), and cirrhosis (F4). Two pathologists independently examined pathological specimens postoperatively, and consensus was reached by discussion in case of disagreement.

Surgical Therapies

The Couinaud liver segmentation criteria[50] were adopted; curative open laparotomy was performed in 276 cases and curative laparoscopic hepatectomy was performed in 218 cases. The type of surgery depended on clinical guidelines and surgeons' preference. The same oncological principle and management guidelines were applied for all open and laparoscopic liver resections. Curative hepatectomy was defined as complete resection of all tumor nodules without involvement of any major branch of the portal or hepatic vein.[48] Hepatectomy modality selection was usually based on clinical guidelines combined with the remnant liver volume and hepatic functional reserve, expressed as the Child-Turcotte-Pugh (CTP) score. Intraoperative ultrasound examination was used to identify occult nodules that were not visible on preoperative radiological examination, and to further clarify relationships between tumors and main vascular structures, guaranteeing a safe and effective parenchymal transection plane. Additional nodules detected during the procedures were also removed.

The type of hepatectomy (anatomic or non-anatomic resection[51]) performed was selected as follows. Anatomic resection, defined as complete excision of at least one segment [ie, segmentectomy, sectoriectomy, or (tri-) hemihepatectomy] based on Couinaud's classification, was preferred for patients with satisfactory liver function reserve. Subsegmentectomy (of <1 Couinaud segment) was performed under ultrasound guidance, with complete removal of the liver tissue supplied by the third-order portal vein branch.[51] Non-anatomic resection was performed as wedge resection and tumor enucleation. In principle, the goal of hepatectomy was the achievement of an incisional margin ≥2 cm, or confirmation of a tumor-free incisional margin when this goal could not be attained. Hepatectomy was facilitated by forceps crushing or harmonic scalpel instrumentation with intermittent Pringle maneuvers; when necessary, blood flow in the liver was selectively occluded (in cycles of 15 min vascular clamping and 5 min release) to prevent massive blood loss. Patients whose preoperative HBV-DNA levels exceeded 1.00E + 02 copies/mL were given oral nucleoside/nucleotide analogs (eg, entecavir, 0.5 mg/day) before surgery. Postoperative adjuvant therapies such as transcatheter arterial chemoembolization (TACE) or targeted drug were recommended based on individual assessments of postoperative recurrence risk. Complications occurring within 90 days of surgery were graded (I–V) based on the Clavien-Dindo classification system.[52]

Postoperative Recurrence and Treatment

HCC recurrence or metastasis was detected by confirmative imaging (contrast-enhanced CT/MRI) findings; contrast-enhanced ultrasound and chest/bone CT were

performed when necessary. Hepatic arteriography or PET/CT was performed for patients with postoperative serum AFP elevation, which raised strong suspicion of recurrence without imaging evidence. The date of recurrence, site of recurrence (intrahepatic and/or extrahepatic), and size and number of recurrent nodules were recorded. Early recurrence (ER) and late recurrence (LR) were defined as recurrence at ≤2 and >2 years after hepatectomy, respectively.

Patients with tumor recurrence were managed with various therapeutic modalities. Re-resection or metastasectomy was preferred for those with resectable tumors. Microwave ablation was offered to patients whose tumors could not be removed surgically (ie, those with recurrent intrahepatic tumors <3 cm, numerous tumors, scattered recurrence, or poor liver function reserve). Other treatment modalities, such as TACE, radiation therapy, and targeted therapy with sorafenib (Nexavar™; Bayer Health Care Pharmaceuticals, Inc. Whippany, NJ, USA), were used for those in satisfactory physical condition but who could not tolerate the above-mentioned treatments. Best supportive care was provided for patients with poor health status.

Follow-Up

All patients included in this study were followed by telephone inquiry or clinical re-examination. Follow-up assessments included routine evaluation of liver function, HBV-DNA and serum AFP levels, and imaging examination (ultrasonography, enhanced CT or MRI) every 3 months for the first 2 years and every 6 months thereafter. For patients in whom recurrence or metastasis was strongly suspected (based on abnormal AFP levels, but without radiological evidence), hepatic arteriography, PET/CT, or bone scintigraphy was performed. The clinical endpoints were 3- and 5-year OS, and follow-up was censored on 31 October 2019. The TTR was defined as the interval between the date of surgery and the date of tumor recurrence diagnosis. OS was calculated as the time from the date of surgery to the date of patient death or last follow-up. PRS was calculated from the date of tumor recurrence to the date of patient death or last follow-up. Information on deaths was obtained by notification from family members of the deceased.

Statistical Analyses

Descriptive analysis was performed for all demographic study variables. Frequencies and proportions were calculated for categorical variables, and medians and standard deviations were calculated for continuous variables. Categorical variables were compared using the Wilcoxon rank sum test. The Log rank test was used to compare PRS after the management of ER and LR. Cox proportional-hazard regression analysis was used to identify factors potentially associated with 3- and 5-year OS. Predictors that were significant ($P < 0.05$) in univariate analysis were selected for multivariate analysis using the backward stepwise method (threshold $P < 0.05$), for the construction of nomograms for the prediction of 3- and 5-year OS. Corresponding 95% confidence intervals (CIs) and hazard ratios were calculated. Areas under time-dependent receiver operating characteristic curves (AUCs) for 3- and 5-year OS on the nomograms were calculated to verify predictive accuracy. The nomograms were internally validated by 2000 bootstrap resampling of 75% of the original data. The discriminability of the nomograms was assessed by constructing AUCs and calculating Harrell's concordance (C-) index values (range, 0.5–1). Calibration curves were plotted to assess the predictive performance of the nomograms. The calibration ability (agreement between predicted and observed frequency probabilities) was verified using the Hosmer-Lemeshow (H-L) chi-squared and goodness-of-fit tests, with $P > 0.05$ considered to indicate good fit. The ability to predict 3- and 5-year OS was evaluated by comparing AUCs from time-dependent ROC and C-index analyses between the proposed nomograms and the three HCC staging systems (8th AJCC-TNM, BCLC, and HKLC systems). All statistical analyses (which yielded two-tailed values) were performed using the R software (version 3.3.0) with the rms package (version 5.1-1; http://www.R-project.org) and SPSS software (version 23.0; IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered to indicate significance.

Results

Clinicopathological Characteristics

A flow diagram of cohort selection is shown in Figure 1. In total, 494 of 835 patients with HCC receiving hepatectomy met the eligibility criteria and were enrolled in this study. Of the patients excluded, 84 had portal-vein tumor thrombosis, 11 had hepatic-vein tumor thrombosis, 23 had biliary tumor thrombus, 9 had positive resection margins, 45 had incomplete clinical data, 7 died within 90 days postoperatively, and 162 had missing follow-up data. The characteristics of the 494 patients included in this study are summarized in Table 1. The majority (86.8%) of patients were male, the median age was 53.0 years

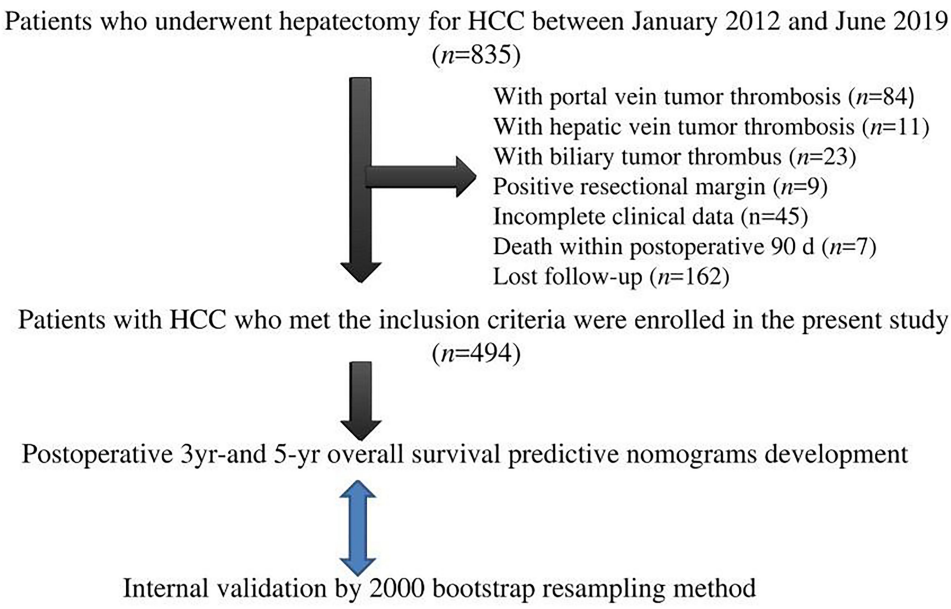

Figure 1 Diagram of study flow.

(range, 15–85 years), and 82.6% of patients were HBsAg positive. Most (96.2%) patients were classified as Child-Pugh grade A, and 19 (3.8%) patients were classified as Child-Pugh grade B. The median follow-up period was 30.0 months (range, 3.2–113.5 months).

Recurrence, Survival, and Post-Recurrence Management

Postoperative recurrence was detected in 249 patients by the end of the follow-up period. The median TTR was 10.4 months (range, 1.0–153.0 months). The cumulative recurrence rates at 1–5 years were 28.1% (139/494), 41.1% (203/494), 46.8% (231/494), 48.6% (240/494), and 49.8% (246/494), respectively. The OS rates at 1–5 years were 77.5% (383/494), 51.8% (256/494), 30.4% (150/494), 16.6% (82/494), and 8.1% (40/494), respectively.

ER occurred in 203 patients. One hundred fifty-three of these patients had intrahepatic recurrence alone; 32 patients had synchronous intrahepatic and extrahepatic recurrence with metastasis to the lung (n = 18), peritoneal cavity (n = 8), lymph node (n = 3), bone (n = 1), right adrenal gland (n = 1), and brain (n = 1); and 18 patients had extrahepatic recurrence alone with metastasis to the peritoneal cavity (n = 4), lung (n = 7), lymph node (n = 3), bone (n = 3), and brain (n = 1). ER was treated by re-resection (n = 29), microwave ablation (n = 17), TACE (n = 107), radiotherapy (n = 2), targeted drugs (n = 12), and supportive care (n = 36).

LR was detected in 46 patients. Forty-one patients had intrahepatic recurrence alone; one patient had synchronous intrahepatic and extrahepatic recurrence with metastasis to the lung; and four patients had extrahepatic recurrence alone with metastasis to the peritoneal cavity (n = 1), right adrenal gland and brain (n = 1), and chest wall and mediastinal lymph nodes (n = 2). Recurrence was detected in 3 of these 46 patients at 62.3, 67.6, and 86.1 months, respectively. LR was treated by re-resection (n = 21), microwave ablation (n = 4), TACE (n = 10), and supportive care (n = 11). The recurrence site and treatment differed significantly between ER and LR cases (Wilcoxon rank sum test, P =0.029 and 0.004, respectively; Table 2).

PRS of Patients with ER After Post-Recurrence Treatment

Among patients with intrahepatic ER, PRS did not differ between patients undergoing curative hepatectomy and microwave ablation (51.0 and 41.2 months, respectively). PRS was superior in these two groups of patients to that of those receiving TACE (14.2 months; χ^2 = 16.630 and 13.072, respectively; both $P < 0.0001$) and conservative treatment (6.5 months; χ^2 = 26.951 and 23.208, respectively; both $P < 0.0001$). The PRS of patients undergoing TACE was superior to that of those receiving conservative treatment (χ^2 = 17.781, $P < 0.0001$). The PRS of patients receiving immunotargeted therapy (27.6 months) did not

Table 1 Patient Characteristics and Univariate Results for 3- and 5-Year Postoperative Overall Survival

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	P	n (%) or Median (Range)	HR	(95% CI)	P
Gender								
Female (65)	17 (11.3)	0.890	(0.536,1.477)	0.651	4 (10.0)	0.926	(0.325, 2.637)	0.886
Male (429)	133 (88.7)	1			36 (90.0)	1		
Age (year)								
≥60 (154)	44 (29.3)	0.773	(0.534, 1.117)	0.170	10 (25.0)	0.760	(0.350, 1.647)	0.486
40–60 (269)	84 (56.0)	0.783	(0.468, 1.310)	0.352	22 (55.0)	1.107	(0.431, 2.837)	0.833
≤40 (71)	22 (14.7)	1		0.370	8 (20.0)	1		0.611
Dis-course (mon)	0.3 (0.02–18.0)	1.004	(0.936, 1.076)	0.916	0.3 (0.07–18.0)	1.029	(0.930,1.138)	0.580
Smoking								
None (323)	100 (66.7)	0.923	(0.650, 1.311)	0.654	27 (67.5)	0.791	(0.397, 1.577)	0.505
Sometimes (10)	3 (2.0)	1.391	(0.430, 2.504)	0.582	0 (0)	–	–	–
Often (161)	47 (18.7)	1		0.731	13 (32.5)	1		0.505
Drinking								
None (345)	104 (69.3)	0.112	(0.015, 0.849)	0.034	28 (70.0)	0.846	(0.450, 1.591)	0.604
Sometimes (52)	18 (12.0)	0.142	(0.018, 1.118)	0.064	3 (7.5)	0.823	(0.367, 1.848)	0.638
Often (97)	28 (36.2)	1		0.118	9 (22.5)	1		0.869
Symptom								
No (254)	79 (52.7)	0.981	(0.710, 1.355)	0.908	22 (55.0)	0.930	(0.491, 1.761)	0.824
Yes (240)	71 (47.3)	1			18 (45.0)	1		
Weight loss								
<5kg (434)	144 (96.0)	0.629	(0.338, 1.169)	0.143	39 (97.5)	0.454	(0.104, 1.982)	0.294
≥5kg (60)	6 (4.0)	1			1 (2.5)	1		
With DM								
No (291)	135 (90.0)	0.457	(0.262, 0.796)	0.006	40 (100)	–	–	–
Yes (27)	15 (10.0)	1			0 (0)	1		
HVdetection (year)	10.5 (0–51.0)	0.998	(0.984, 1.012)	0.762	5.0 (0–33.0)	0.985	(0.959, 1.012)	0.276
Antiviral therapy								
Entecavir (40)	9 (6.0)	0.723	(0.100, 5.210)	0.748	0 ()	–	–	–
Lamivudine (6)	2 (1.3)	0.410	(0.025, 6.609)	0.529	0 ()	–	–	–
Interferon (7)	3 (2.0)	0.566	(0.079, 4.064)	0.572	1 (2.5)	0.483	(0.064, 3.665)	0.482
None (441)	136 (90.7)	1		0.309	39 (97.5)	1		0.482
Antivirus (year)	1.6 (0.2–2.0)	1.152	(0.968, 1.372)	0.111	0 (0–2.0)	1.438	(0.522, 3.960)	0.482
Perioperative antiviral therapy								
Yes (299)	72 (48.0)	0.633	(0.454, 0.883)	0.007	14 (35.0)	0.473	(0.240, 0.934)	0.031
No (195)	78 (52.0)	1			26 (65.0)	1		
HBsAg level	208.1 (0–3489.2)	1.000	(1.000, 1.000)	0.965	225.0 (0–3489.2)	1.000	(1.000, 1.001)	0.163
HBsAg (+)								
No (86)	31 (20.7)	0.815	(0.548, 1.214)	0.314	7 (17.5)	0.973	(0.424, 2.230)	0.948
Yes (408)	119 (79.3)	1			33 (82.5)	1		
Spontaneous HBsAg seroclearance								
Yes (52)	18 (12.0)	0.916	(0.558, 1.505)	0.730	6 (15.0)	0.938	(0.387, 2.273)	0.888
No (442)	132 (88.0)	1			34 (85.0)	1		

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	*P*	n (%) or Median (Range)	HR	(95% CI)	*P*
HBV-DNA	1090.0 (0–1.6×10^8)	1.000	(1.000, 1.000)	0.859	3720.0 (0–7.7×10^6)	1.000	(1.000, 1.000)	0.048
HBVDNA<5×10^2								
Yes (218)	67 (44.7)	0.817	(0.591, 1.130)	0.222	16 (40.0)	0.908	(0.477, 1.727)	0.769
No (276)	83 (55.3)	1			24 (60.0)	1		
HBsAb								
- (448)	137 (91.3)	0.854	(0.482, 1.512)	0.587	37 (92.5)	0.830	(0.251, 2.747)	0.760
+ (46)	13 (8.7)	1			3 (7.5)	1		
Anti-HCV								
- (476)	146 (97.3)	0.765	(0.313, 1.870)	0.556	39 (97.5)	0.830	(0.112, 6.173)	0.855
+ (18)	4 (2.7)	1			1 (2.5)	1		
HBeAg								
- (458)	141 (94.0)	0.734	(0.372, 1.451)	0.374	38 (95.0)	0.062	(0.011, 0.342)	0.001
+ (36)	9 (6.0)	1			2 (5.0)	1		
HBeAb								
- (138)	49 (32.7)	0.700	(0.494, 0.992)	0.045	8 (20.0)	0.672	(0.306, 1.475)	0.321
+ (356)	101 (67.3)	1			32 (80.0)	1		
HBcAb								
- (44)	16 (10.7)	0.417	(0.244, 0.710)	0.001	1 (2.5)	0.830	(0.112, 6.173)	0.855
+ (450)	134 (89.3)	1			39 (97.5)	1		
With PH								
No (398)	127 (84.7)	0.821	(0.114, 5.907)	0.844	38 (95.0)	0.251	(0.033, 1.923)	0.183
Mild (66)	20 (13.3)	0.317	(0.076, 1.322)	0.115	2 (5.0)	1		
Moderate (20)	3 (2.0)	1		0.648	0 (0)	–	–	–
Severe (10)	0	0 (0)	–	–	0 (0)	–	–	–
With SR								
No (430)	133 (88.7)	0.971	(0.583, 1.618)	0.911	35 (87.5)	0.389	(0.145, 1.044)	0.061
Yes (64)	17 (11.3)	1			5 (12.5)	1		
CTP grade								
A (475)	147 (98.0)	0.497	(0.157, 1.575)	0.235	40 (100)	–	–	–
B (19)	3 (2.0)	1			0 (0)			
Tumor MD (cm)								
≤5 (245)	81 (54.0)	0.869	(0.471, 1.604)	0.654	20 (50.0)	0.336	(0.109, 1.031)	0.057
5–10 (171)	57 (38.0)	1.002	(0.713, 1.408)	0.991	15 (37.5)	0.289	(0.097, 0.863)	0.026
≥10 (78)	12 (8.0)	1		0.898	5 (12.5)	1		0.083
Tumor number								
1 (377)	123 (82.0)	0.606	(0.260, 0.780)	0.004	37 (92.5)	0.739	(0.174, 3.139)	0.121
2 (58)	15 (10.0)	0.520	(0.138, 1.017)	0.056	3 (7.5)	1		0.682
3 (16)	2 (1.3)	0.419	(0.056, 3.119)	0.396	0 (0)	–	–	–
≥4 (43)	10 (6.7)	1		0.010	0 (0)	–	–	–
Tumor location								
Bilobar (40)	6 (4.0)	1.448	(0.347, 6.046)	0.611	0 (0)	–	–	–
Righthemihepatic (351)	106 (70.7)	0.981	(0.671, 1.435)	0.922	30 (75.0)	0.878	(0.423, 1.820)	0.726
Left hemihepatic (103)	38 (25.3)	1		0.420	10 (25.0)	1		

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	P	n (%) or Median (Range)	HR	(95% CI)	P
Pedunculated HCC								
Completely (31)	10 (6.7)	0.878	(0.566, 1.360)	0.559	4 (10.0)	0.951	(0.332, 2.725)	0.925
Partially (28)	11 (7.3)	0.831	(0.470, 1.467)	0.523	2 (5.0)	0.526	(0.358, 1.509)	0.568
No (435)	129 (86.0)	1		0.762	34 (85.0)	1		0.842
Tumor capsular								
Yes (204)	64 (42.7)	0.803	(0.577, 1.119)	0.195	21 (52.5)	0.965	(0.508, 1.833)	0.914
No (290)	86 (57.3)	1			19 (47.5)	1		
AJCC-TNM stage								
IA (35)	14 (9.3)	0.885	(0.317, 2.469)	0.816	4 (10.0)	0.416	(0.094, 1.835)	0.247
IB (236)	85 (56.7)	0.833	(0.337, 2.058)	0.691	26 (65.0)	0.344	(0.060, 1.968)	0.230
II (130)	35 (23.3)	0.864	(0.336, 2.222)	0.762	8 (20.0)	0.254	(0.050, 1.293)	0.099
IIIA (49)	11 (7.3)	0.740	(0.217, 2.523)	0.630	0 (0)	–	–	–
IIIB (41)	5 (3.3)	1		0.173	2 (5.0)	1		0.379
IVA (3)	0 (0)	–	–	–	0 (0)	–	–	–
BCLC stage								
0 (21)	10 (6.7)	0.784	(0.400, 1.536)	0.478	4 (10.0)	0.850	(0.299, 2.418)	0.760
A (349)	117 (78.0)	0.780	(0.401, 1.515)	0.463	33 (82.5)	0.793	(0.323, 1.947)	0.613
B (88)	19 (12.7)	1.013	(0.641, 3.115)	0.391	1 (2.5)	1.067	(0.373, 3.054)	0.904
C (36)	4 (2.7)	1		0.757	2 (5.0)	1		0.762
HKLC stage								
I (231)	78 (52.0)	0.595	(0.389, 0.909)	0.016	20 (50.0)	0.268	(0.074, 0.974)	0.046
IIA (5)	0 (0)	–	–	–	0 (0)	–	–	–
IIB (197)	62 (41.3)	0.626	(0.332, 1.182)	0.149	17 (42.5)	0.217	(0.060, 0.786)	0.020
IIIA (2)	0 (0)	–	–	–	0 (0)	–	–	–
IIIB (56)	10 (6.7)	1		0.009	3 (7.5)	1		0.067
IVA (3)	0 (0)	–	–	–	0 (0)	–	–	–
Preoperative TACE								
Yes (25)	7 (4.7)	0.947	(0.463, 1.935)	0.881	1 (2.5)	0.529	(0.072, 3.910)	0.533
No (469)	143 (95.3)	1			39 (97.5)	1		
ALT (U/L)	36.8 (11.5–244.6)	1.001	(0.996, 1.006)	0.741	37.2 (11.5–167.1)	1.005	(0.995, 1.016)	0.332
AST (U/L)	36.3 (16.8–236.7)	1.003	(0.997, 1.009)	0.396	32.1 (17.7–82.4)	1.016	(0.995, 1.036)	0.132
ALT/AST	1.0 (0.2–3.0)	0.889	(0.607, 1.302)	0.544	1.1 (0.2–3.0)	1.088	(0.489, 2.417)	0.837
APRI	0.6 (0.1–4.7)	1.298	(1.020, 1.651)	0.034	0.5 (0.2–1.6)	1.926	(0.513, 7.226)	0.331
Fib-4	2.2 (0.4–10.4)	1.140	(1.030, 1.261)	0.011	1.9 (0.7–7.4)	1.112	(0.788, 1.568)	0.545
ALP (U/L)	103.5 (35.0–347.0)	1.006	(1.002, 1.010)	0.002	86.7 (40.0–182.0)	0.999	(0.985, 1.013)	0.879
PA (mg/L)	200.0 (37.0–444.1)	0.999	(0.996, 1.002)	0.529	225.0 (138.0–326.0)	1.006	(0.998, 1.013)	0.122
γ-GGT (U/L)	53.9 (13.7–438.8)	1.003	(1.001, 1.005)	0.006	36.5 (13.7–281.0)	1.003	(0.997, 1.009)	0.313
γ-GGT>60U/L								
No (277)	92 (61.3)	0.464	(0.324, 0.664)	0.000	33 (82.5)	0.336	(0.131, 0.865)	0.024
Yes (217)	58 (38.7)	1			7 (17.5)	1		
GPR	0.6 (0.1–14.4)	1.176	(1.077, 1.283)	0.000	0.4 (0.2–2.6)	1.451	(0.745, 2.824)	0.274
5′-NT (U/L)	9.5 (1.5–77.9)	0.996	(0.982, 1.010)	0.555	9.9 (2.0–77.9)	1.009	(0.988, 1.031)	0.409
LDH (U/L)	186.5 (114.6–384.3)	1.000	(0.996, 1.005)	0.846	167.4 (132.1–384.3)	1.006	(0.994, 1.018)	0.341
TBA (μmol/L)	5.0 (1.0–162.7)	1.001	(0.992, 1.009)	0.859	4.2 (1.0–162.7)	1.014	(0.995, 1.033)	0.140
TP (g/L)	65.6 (49.1–66.1)	0.998	(0.994, 1.002)	0.333	62.3 (55.6–66.1)	1.000	(0.997, 1.004)	0.959
ALB (g/L)	40.7 (28.7–50.7)	0.956	(0.921, 0.993)	0.020	41.4 (34.6–50.5)	1.029	(0.941, 1.124)	0.533

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	*P*	n (%) or Median (Range)	HR	(95% CI)	*P*
GLB (g/L)	24.6 (14.2–35.7)	1.002	(0.994, 1.010)	0.596	23.6 (16.8–35.7)	1.011	(0.939, 1.088)	0.774
AG<1.5								
No (292)		0.681	(0.485, 0.958)	0.027	29 (72.5)	0.842	(0.413, 1.715)	0.635
Yes (202)		1			11 (27.5)	1		
ALBI grade								
1 (256)	84 (56.0)	0.601	(0.428, 0.843)	0.003	28 (70.0)	0.866	(0.403, 1.859)	0.712
2 (236)	66 (44.0)	1			12 (30.0)	1		
3 (2)	0 (0)		–	–	0 (0)	–	–	–
IMA	69.1 (16.3–200.4)	0.992	(0.981, 1.003)	0.152	75.9 (66.3–200.4)	1.037	(0.951, 1.131)	0.411
TBIL (mmol/L)	14.7 (5.4–40.0)	1.044	(1.017, 1.071)	0.001	12.9 (5.9–30.3)	1.066	(0.982, 1.158)	0.128
DBIL (mmol/L)	5.6 (1.9–14.1)	1.088	(1.018, 1.164)	0.014	4.8 (1.9–10.5)	1.271	(1.012, 1.595)	0.039
Na+	140.0 (128.0–154.2)	0.942	(0.892, 0.995)	0.033	140.0 (132.0–146.6)	0.880	(0.786, 0.985)	0.026
RBC ($\times10^9$)	4.5 (3.1–5.9)	0.981	(0.727, 1.324)	0.899	4.4 (3.2–5.6)	1.250	(0.616, 2.538)	0.536
WBC ($\times10^9$)	5.8 (2.2–17.2)	0.961	(0.890, 1.038)	0.314	6.5 (3.2–12.4)	1.029	(0.875, 1.211)	0.727
N	3.5 (1.2–14.5)	0.965	(0.881, 1.058)	0.446	3.9 (1.2–8.9)	1.050	(0.860, 1.281)	0.632
L	1.5 (0.4–3.7)	0.924	(0.688, 1.239)	0.597	1.6 (0.6–3.1)	1.384	(0.695, 2.753)	0.355
NLR	2.4 (0.6–10.5)	1.016	(0.905, 1.141)	0.787	2.2 (0.6–6.8)	1.125	(0.832, 1.521)	0.446
MONO	0.5 (0.2–1.8)	1.188	(0.577, 2.447)	0.639	0.5 (0.3–1.0)	8.008	(0.961, 9.715)	0.054
MLR	0.3 (0.1–0.9)	1.591	(0.508, 4.989)	0.425	0.3 (0.2–0.9)	3.839	(0.383, 5.478)	0.253
Hb (g/L)	139.0 (81–177)	0.999	(0.990, 1.008)	0.829	138.0 (83–167)	0.991	(0.969, 1.013)	0.402
Hct	42.3 (22.8–54.5)	1.001	(0.969, 1.034)	0.965	42.2 (22.8–50.7)	0.995	(0.916, 1.081)	0.908
PLT ($\times10^{12}$)	154.0 (34.0–350.0)	0.997	(0.994, 1.000)	0.069	177.0 (70.0–350.0)	1.000	(0.995, 1.006)	0.941
PLR	93.9 (38.7–298.6)	0.998	(0.995, 1.001)	0.260	108.0 (38.7–289.2)	1.000	(0.993, 1.007)	0.905
PT>17s								
No (492)	149 (99.3)	0.754	(0.105, 5.420)	0.779	40 (100)	–	–	–
Yes (2)	1 (0.7)	1			0 (0)	1		
APPT>40s								
No (426)	127 (84.7)	0.733	(0.467, 1.149)	0.175	35 (87.5)	0.510	(0.195, 1.335)	0.170
Yes (68)	23 (15.3)	1			5 (12.5)	1		
4								
No (435)	131 (87.3)	0.654	(0.400, 1.071)	0.092	38 (95.0)	0.989	(0.959, 1.020)	0.495
Yes (59)	19 (12.7)	1			2 (5.0)	1		
INR	1.0 (0.8–1.4)	0.448	(0.067, 2.986)	0.407	1.0 (0.8–1.3)	1.462	(0.370, 2.757)	0.139
FIB (g/L)	2.3 (1.4–7.0)	0.924	(0.749, 1.139)	0.459	2.3 (1.7–4.6)	0.746	(0.442, 1.261)	0.274
DD	0.3 (0.1–13.2)	0.981	(0.873, 1.103)	0.748	0.3 (0.1–6.0)	1.148	(0.777, 1.696)	0.487
BUN	5.0 (2.5–14.3)	0.884	(0.792, 0.986)	0.027	5.5 (3.0–14.3)	0.986	(0.780, 1.247)	0.909
Cr	69.0 (37.0–231.7)	0.993	(0.985, 1.001)	0.072	77.0 (47.0–172.0)	1.006	(0.991, 1.022)	0.426
AFP (μg/L)								
0–20 (205)	62 (41.3)	0.869	(0.698, 1.083)	0.212	21 (52.5)	0.943	(0.427, 2.082)	0.884
20–400 (151)	50 (33.3)	0.886	(0.589, 1.334)	0.563	9 (22.5)	0.890	(0.402, 1.968)	0.773
>400 (138)	38 (25.3)	1		0.296	10 (25.0)	1		0.957
Operative time>4h								
No (271)	95 (63.3)	0.946	(0.677, 1.321)	0.744	25 (62.5)	0.905	(0.471, 1.740)	0.765
Yes (223)	55 (36.7)	1			15 (37.5)	1		

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	P	n (%) or Median (Range)	HR	(95% CI)	P
Surgical approach								
Laparoscopy (218)	48 (32.0)	0.348	(0.047, 2.582)	0.299	5 (12.5)	0.607	(0.234, 1.576)	0.305
Open (276)	102 (68.0)	1			35 (87.5)	1		
Type of hepatectomy								
Anatomic (271)	73 (48.7)	0.862	(0.623, 1.193)	0.371	20 (50.0)	0.523	(0.275, 0.997)	0.049
Nonanatomic (223)	77 (51.3)	1			20 (50.0)	1		
Extent of hepatectomy								
Wedge resection (208)	73 (48.7)	1.196	(0.777, 1.840)	0.417	19 (47.5)	3.153	(1.230, 4.084)	0.017
1 segment (52)	16 (10.7)	0.957	(0.689, 1.330)	0.794	3 (7.5)	0.555	(0.307, 1.005)	0.052
2 segment s (121)	34 (22.7)	0.920	(0.554, 1.528)	0.748	12 (30.0)	0.348	(0.105, 1.154)	0.084
3 segment s (51)	11 (7.3)	1.096	(0.711, 1.691)	0.677	2 (5.0)	1.384	(0.740, 2.587)	0.309
≥4 segment s (62)	16 (10.7)	1		0.786	4 (10.0)	1		0.020
Intraoperative vascular occlusion								
Pringle maneuver + hemi-hepatic occlusion (196)	47 (31.3)	0.207	(0.037, 1.167)	0.074	12 (30.0)	0.692	(0.344, 1.393)	0.303
hemi-hepatic occlusion (10)	4 (2.7)	0.190	(0.045, 0.803)	0.024	1 (2.5)	0.361	(0.290, 1.226)	0.422
Pringle maneuver (288)	99 (66.0)	1		0.123	27 (67.5)	1		0.339
Vascular occlusion time (min)	40.0 (10–165)	1.002	(0.994, 1.009)	0.670	40.0 (10.0–120.0)	1.012	(0.995, 1.029)	0.171
Estimated blood loss (mL)	100 (5–1300)	1.000	(0.999, 1.000)	0.427	100.0 (5.0–1200.0)	1.000	(0.999, 1.001)	0.989
Intraoperative RBC transfusion (U)	0 (0–7)	0.969	(0.808, 1.162)	0.735	0 (0–3)	0.784	(0.402, 1.527)	0.474
Intraoperative Plasma transfusion (mL)	0 (0–400)	1.001	(0.998, 1.004)	0.469	0 (0–0)	–	–	–
Incisal margin distance								
≥2cm (172)	64 (42.7)	0.671	(0.436, 1.031)	0.069	20 (50.0)	0.889	(0.341, 2.317)	0.810
1–2cm (113)	42 (28.0)	0.698	(0.473, 1.031)	0.707	13 (32.5)	0.956	(0.393, 2.329)	0.921
≤1cm (209)	44 (29.3)	1		0.118	7 (17.5)	1		0.967
Histological subtype								
Trabecular (259)	128 (85.3)	0.250	(0.034, 1.826)	0.172	39 (97.5)	0.890	(0.267, 2.969)	0.850
Pseudoductular (26)	17 (11.3)	0.214	(0.013, 3.482)	0.278	1 (2.5)	0.609	(0.062, 6.020)	0.671
Solid lesion (29)	5 (3.3)	1		0.209	0 (0)	1		0.914
Edmondson-Steiner stage								
I (18)	11 (7.3)	0.567	(0.139, 2.320)	0.430	2 (5.0)	0.412	(0.202, 1.352)	0.015
II (203)	83 (55.3)	0.875	(0.212, 3.604)	0.853	25 (62.5)	0.299	(0.066, 1.352)	0.117
III (253)	55 (36.7)	1.426	(0.128, 4.894)	0.773	13 (32.5)	1		0.036
IV (20)	1 (0.7)	1		0.453	0 (0)	–	–	–
Metavir inflammation activity grade								
A0 (54)	28 (18.7)	0.522	(0.289, 0.944)	0.031	7 (17.5)	0.437	(0.122, 1.565)	0.203
A1 (272)	73 (48.7)	0.494	(0.300, 0.814)	0.006	19 (47.5)	0.315	(0.081, 1.219)	0.094
A2 (136)	35 (23.3)	0.360	(0.167, 0.779)	0.009	11 (27.5)	0.219	(0.031, 3.163)	0.326
A3 (32)	14 (9.3)	1		0.047	3 (7.5)	1		0.358
Metavir fibrosis grade								
F0 (17)	10 (6.7)	0.875	(0.492, 1.556)	0.650	4 (10.0)	0.599	(0.122, 2.950)	0.529
F1 (47)	24 (16.0)	0.727	(0.378, 1.397)	0.339	6 (15.0)	0.577	(0.131, 2.545)	0.468
F2 (186)	67 (44.7)	0.565	(0.319, 0.999)	0.050	21 (52.5)	0.506	(0.101, 2.549)	0.409

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	*P*	n (%) or Median (Range)	HR	(95% CI)	*P*
F3 (111)	28 (18.7)	0.321	(0.042, 2.465)	0.275	7 (17.5)	0.350	(0.062, 1.987)	0.236
F4 (133)	21 (14.0)	1		0.637	2 (5.0)	1		0.807
MVI								
M0 (283)	115 (76.7)	0.640	(0.464, 0.798)	0.000	37 (92.5)	0.684	(0.162, 2.897)	0.606
M1 (139)	23 (15.3)	0.609	(0.352, 1.166)	0.145	1 (2.5)	1.225	(0.108, 3.862)	0.870
M2 (72)	12 (8.0)	1		0.000	2 (5.0)	1		0.757
HepParI								
- (59)	23 (15.3)	0.597	(0.364, 0.978)	0.040	2 (5.0)	0.675	(0.057, 1.527)	0.756
+ (435)	127 (84.7)	1			38 (95.0)	1		
P53								
- (225)	88 (58.7)	0.504	(0.385, 1.992)	0.121	25 (62.5)	1		0.277
± (27)	3 (2.0)	0.859	(0.547, 1.350)	0.510	0 (0)	0.333	(0.041, 2.684)	0.302
+ (101)	39 (26.0)	0.853	(0.521, 1.395)	0.526	11 (27.5)	–	–	–
++ (98)	15 (10.0)	0.988	(0.529, 1.843)	0.969	2 (5.0)	–	–	–
+++ (43)	5 (3.3)	1		0.596	2 (5.0)	1		0.199
Ki67 (%)	15.0 (0–75)	1.012	(1.003, 1.021)	0.010	10.0 (0–75)	1.007	(0.982, 1.032)	0.595
Glypican3								
- (73)	29 (19.3)	0.879	(0.264, 2.926)	0.833	9 (22.5)	0.199	(0.023, 1.687)	0.139
+ (421)	121 (80.7)	1			31 (77.5)	1		
Postoperative CC								
None (437)	135 (90.0)	0.503	(0.124, 2.047)	0.337	35 (87.5)	0.201	(0.020, 2. 001)	0.171
I (15)	2 (1.3)	0.776	(0.389, 1.510)	0.442	0 (0)	–	–	–
II (2)	1 (0.7)	0.874	(0.235, 3.250)	0.841	0 (0)	–	–	–
IIIa (30)	9 (6.0)	0.877	(0.278, 2.763)	0.822	4 (10.0)	0.196	(0.024, 1.599)	0.128
IIIb (7)	3 (2.0)	1		0.141	1 (2.5)	1		0.314
Postoperative RBC transfusion (U)								
No (487)	148 (98.7)	0.736	(0.182, 2.983)	0.668	39 (97.5)	0.197	(0.024, 1.598)	0.128
Yes (7)	2 (1.3)	1			1 (2.5)	1		
Postoperative Plasma transfusion (mL)								
No (476)	145 (96.7)	0.251	(0.035, 1.819)	0.171	37 (92.5)	0.389	(0.052, 2.902)	0.357
Yes (18)	5 (3.3)	1			3 (7.5)	1		
Postoperative AT								
Targeted therapy (6)	2 (1.3)	0.787	(0.194, 3.192)	0.737	1 (2.5)	0.014	(0.001, 0.318)	0.007
TACE (70)	13 (8.7)	0.518	(0.148, 2.070)	0.620	1 (2.5)	0.053	(0.005, 0.587)	0.017
None (418)	135 (90.0)	1		0.831	38 (95.0)	1		0.024
Postoperative anti-HBV								
Yes (340)	89 (59.3)	0.748	(0.534, 1.047)	0.090	20 (50.0)	0.547	(0.289, 1.034)	0.063
No (154)	61 (40.7)	1			20 (50.0)	1		
Postoperative recurrence								
No (245)	87 (58.0)	0.825	(0.592, 1.148)	0.254	24 (60.0)	0.494	(0.251, 0.974)	0.042
Yes (249)	63 (42.0)	1			16 (40.0)	1		

(*Continued*)

Table 1 (Continued).

Factors (n=494)	3-Yr OS (n=150)				5-Yr OS (n=40)			
	n (%) or Median (Range)	HR	(95% CI)	P	n (%) or Median (Range)	HR	(95% CI)	P
Site of recurrence[a]								
Intrahepatic (177)	53 (84.1)	1		0.008	15 (93.8)	1		
Extrahepatic (15)	4 (6.3)	2.390	(0.835, 6.841)	0.104	1 (6.3)	1.572	(0.863, 2.864)	0.139
Intra-+extrahepatic (56)	6 (9.5)	9.151	(1.941, 13.153)	0.005	–	–	–	–
Post-recurrence management[a]								
Re-resection (51)	26 (41.3)	1		0.004	9 (56.3)	1		0.000
Microwave ablation (21)	7 (11.1)	0.764	(0.327, 1.783)	0.534	3 (18.8)	0.549	(0.159, 1.895)	0.343
TACE (131)	21 (33.3)	2.735	(1.486, 5.033)	0.001	3 (18.8)	4.590	(2.642, 7.973)	0.000
Radiotherapy (2)	0 (0)	–	–	–	0 (0)	–	–	–
Targeted therapy	2 (3.2)	2.091	(0.485, 9.025)	0.323	0 (0)	–	–	–
Best supportive care (43)	7 (11.1)	2.933	(1.219, 7.058)	0.016	1 (6.3)	12.383	(6.659, 19.026)	0.000
TTR (≤1year)								
No (109)	51 (81.0)	0.835	(0.462, 1.510)	0.551	13 (81.3)	0.677	(0.204, 2.248)	0.524
Yes (139)	12 (19.0)	1			3 (18.8)	1		
ER (≤2years)								
No (46)	35 (55.6)	0.684	(0.478, 0.977)	0.037	11 (68.8)	0.787	(0.300, 2.061)	0.787
Yes (203)	28 (44.4)	1			5 (31.3)	1		
TTR (≤3years)								
No (263)	106 (70.7)	0.741	(0.489, 1.122)	0.157	34 (85.0)	0.947	(0.393, 2.280)	0.903
Yes (231)	44 (29.3)	1			6 (15.0)	1		
LR (>2years)								
No (202)	28 (44.4)	0.716	(0.472, 1.087)	0.117	5 (31.3)	0.378	(0.172, 0.835)	0.016
Yes (46)	35 (55.6)	1			11 (68.8)	1		

Note: [a]Three-year OS, n = 63; 5-year OS, n = 16.

Abbreviations: HR, hazard ratio; Dis-course, disease course; DM, diabetes mellitus; HV, hepatitis virus; MD, maximum diameter; PH, portal hypertension; SR, spontaneous rupture; BS, blood sugar; ALT, glutamic pyruvic transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; PA, prealbumin; γ-GGT, γ-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; NT, nucleotidase; LDH, lactate dehydrogenase; TBA, total bile acid; TP, total protein; ALB, albumin; GLB, globulin; AG, albumin-to-globulin ratio; IMA, ischemia-modified albumin; TBIL, total bilirubin; DBIL, direct bilirubin; RBC, red blood cell; WBC, white blood cell; N, neutrophil; L, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; MONO, monocyte; MLR, monocyte-to-lymphocyte ratio; Hb, hemoglobin; PLT, platelet; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, plasma fibrinogen; D-D, D-dimer; AFP, alpha fetoprotein; CC, complication classification; AT, adjuvant therapy; TTR, time to recurrence; ER, early recurrence; LR, late recurrence.

differ from that of those undergoing curative hepatectomy, microwave ablation, or TACE, but was superior to that of those receiving conservative treatment (χ^2 = 8.381, P = 0.004; Tables 3 and 4). As only one patient each in the extrahepatic ER and intrahepatic and extrahepatic ER groups received microwave ablation and radiation therapy, these treatment modalities were not included in Log rank testing. Among patients with extrahepatic ER, the PRS of patients undergoing curative hepatectomy (11.8 months) did not differ from that of those receiving TACE and conservative treatment (10.7 and 8.3 months, respectively), but was superior to that of those receiving immunotargeted therapy (7.2 months; χ^2 = 4.543, P = 0.033). PRS did not differ among patients receiving TACE, immunotargeted therapy, and conservative treatment (Tables 3 and 4).

In patients with intrahepatic and extrahepatic ER, the PRS of patients undergoing curative hepatectomy (11.933 months) did not differ from that of those receiving TACE, immunotargeted therapy, and conservative treatment (10.010, 16.033, and 5.004 months, respectively). The PRS of patients receiving TACE and immunotargeted therapy was superior to that of those receiving conservative treatment (χ^2 = 4.170, P = 0.041 and χ^2 = 4.021, P = 0.045, respectively; Tables 3 and 4).

PRS of Patients with LR After Post-Recurrence Treatment

Among patients with intrahepatic LR, PRS did not differ between patients undergoing curative hepatectomy and microwave ablation (18.5 and 17.3 months, respectively),

Table 2 Comparison of Recurrence Sites and Treatments Between ER and LR

Factors	ER (n=203)	LR (n=46)	*P* value
Recurrence sites			
Intrahepatic	153 (75.4)	41 (89.1)	0.029
Extrahepatic	18 (8.9)	4 (8.7)	
Intrahepatic + extrahepatic	32 (15.8)	1 (2.2)	
Post-recurrence treatments			
Re-resection	29 (14.3)	21 (45.7)	0.004
Microwave ablation	17 (8.4)	4 (8.7)	
TACE	107 (52.7)	10 (21.7)	
Radiotherapy	2 (1.0)	0 (0)	
Targeted therapy	12 (5.9)	0 (0)	
Best supportive care	36 (17.7)	11 (23.9)	

but was superior in these two groups to that of those undergoing TACE (10.600 months; χ^2 = 11.446, P = 0.001 and χ^2 = 4.914, P = 0.027, respectively) and conservative treatment (7.350 months; χ^2 = 11.983, P = 0.001 and χ^2 = 4.091, P = 0.043, respectively). PRS did not differ between patients receiving TACE and conservative treatment (Tables 5 and 6). As only one patient with extrahepatic LR underwent re-resection and only one patient had intrahepatic and extrahepatic LR, these cases were not included in Log rank testing.

Three- and 5-Year OS

The results of multivariable analyses for the prediction of 3- and 5-year postoperative OS were shown in Tables 7 and 8, respectively. Independent influencing factors for 3-year OS were HKLC stage, γ-glutamyl transferase (γ-GGT) level, METAVIR inflammation activity grade, ER, and post-recurrence treatment modality (Table 7). Predictors associated independently with 5-year OS were γ-GGT level >60 U/L, hepatectomy extent, LR, and post-recurrence treatment modality (Table 8).

Nomograms for 3- and 5-Year OS Prediction

The prognostic nomograms for 3- and 5-year OS are presented in Figures 2A and 3A, respectively. The AUCs of the nomograms for 3- and 5-year OS prediction were 0.891 [95% CI, 0.8364–0.9447; C-index = 0.7945 (95% CI, 0.7054–0.8541); Figure 2B] and 0.864 [95% CI, 0.8041–0.9237; C-index = 0.7033 (95% CI, 0.6879–0.7958);

Table 3 Median Post-Recurrence Survival of Patients with Early Recurrence After Recurrence Management

Recurrence Site (n)	Post-Recurrence Managements (n)	PRS (Median)	SD	95% CI
Intrahepatic (152)	Re-resection (21)	51.000	7.718	(35.872, 66.128)
	Microwave ablation (15)	41.173	7.283	(26.899, 55.448)
	TACE (95)	14.215	1.230	(11.804,16.625)
	Radiation therapy (0)	—	—	—
	Targeted therapy (6)	27.633	8.545	(10.885, 44.380)
	Best supportive care (15)	6.500	1.846	(2.882,10.118)
	Total (152)	19.716	1.913	(15.968, 23.465)
Extrahepatic (17)	Re-resection (5)	11.840	9.493	(3.800,28.300)
	Microwave ablation (1)	9.200	0.000	(9.200, 9.200)
	TACE (2)	10.700	3.394	(8.300,13.100)
	Radiation therapy (1)	7.400	0.000	(7.400,7.400)
	Targeted therapy (3)	7.200	5.603	(1.900,13.200)
	Best supportive care (5)	8.300	3.798	(2.100,11.423)
	Total (17)	8.950	5.853	(1.900,28.300)
Intra-+Extrahepatic (30)	Re-resection (3)	11.933	2.700	(6.642, 17.225)
	Microwave ablation (1)	4.200	0.000	(4.200, 4.200)
	TACE (10)	10.010	1.932	(6.223, 13.797)
	Radiation therapy (1)	7.200	0.000	(7.200,7.200)
	Targeted therapy (3)	16.033	5.807	(4.651,27.416)
	Best supportive care (12)	5.004	1.162	(2.726, 7.282)
	Total (30)	8.614	1.177	(6.308,10.921)

Abbreviations: PRS, post-recurrence survival; SD, standard deviation; CI, confidence interval; TACE, transcatheter arterial chemoembolization.

Table 4 Comparison of Post-Recurrence Survival After Early Recurrence (Log Rank Test)

Recurrence Site	Post-Recurrence Managements	Re-Resection		Microwave Ablation		TACE		Targeted Therapy		Best Supportive Care	
		χ^2	P	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Intrahepatic	Re-resection	–	–	0.821	0.365	16.630	0.000	0.204	0.651	26.951	0.000
	Microwave ablation	0.821	0.365	–	–	13.072	0.000	1.558	0.212	23.208	0.000
	TACE	16.630	0.000	13.072	0.000	–	–	3.797	0.051	17.781	0.000
	Targeted therapy	0.204	0.651	1.558	0.212	3.797	0.051	–	–	8.381	0.004
	Best supportive care	26.951	0.000	23.208	0.000	17.781	0.000	8.381	0.004	–	–
Extrahepatic	Re-resection	–	–	–	–	1.500	0.221	4.543	0.033	3.457	0.063
	TACE	1.500	0.221	–	–	–	–	1.182	0.277	0.886	0.347
	Targeted therapy	4.543	0.033	–	–	1.182	0.277	–	–	0.027	0.869
	Best supportive care	3.457	0.063	–	–	0.886	0.347	0.027	0.869	–	–
Intra-+Extrahepatic	Re-resection	–	–	–	–	0.004	0.947	0.155	0.694	2.925	0.087
	TACE	0.004	0.947	–	–	–	–	1.551	0.213	4.170	0.041
	Targeted therapy	0.155	0.694	–	–	1.551	0.213	–	–	4.021	0.045
	Best supportive care	2.925	0.087	–	–	4.170	0.041	4.021	0.045	–	–

Notes: One patient each in the extrahepatic, and intrahepatic + extrahepatic recurrence groups received microwave ablation and radiation therapy; thus, these cases were not included in Log rank testing.
Abbreviation: TACE, transcatheter arterial chemoembolization.

Table 5 Median Post-Recurrence Survival of Patients with Late Recurrence After Recurrence Management

Recurrence Site (n)	Post-Recurrence Managements (n)	PRS (Median)	SD	95% CI
Intrahepatic (41)	Re-resection (20)	18.470	8.027	(1.200, 61.300)
	Microwave ablation (4)	17.300	2.806	(4.300, 55.600)
	TACE (9)	10.600	6.183	(4.300,24.100)
	Best supportive care (8)	7.350	4.566	(2.200, 13.700)
Extrahepatic (4)	Re-resection (1)	5.700	0.000	(5.700, 5.700)
	Best supportive care (3)	3.433	0.423	(2.603,4.263)
Intra-+Extrahepatic (1)	TACE (1)	7.800	0.000	(7.800, 7.800)

Abbreviations: PRS, post-recurrence survival; SD, standard deviation; CI, confidence interval; TACE, transcatheter arterial chemoembolization.

Figure 3B], respectively. In bootstrap analysis for internal validation, the AUCs for 3-year OS prediction in the development and validation sets were 0.886 [95% CI, 0.7986–0.9137; C-index = 0.8050 (95% CI, 0.7000–0.8970)] and 0.792 [95% CI, 0.7280–0.8605; C-index = 0.7710 (95% CI, 0.7039–0.8374)], respectively (Figure 2C); the AUCs for 5-year OS prediction in the development and validation sets were 0.815 [95% CI, 0.7235–0.9011; C-index = 0.7870 (95% CI, 0.6420–0.9322)] and 0.774 [95% CI, 0.6553–0.8329; C-index = 0.7227 (95% CI, 0.6460–0.8830)], respectively (Figure 3C). The bootstrap-corrected calibration plots showed good concordance between the predicted and actual observation cohorts, indicating the reliability of the nomograms (Figures 2D and 3D, respectively). The H-L chi-squared calibration values of 3- and 5-year OS were 8.678 ($P = 0.370$) and 5.453 ($P = 0.708$), respectively.

Comparison of 3-Year OS Prediction Using the Nomogram and Representative HCC Staging Systems

The AUC from the time-dependent ROC analysis for the proposed nomogram for 3-year OS prediction was 0.891 (95% CI, 0.8364–0.9447; Figure 2A), which was greater than the AUCs obtained for the three representative HCC staging systems (8th AJCC-TNM system, 0.5370; BCLC system, 0.4901; HKLC system, 0.5396; Figure 4A–C).

Table 6 Comparison of Post-Recurrence Survival After Late Recurrence (Log Rank Test)

Recurrence Site	Post-Recurrence Managements	Re-Resection		Microwave Ablation		TACE		Best Supportive Care	
		χ^2	P	χ^2	P	χ^2	P	χ^2	P
Intrahepatic	Re-resection	–	–	0.772	0.380	11.446	0.001	11.983	0.001
	Microwave ablation	0.772	0.380	–	–	4.914	0.027	4.091	0.043
	TACE	11.446	0.001	4.914	0.027	–	–	0.987	0.320
	Best supportive care	11.983	0.001	4.091	0.043	0.987	0.320	–	–
Extrahepatic	Re-resection	–	–	–	–	–	–	–	–
	Best supportive care	–	–	–	–	–	–	–	–
Intra-+ Extrahepatic	TACE	–	–	–	–	–	–	–	–

Notes: One patient with extrahepatic recurrence received re-resection and one patient with intra-+extrahepatic recurrence received TACE; thus, these cases were not included in Log rank testing.
Abbreviation: TACE, transcatheter arterial chemoembolization.

The C-index for the proposed 3-year OS predictive nomogram [0.7945 (95% CI, 0.7054–0.8541)] was much higher than those obtained with the three staging systems [8th AJCC-TNM system, 0.5316 (95% CI, 0.4815–0.5817); BCLC system, 0.4995 (95% CI, 0.4518–0.5472); HKLC system, 0.5440 (95% CI, 0.5031–0.5848)].

Table 7 Multivariate Results for Postoperative 3-Year Overall Survival

Factors	HR	(95% CI)	P
γ-GGT (U/L)	1.052	(1.019, 1.087)	0.002
HKLC stage			
I	0.714	(0.060, 0.964)	0.018
IIA	–	–	–
IIB	1.123	(0.571, 2.210)	0.737
IIIA	–	–	–
IIIB	1		0.332
IVA	–	–	–
Metavir inflammation activity grade			
A0	0.507	(0.282, 0.913)	0.024
A1	0.400	(0.191, 0.840)	0.015
A2	0.359	(0.143, 0.904)	0.030
A3	1		0.071
ER			
No	0.090	(0.036, 0.224)	0.000
Yes	1		
Post-recurrence managements			
Re-resection	1		0.000
Microwave ablation	0.485	(0.197, 1.194)	0.115
TACE	3.140	(1.516, 6.504)	0.002
Targeted therapy	2.072	(0.414, 10.372)	0.375
Radiotherapy	–	–	–
Best supportive care	4.815	(1.821,12.727)	0.002

Abbreviations: HR, hazard ratio; CI, confidence interval; γ-GGT, γ-glutamyl transferase; HKLC, Hong Kong Liver Cancer; ER, early recurrence; TACE, transcatheter arterial chemoembolization.

Comparison of 5-Year OS Prediction Using the Nomogram and Representative HCC Staging Systems

The AUC from the time-dependent ROC analysis for the proposed nomogram for 5-year OS prediction was 0.864

Table 8 Multivariate Results for Postoperative 5-Year Overall Survival

Factors	HR	(95% CI)	P
γ-GGT>60U/L			
No	0.044	(0.006, 0.335)	0.003
Yes	1		
Extent of hepatectomy			
Wedge resection	3.770	(0.871, 5.319)	0.076
1 segment	1.329	(0.659, 2.679)	0.426
2 segments	0.297	(0.084, 1.055)	0.061
3 segments	0.487	(0.245, 0.965)	0.039
≥4 segments	1		0.031
LR			
No	0.195	(0.071, 0.536)	0.002
Yes	1		
Post-recurrence managements			
Re-resection	1		0.019
Microwave ablation	2.137	(0.600, 7.609)	0.241
TACE	5.058	(1.708,18.879)	0.005
Best supportive care	5.679	(1.154,22.170)	0.032

Abbreviations: HR, hazard ratio; CI, confidence interval; γ-GGT, γ-glutamyl transferase; LR, late recurrence; TACE, transcatheter arterial chemoembolization.

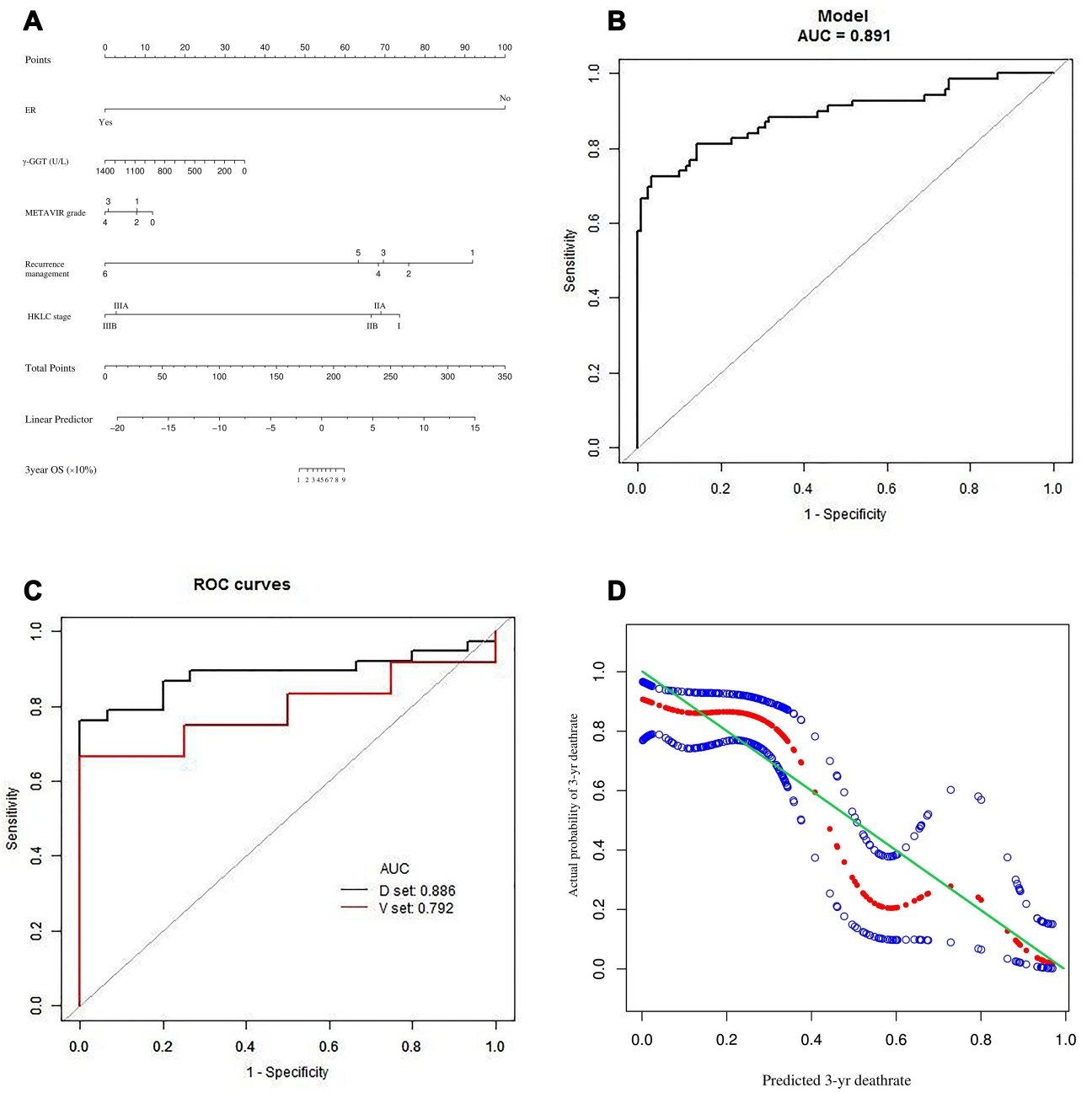

Figure 2 (**A**) Nomogram for the assessment of 3-year overall survival (OS) of patients with hepatocellular carcinoma who have undergone curative hepatectomy. Individual patient values are placed on the variable axes, and a line is drawn upward to determine the number of points that each variable value is worth. The sum of these numbers is placed on the total points axis, and a line is drawn downward to the survival axes to determine the likelihood of 3-year OS. γ-GGT, γ-glutamyl transferase; HKLC, Hong Kong Liver Cancer. Recurrence managements: 1 = re-resection, 2 = microwave ablation, 3 = transarterial chemoembolization, 4 = targeted therapy, 5 = radiation therapy, 6 = best supportive care. (**B**) The area under the time-dependent receiver operating characteristic (ROC) curve (AUC) of the nomogram for 3-year OS. (**C**) Internal validation by bootstrap analysis. D, development; V, validation. (**D**) Calibration plot showing the relationships between predicted and actual probabilities based on the nomogram. The *x* and *y* axes represent the nomogram-predicted and actual probabilities, respectively, of 3-year death. Red solid circles represent the curve fitting line, and blue hollow circles represent nomogram-predicted probabilities with 95% confidence intervals. The green reference line indicates the ideal nomogram, in which actual and predicted probabilities are perfectly identical. The calibration curve shows good prognostic performance. The Hosmer-Lemeshow chi-squared value for calibration was 8.678 (*P* = 0.370).

(95% CI, 0.8041–0.9237; Figure 3A), which was greater than the AUCs obtained for the three representative HCC stage systems (8th AJCC-TNM system, 0.5459; BCLC system, 0.5269; HKLC system, 0.5944; Figure 5A–C). The C-index for the proposed 5-year OS predictive nomogram [0.7033 (95% CI, 0.6879–0.7958)] was much higher than those

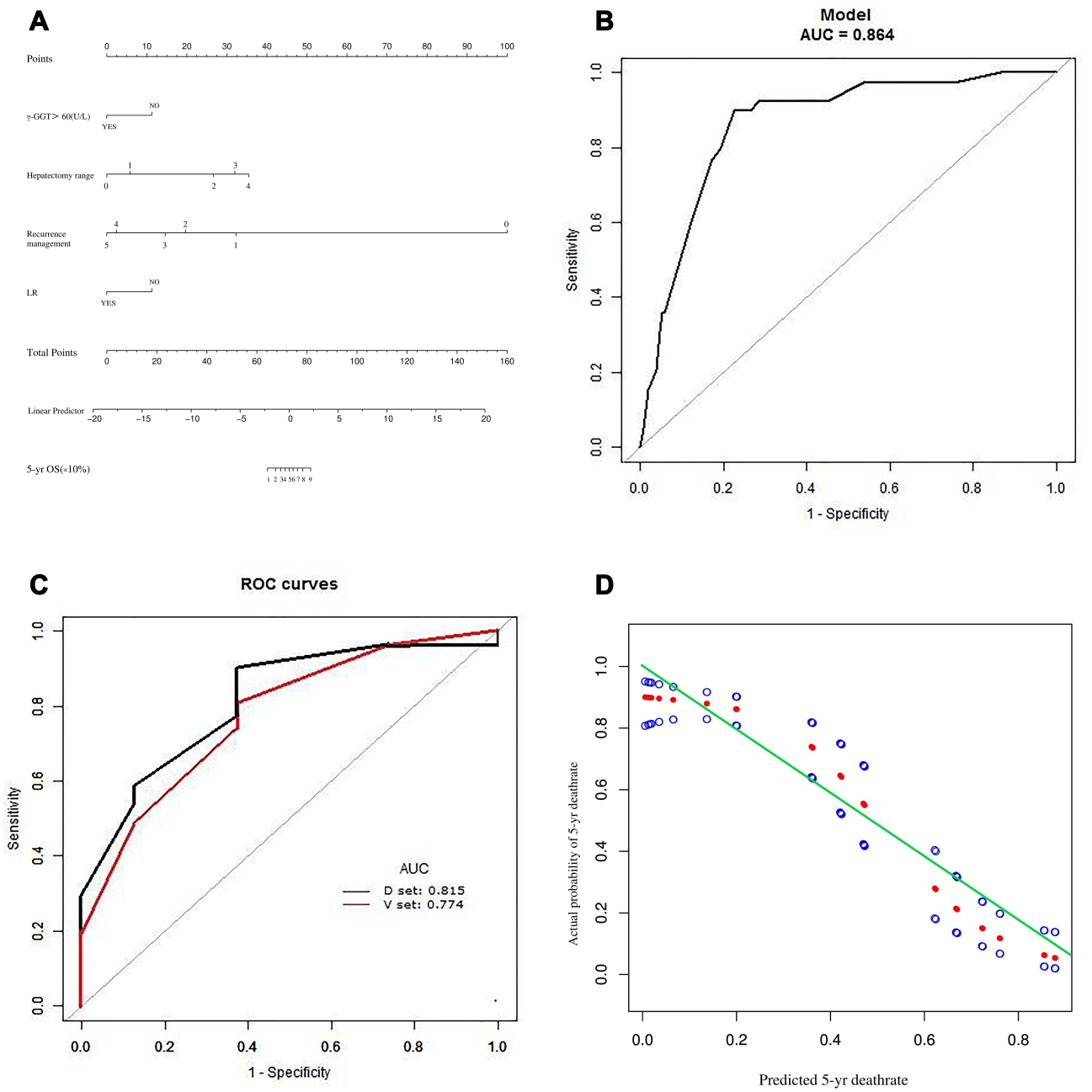

Figure 3 (**A**) Nomogram for the assessment of 5-year overall survival (OS) of patients with hepatocellular carcinoma who have undergone curative hepatectomy. The nomogram is used as described for Figure 2. (a). γ-GGT, γ-glutamyl transferase; LR, late recurrence. Extent of hepatectomy: 0 = wedge resection, 1 = one Couinaud segment, 2 = two Couinaud segments, 3 = 3 Couinaud segments, 4 = ≥4 Couinaud segments. Recurrence management: 0 = no recurrence, 1 = re-resection; 2 = microwave ablation, 3 = transarterial chemoembolization, 4 = supportive care. (**B**) The area under the time-dependent receiver operating characteristic curve (AUC) of the nomogram for 5-year OS. (**C**) Internal validation by bootstrap analysis. ROC, receiver operating characteristic; D, development; V, validation. (**D**) Calibration plot showing the relationships between predicted and actual probabilities based on the nomogram. The *x* and *y* axes represent the nomogram-predicted and actual probabilities, respectively, of 5-year death. Red solid circles represent the curve fitting line, and blue hollow circles represent nomogram-predicted probabilities with 95% confidence intervals. The green reference line indicates the ideal nomogram, in which actual and predicted probabilities are perfectly identical. The calibration curve shows good prognostic performance. The Hosmer-Lemeshow chi-squared value for calibration was 5.453 (P = 0.708).

obtained with the three staging systems [8th AJCC-TNM system, 0.5552 (95% CI, 0.4389–0.6255); BCLC system, 0.4961 (95% CI, 0.3969–0.5953); HKLC system, 0.5656 (95% CI, 0.4714–0.6199)].

Discussion

In this study, factors potentially influencing OS among Chinese patients with HCC undergoing curative hepatectomy were explored. Using accessible clinical parameters

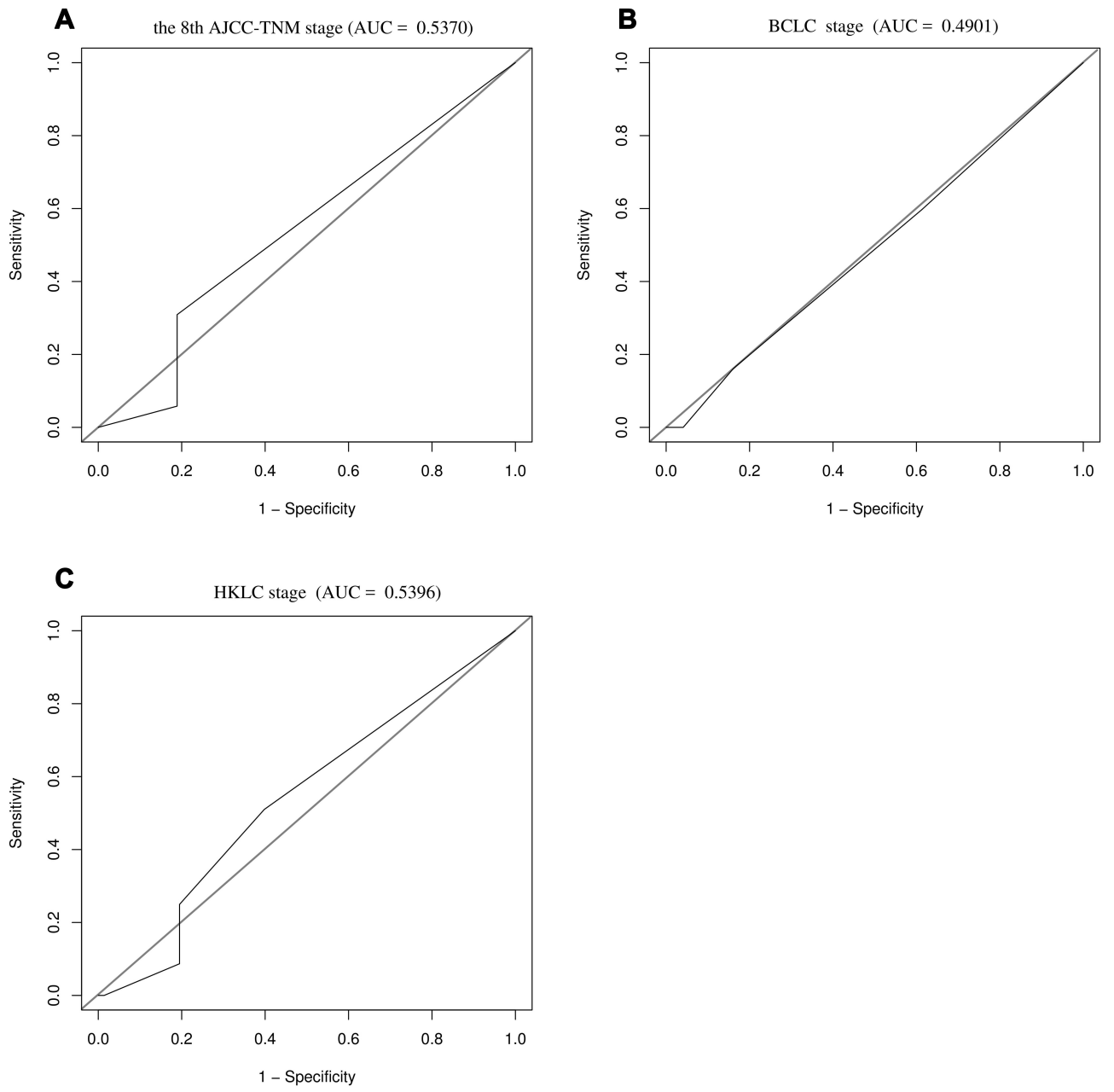

Figure 4 Areas under the time-dependent receiver operating characteristic curves (AUCs) for the three representative hepatocellular carcinoma staging systems for the prediction of 3-year overall survival. (**A**) 8th AJCC-TNM system, (**B**) BCLC system, and (**C**) HKLC system.
Abbreviations: AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; HKLC, Hong Kong Liver Cancer.

(preoperative and pathological characteristics), clear classifications of ER and LR, and consideration of post-recurrence treatment modality, novel prognostic nomograms for postoperative 3- and 5-year OS were proposed. These nomograms overcome the shortcomings of previous prediction systems and nomograms, which were constructed without consideration of the timing of postoperative recurrence or the post-recurrence treatment modality. The prognostic performance of the proposed nomograms was verified by internal validation, and C-index values were superior to those reported for other nomograms and scoring systems (Table 9).[4–30] The use of these nomograms is expected to improve the survival of patients with HCC who are eligible for curative therapy, allowing clinicians to make appropriate predictions and perform effective surveillance as early as possible. The inclusion of variables reflecting recurrence status and post-recurrence treatment effectiveness significantly improves predictive accuracy.

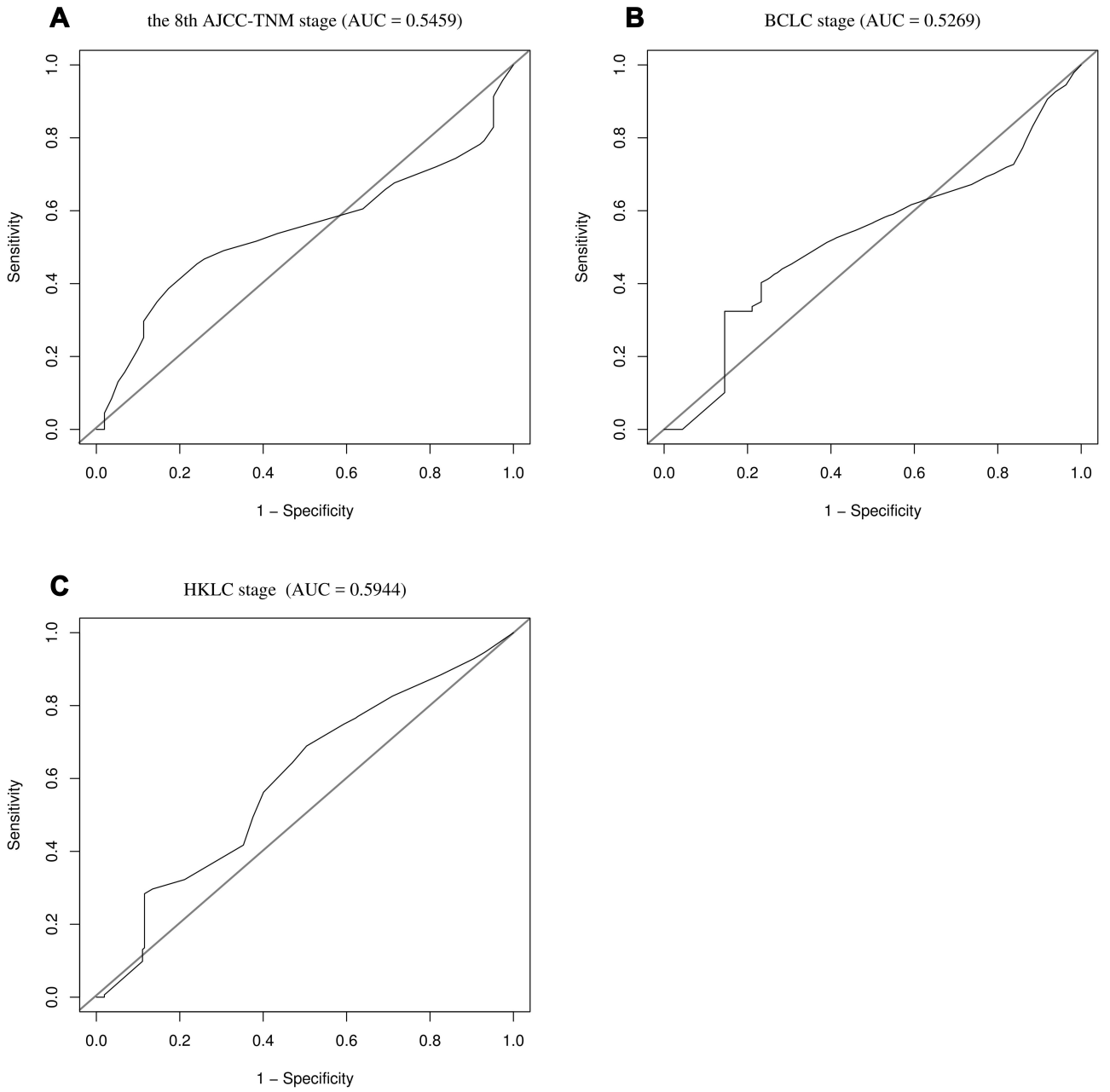

Figure 5 Areas under the time-dependent receiver operating characteristic curves (AUCs) for the three representative hepatocellular carcinoma staging systems for the prediction of 5-year overall survival. (**A**) 8th AJCC-TNM system, (**B**) BCLC system, and (**C**) HKLC system.
Abbreviations: AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; HKLC, Hong Kong Liver Cancer.

Recurrence after curative hepatectomy leads to the poor OS of patients with HCC. However, multivariate analyses performed with the simple dichotomization of recurrence as present or absent showed no effect on postoperative 3- or 5-year OS. We examined the effects of other variables (ie, TTR ≤ 1 year, ER, TTR ≤ 3 years, and LR) to clarify the effects of recurrence timing on postoperative OS. ER and LR have distinct underlying mechanisms[53] and seem to have different effects on patients' postoperative survival. ER may represent "true recurrence," reflecting the latent aggressive biological behavior of HCC at the time of initial surgical resection. LR is assumed to be caused by the multicentric metastasis of de-novo tumors in the background of liver fibrosis or cirrhosis.[53] In this study, the re-resection rate was significantly higher in the LR group, indicating that re-resection of recurrent HCC is suitable for and would prolong PRS in only a small proportion of patients with ER. Thus, the

Table 9 Published Nomograms for the Assessment of Overall Survival After Curative Hepatectomy

Author	Country	Year	Study				C-Index of Model	Recurrence Status		Post-Recurrence Management	
			Object	Endpoint (OS)	PVTT	BDTT		Classification	IF	Classification	IF
Cho[4]	USA	2008		3-,5yr	Yes	NA	0.74	NA	NA	NA	NA
Huang[5]	China	2015		1-,3yr	Yes	NA	NA	NA	NA	NA	NA
Shim[6]	Korea	2015		5yr	No	NA	0.66	NA	NA	NA	NA
Li[7]	China	2015	Huge HCC	4yr	Yes	NA	0.75;0.78	NA	NA	NA	NA
Shen[8]	China	2016		3-,5yr	NA	NA	0.767	Yes	NA	Yes	NA
Li[9]	China	2016	BCLC-0 HCC	3-,5yr	No	No	0.79	NA	NA	NA	NA
Yang[10]	China	2016	Multiple HCC	3-,5yr	NA	NA	0.75;0.80	NA	NA	NA	NA
Hu[11]	China	2016	+TACE	1-,3-,5yr	Yes	NA	0.75	NA	NA	NA	NA
Hsu[12]	Taiwan, China	2016	HCC beyond Milan criteria	1-,3-yr	Yes	NA	0.694	NA	NA	NA	NA
Torzilli[13]	Italy	2016		5yr	NA	NA	0.62	NA	NA	NA	NA
Fu[14]	China	2016		1-,3-,5yr	NA	NA	0.777	NA	NA	NA	NA
Feng[15]	China	2017		1-,3-,5yr	No	NA	0.78	NA	NA	NA	NA
Shen[16]	China	2017	Solitary HCC	3-,5yr	NA	NA	0.75	Yes	NA	NA	NA
Fu[17]	China	2017		2-,3yr	No	NA	0.755	NA	NA	NA	NA
Zhang[18]	China	2017	Adolescent and young adult HCC	1-,3-,5yr	NA	NA	0.75	NA	NA	NA	NA
Jing[19]	China	2017	+TACE	2-,3yr	NA	NA	0.787	NA	NA	NA	NA
Sun[20]	China	2017	+TACE\IFN	1,2,3,5,9yr	NA	NA	0.74	NA	NA	NA	NA
Zheng[21]	China	2018	Solitary HCC	3-,5yr	NA	NA	0.714	NA	NA	NA	NA
Huang[22]	China	2018		3-,5yr	NA	NA	0.779	NA	NA	NA	NA
Gan[23]	China	2018		1-,3-,5yr	Yes	NA	0.746	NA	NA	NA	NA
Cai[24]	China	2018		1-,3-,5yr	NA	NA	0.875, 0.829, 0.822,	NA	NA	NA	NA
Cao[25]	China	2018	Solitary HCC	3-,5yr	NA	NA	0.81	NA	NA	NA	NA
Hu[26]	China	2019	HCC with PVTT	1yr	Yes	NA	0.78	NA	NA	NA	NA
Wang[27]	China	2019		1-,2-,3yr	Yes	NA	0.761	NA	NA	NA	NA
Kim[28]	Korea	2019		1-,3-,5yr	Yes	Yes	0.810	NA	NA	NA	NA
Chen[29]	China	2019		1-,3-,5yr	Yes	NA	0.768;0.757; 0.737	NA	NA	NA	NA
Lin[30]	China	2020		2-,3-,5yr	No	NA	0.71	NA	NA	NA	NA

Abbreviations: OS, overall survival; PVTT, portal vein tumor thrombosis; BDTT, bile duct tumor thrombosis; IF, influencing factor; NA, not available; TACE, transcatheter arterial chemoembolization; IFN, interferon.

timepoint distinguishing ER and LR should be included in prognostic nomograms.

Chronic liver disease staging affected postoperative 3-year OS, with significant differences between grades A0–A2 and the indicator category of grade A3 ($P = 0.030$, 0.015, and 0.024, respectively). Viral replicative activity in the non-neoplastic liver has been reported to be associated with poor OS, independent of fibrosis stage. Moreover, viral infection and inflammatory response increase the potential for malignant transformation.[54] We found that neither initial tumor characteristics nor HCC staging influenced postoperative 5-year OS. Moreover, some indicators used in the evaluation of liver fibrosis and cirrhosis, such as the APRI, FIB-4, ALBI, CTP grade, GPR, and METAVIR score for the postoperative pathological evaluation of non-neoplastic liver tissue, did not affect 5-year OS. In view of these results, we speculate that a) obvious inflammation and/or fibrosis heterogeneities may exist among different regions of liver tissue, meaning that inflammation and fibrosis staging of non-tumor hepatic segments after curative hepatectomy would not represent the whole liver status; and b) the correlation between HCC development and chronic liver inflammation may be more complex than recognized, and monitoring systems/models and follow-up strategies based on the management of chronic liver disease may not be suitable for patients with HCC after curative hepatectomy.

The extent of hepatectomy was found to influence the 5-year OS of patients with HCC after curative hepatectomy. Although the extent of liver resection reflects the surgical technique used, it is likely also a surrogate indicator of tumor aggressiveness. Patients with HCC who have good liver function reserves can better tolerate extensive liver resection, which in turn reduces the impact of MVI on postoperative recurrence and survival. Moreover, good liver function reserve after recurrence permits reoperation, microwave ablation, or TACE. Thus, the effect of extensive hepatectomy on postoperative 5-year OS cannot be explained solely by the liver function reserve.

We found that postoperative PRS was influenced significantly by the post-recurrence treatment modality. The implementation of effective therapeutic strategies is important to prolong survival after curative hepatectomy. However, previous prognostic nomograms did not take these factors into consideration. In this study, PRS was predicted with differentiation of ER and LR at different sites after different post-recurrence treatments, rather than simple comparison of post-recurrence treatments. Re-resection and microwave ablation were found to be associated with improved 3 and 5-year PRS. The significant correlation between post-recurrence treatment and PRS indicates that patient survival can be improved by repeated treatment after recurrence. Curative treatments, such as re-resection and microwave ablation, lead to better survival outcomes, as confirmed in this study and a previous study.[55] However, clinical decisions about the post-recurrence treatment modality can be difficult to make due to the lack of universally recognized consensus.[56] The significant correlation between post-recurrence treatment and PRS indicates that patient survival can be improved by repeated treatment after recurrence.

This study revealed no significant difference in OS between curative resection and conservative treatment, although curative resection was superior to immunotargeted drug therapy for patients with extrahepatic ER. Moreover, no significant difference was found in the benefits provided by TACE, immunotargeted drug therapy, and conservative treatment in these patients. Thus, various therapeutic approaches for extrahepatic ER and LR after curative hepatectomy need to be evaluated in further large-sample multicenter studies. However, few studies have shown beneficial effects of isolated extrahepatic recurrence resection.[56] In our study, TACE was found to be an inferior post-recurrence modality for patients who could not tolerate secondary excision or microwave ablation. Radiotherapy is an effective and safe therapeutic approach for patients with HCC after recurrence, even for those with inferior vena cava/right atrium tumor thrombi.[57] Immunotargeted drug therapy has been applied in a small proportion of cases due to its limited cost effectiveness. Thus, further studies are needed to evaluate the efficacy of different and combined treatment modalities for patients with recurrence after curative hepatectomy.

The γ-GGT level was found to affect 3- and 5-year OS after recurrence in this study. It is a cell membrane-bound enzyme that plays crucial roles in glutathione metabolic processes. The pretreatment serum γ-GGT level reflects the chronic inflammatory status of HCC, especially that caused by HBV.[58] HBV infection is the main etiology of HCC in China.[2] In this study, 82.6% of patients were HBV infected and some patients showed HBsAg or hepatitis B antigen serological conversion. Further clinical studies are needed to verify the effects of γ-GGT, determine cut-off values for this indicator, and assess its prognostic performance for patients with HCC.

Study Limitations

This study has several limitations. a) The proposed nomograms were based on single-center retrospective and

prospective data. Given the low prevalence of 5-year OS, we could not create an external validation group; instead, we internally validated the nomogram. External validation in large-sample multicenter prospective studies is required. b) The proposed nomograms may be suitable primarily for patients with HBV-related HCC; such patients comprised the majority of our sample. Thus, the nomograms should be applied cautiously to HCC populations with HCV infection, non-alcoholic steatohepatitis, and other etiological backgrounds. c) In this study, decisions about the postoperative recurrence management strategies adopted were based primarily on existing guidelines, with consideration of patients' clinical status and recurrent tumor characteristics. However, management decisions may have been affected by patients' preference for less-invasive treatment and a lesser financial burden, which may have introduced bias. In addition, we considered only primary postoperative recurrence treatment modalities, although some patients received sequential treatments. The use of multiple and/or sequential treatment modalities may provide additional benefits that were not accounted for, which would reduce the quality of the evidence obtained in this study.

Conclusion

In this study, novel nomograms for the prediction of 3- and 5-year OS of patients with HCC after curative hepatectomy performed well in the context of real clinical practice in China. These nomograms were constructed with the distinction of postoperative ER and LR and the inclusion of post-recurrence treatment modality, which improves predictive efficacy for OS. The current study illustrates the importance not only of distinguishing ER and LR but also of comparing PRS according to recurrence site and treatment type. Our novel nomograms showed better calibration ability and prognostic performance than previously proposed systems and nomograms.

Data Sharing Statement

All data are available from the corresponding author, Wei XU, upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Institutional Review Board of Hunan Provincial People's Hospital (The First Hospital Affiliated with Hunan Normal University; no. 2015-01). For patients recruited retrospectively between January 2012 and December 2014, ethical approval was waived in view of the retrospective nature of the study; the patients' privacy was ensured and the data were anonymized or maintained with confidentiality. Patients recruited prospectively between January 2015 and June 2019 provided written informed consent prior to study inclusion.

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Disclosure

The authors declare that they have no competing interest.

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