Original Article

Development of a novel prognostic nomogram for the early recurrence of liver cancer after curative hepatectomy

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Background: Hepatocellular carcinoma (HCC) is one of the most common malignant cancers worldwide. Curative resection is an effective treatment but HCC recurrence rates remain high. This study aimed to establish a novel prognostic nomogram to assess the risk of recurrence in patients following curative resection.

Methods: A total of 410 patients undergoing HCC curative resection were recruited from the Guangdong Provincial People's Hospital (GDPH). The cohort was divided into a training group (n=291) and a validation group (n=97). The risk factors for HCC early recurrence within 1 year of curative hepatectomy were identified. Finally, a multivariate prognostic nomogram was developed and validated.

Results: Age, tumor number, tumor capsule, portal vein tumor thrombi, pathological grade, vascular tumor emboli, activated partial thromboplastin time (APTT), and tumor size were identified as independent prognostic risk factors for HCC early recurrence within 1 year of curative hepatectomy. The area under the receiver operating characteristic (ROC) curve (AUC) was 0.806 [95% confidence interval (CI): 0.755 to 0.857; P<0.001], and no AUC/ROC statistical difference was detected between the training and validation sets.

Conclusions: The nomogram effectively predicted postoperative HCC recurrence within 1 year after curative hepatectomy, which may be a useful tool for the postoperative treatment or follow up for HCC patients.

Keywords: Hepatocellular carcinoma (HCC); resection; recurrence; nomogram

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Introduction

Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancers and is known as one of the most common malignant cancers worldwide, being the fourth leading cause of cancer-related mortality in 2018 (1). Additionally, there is a high incidence of hepatitis B virus (HBV) in China, which is an independent risk factor for HCC (2). While surgery is the most efficient treatment

for early-stage HCC patients, most patients present with progressive disease at the time of diagnosis. Although advances in surgical resection have resulted in a 5-year survival rate of 11–30% (3), prognosis and survival remain unsatisfactory due to intrahepatic metastasis and early tumor recurrence (4). Thus, in clinical practice, it is important to identify patients with a high risk of recurrence after curative resection. Previous studies have demonstrated that tumor multifocality, tumor size, and portal vein tumor thrombus occurrence are independent risk factors for HCC recurrence (5-8). There are several internationally accepted recurrence evaluation systems, including the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual [2017], the Barcelona Clinic Liver Cancer (BCLC) system (9), and the American Association for the Study of Liver Diseases (AASLD) guideline (10). However, these systems are used only for the evaluation of recurrence and not for evaluating patient prognosis. There were also different explanations of early HCC recurrence after hepatectomy, which ranges from 0.5 years to 5 years after surgery (11). Early recurrence is more likely associated with micrometastasis from the initial tumor, whereas late recurrence is more likely to cirrhosis, multi-nodularity and hepatitis activity (12,13). It is recommended that patients with invasive tumors or previous tumor rupture should be closely monitored in the first year due to risk of early recurrence (14).

To date, there have been few studies examining the prognostic predictors for HCC early recurrence with a 1-year cut-off. Clinical and pathological parameters were used to develop a novel prognostic model to assess the risk of early HCC recurrence within 1 year in patients who have undergone curative hepatectomy. Although the importance of timely therapeutic strategies of HCC patients postoperatively have been revealed. Few studies took both preoperative neo-adjuvant chemotherapy and postoperative adjuvant therapy into consideration as we did in this study. This novel evaluation system may assist in the implementation of early therapeutic strategies for the management of patients with HCC. We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4837).

Methods

This retrospective study was based on the guidelines listed in the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) (15). Ethical approval was obtained from the Ethics Committee of Guangdong Provincial People's Hospital (GDPH). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019191H). Individual consent for this retrospective analysis was waived.

Patients and data

A total of 573 patients with HCC who underwent curative hepatectomy at GDPH between 2014 and 2018 were retrospectively included in this study. The diagnosis of HCC was confirmed by postoperative routine paraffin pathology. Curative hepatectomy was defined as the complete resection of all tumors, with a resection margin over 1 cm from the tumor boundaries. The following exclusion criteria were applied: (I) patients who underwent preoperative adjuvant therapy, radiofrequency ablation during the operation, or palliative hepatectomy; (II) patients in whom postoperative mortality occurred within 30 days or death was caused by other diseases; (III) patients with incomplete clinical and pathological data; and (IV) patients who did not provide signed informed consent. A total of 149 patients were excluded due to incomplete data and 36 were excluded due to incomplete follow-up information. Consequently, 388 HCC patients were enrolled in this analysis. All patients were followed up for at least 1 year. A total of 291 consecutive patients who underwent early curative hepatectomy were assigned to the study group and the other 97 patients who underwent late curative hepatectomy were assigned to the validation group.

Data collection

All clinical and pathological parameters which may be associated with early recurrence were reviewed from the medical records. Basic characteristics including gender, age, ascites, and preoperative laboratory values of alanine transaminase (ALT), aspartate transaminase (AST), r gamma-glutamyl transpeptidase (rGGT), alkaline phosphatase (ALP), albumin (ALB), total bilirubin (Tbil), direct bilirubin (Dbil), prothrombin Time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), white blood cell count (WBC), hemoglobin (HGB), blood platelet count (PLT), alpha-

fetoprotein (AFP), hepatitis B virus (HBV), hepatitis C virus (HCV), and HBV copy number were collated. The normal value range of laboratory parameters in our hospital was regarded as the cut-off. Ascites condition was based on imageological examinations, such as B-mode ultrasound, contrast-enhanced computed tomography (CT) scan, and magnetic resonance imaging (MRI).

Tumor characteristics including the maximum tumor size; nodule number; tumor location; tumor encapsulation; cancer embolus in hepatic vein, portal vein, bile duct or inferior vena cava; peripheral organ invasion; and histologic grade were documented. The Edmondson grading system was used to assess the histologic grade of tumor differentiation (16).

For the operation, the modus operandi, method of resection, intraoperative blood loss, intraoperative blood transfusion, postoperative complications, and postoperative adjuvant therapy were noted. Modus operandi included laparoscopic surgery, conversion to open operations, and laparotomy. Based on previous studies, the method of resection consisted of anatomical hepatectomy and non-anatomical hepatectomy (17).

Follow-up

Post-surgery, all patients were followed up monthly for the first six months. Serum AFP levels, liver function tests, HBV-DNA levels, and radiology examinations including ultrasound, CT, MRI, and positron emission tomography (PET), were assessed. During the next half-year, patients were followed up every 3 months, and half-yearly thereafter. If a recurrence or distant metastasis was suspected, radiology examinations such as ultrasound, CT, MRI, or PET were performed to verify the suspicion. Tumor recurrence was defined as a new intrahepatic or extrahepatic mass confirmed by at least two imageological examinations. Recurrence time was defined as the interval from the operation to the recurrence of the new intrahepatic or extrahepatic tumor. The final follow-up timepoint was December 2019. For patients who died or were lost to follow up prior to December 2019, the endpoint was defined as the time of death or the last follow-up visit.

Statistical analysis

All patients were divided into two groups, namely, an early recurrence group and a non-recurrence group. In the early recurrence group, the tumor recurred within 1 year after liver cancer resection. In the non-recurrence group, the tumor did not recur within 1 year after resection. All continuous data are presented as mean ± standard error of the mean, or as the median value. Data were evaluated using the Student's *t*-test. Nominal data were analyzed using the Pearson χ^2 test or Fisher exact probability test. The Kaplan-Meier method was used to assess recurrence-free survival (RFS), and the difference was compared using the log-rank test. RFS was calculated between the date of radical operation and the date when the tumor recurred or the date of the final follow-up examination. A multivariate logistics proportional regression model was used to analyze the independent risk factors for early postoperative recurrence. Independent prognostic factors were identified using the backward step-down process based on the Akaike Information Criterion (AIC). The significant prognostic factors identified in the logistic regression model were used to establish a nomogram. The predictive ability of the nomogram was assessed via the area under the curve (AUC) of the receiver operator characteristic (ROC) curve. Data analysis was performed with SPSS (version 23.0) and R software (version 3.5.1, https://www. r-project.org/). A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 summarizes the clinicopathologic characteristics of patients in the training set and the validation set. Of the 291 patients in the training set, 194 experienced early recurrence within 1 year of curative hepatectomy. Of the 97 patients in the validation cohort, 67 patients experienced early recurrence within 1 year of curative hepatectomy.

Univariate analysis of the training cohort

Table 2 lists the relationship between the clinicopathologic variables and early recurrence status of HCC after curative hepatectomy in the training data set. In the univariate analysis, age (P<0.01), TMN stage (P<0.01), AFP (P<0.01), tumor size (P<0.001), tumor number (P<0.01), tumor capsular (P=0.01), portal vein tumor thrombi (P<0.01), vascular tumor emboli (p<0.01), pathological grade (P<0.01), postoperative complication (P<0.01), preoperative neo-adjuvant chemotherapy (P<0.05), postoperative adjuvant therapy (P<0.05), modus operandi (P=0.01), AST (P=0.03),

Table 1 Patient profiles and tumor characteristics

Variables	Number of patients		P value
	Training set (n=291)	Validation set (n=97)	
Age (years): <40/40–59/≥60	37/159/95	10/56/31	0.785
Gender: male/female	256/35	90/7	0.187
TMN stage: T1A/T1B/T2/T3A/T3B	32/116/85/21/37	12/41/26/9/9	0.827
AFP (ng/mL): <100/100–400/>400	165/40/86	62/10/25	0.432
HbsAg: negative/positive	59/232	21/76	0.772
HbeAg: negative/positive	245/46	83/14	0.746
HbcAb: negative/positive	93/198	35/62	0.454
HBVDNA: negative (<500)/positive (≥500)	189/102	62/35	0.854
HCV: negative/positive	260/31	88/9	0.700
Tumor number: ½/3/≥4	1.4±0.9	1.3±0.8	
Tumor location (lobe): right/left/middle/others/multiple	163/67/42/10/9	54/25/15/2/1	0.749
Tumor capsular: complete/incomplete	254/37	83/14	0.664
Hepatic venous cancer plug: present/absent	16/275	4/93	0.596
Portal vein tumor thrombi: present/absent	22/269	4/93	0.241
Cholangiocarcinoma bolt: present/absent	7/284	3/94	0.711
Peripheral organs invaded: present/absent	16/275	7/90	0.535
Pathological grade: I/II/III/IV	6/108/171/6	0/38/59/0	0.247
Cut edge: negative/positive	275/16	93/4	0.596
Vascular tumor emboli: present/absent	93/198	27/70	0.447
Preoperative neo-adjuvant chemotherapy: no/TACE/others	277/13/1	91/6/0	0.675
Modus operandi: open/laparoscopic	184/107	63/34	0.761
Anatomical resection: yes/no	76/215	21/76	0.379
Intraoperative blood loss (mL): ≤400/>400	186/105	68/29	0.267
Intraoperative blood transfusion: No/yes	239/52	82/15	0.587
Postoperative complication: none/post-operation hemorrhage/bile leakage/liver failure/others	268/10/2/2/9	87/2/1/1/6	0.642
Postoperative adjuvant therapy: hyperthermic intraperitoneal perfusion/TACE/Sorafenib/none	26/96/4/165	8/27/1/61	0.755
Recurrent status: yes/no	194/97	67/30	0.662
ALT (U/L), mean ± standard error	47.2±54.0	52.4±60.0	
AST (U/L), mean ± standard error	52.9±52.0	56.0±58.8	
GGT (U/L), mean ± standard error	85.7±85.4	82.4±95.2	
ALP (U/L), mean ± standard error	97.8±47.1	95.4±50.6	
Dbil (μmol/L), mean ± standard error	4.8±5.6	4.5±3.0	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Number of patients		P value
	Training set (n=291)	Validation set (n=97)	
APTT (seconds), mean ± standard error	38.6±5.6	4.5±3.0	
INR, mean ± standard error	1.1±0.2	1.1±0.3	
WBC (10^9/L), mean ± standard error	6.6±2.4	6.4±2.6	
Hemoglobin (g/L), mean ± standard error	135.0±19.3	136.6±18.8	
Platelet (10^9/L), mean ± standard error	194.4±76.5	189.5±79.0	
Tumor size (cm), mean ± standard error	5.7±3.6	5.4±3.4	

ALT, alanine transaminase; AST, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALB, albumin; Tbil, total bilirubin; Dbil, direct bilirubin; PT, prothrombin pime; APTT, activated partial thromboplastin time; INR, international normalized ratio; APF, alpha-fetoprotein; HbsAg, hepatitis B surface antigen; HbeAg, hepatitis B e-antigen; HbcAb, hepatitis B core antibody; HBV-DNA, hepatitis B DNA; HCV; hepatitis C virus; WBC, white blood cell.

Table 2 Univariate analyses of factors associated with hepatocellular carcinoma early recurrence after curative hepatectomy in the training set

Variables	Number of patients		P value
	Patients with early recurrence (n=194)	Patients without early recurrence (n=97)	
Age (years): <40/40–59/≥60	17/106/71	20/53/24	<0.01
Gender: male/female	169/25	87/10	0.52
TMN stage: T1A/T1B/T2/T3A/T3B	30/91/47/8/18	2/25/38/13/19	<0.01
AFP (ng/mL): <100/100–400/>400	120/28/46	45/12/40	<0.01
HbsAg: negative/positive	43/151	16/81	0.26
HbeAg: negative/positive	163/31	82/15	0.91
HbcAb: negative/positive	67/127	26/71	0.18
HBVDNA: negative (<500)/positive (≥500)	130/64	59/38	0.30
HCV: negative/positive	172/22	88/9	0.59
Tumor number: 1/2/3/≥ 4	167/18/1/8	69/12/1/15	<0.01
Tumor location (lobe): right/left/middle/others/multiple	108/44/31/6/5	55/23/11/4/4	0.79
Tumor capsular: complete/incomplete	176/18	78/19	0.01
Hepatic venous cancer plug: present/absent	9/185	7/90	0.36
Portal vein tumor thrombi: present/absent	7/187	15/82	<0.01
Cholangiocarcinoma bolt: present/absent	3/191	4/93	0.34
Peripheral organs invaded: present/absent	12/182	4/93	0.65
Pathological grade: I/II/III/IV	6801044	028672	0.04
Cut edge: negative/positive	186/8	89/8	0.15
Vascular tumor emboli: present/absent	46/148	47/50	<0.01
Preoperative neo-adjuvant chemotherapy: none/TACE/others	188/6/0	89/7/1	0.047

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Number of patients		P value
	Patients with early recurrence (n=194)	Patients without early recurrence (n=97)	
Modus operandi: open/laparoscopic	113/81	71/26	0.01
Anatomical resection: yes/no	46/148	30/67	0.19
Intraoperative blood loss (mL): ≤400/>400	130/64	56/41	0.12
Intraoperative blood transfusion: no/yes	164/30	75/22	0.13
Postoperative complication: none/post-operation hemorrhage/bile leakage/liver failure/others	178/8/0/1/7	90/2/2/1/2	<0.01
Postoperative adjuvant therapy: hyperthermic intraperitoneal perfusion/TACE/Sorafenib/none	18/63/0/113	8/33/4/52/97	0.04
ALT (U/L), mean ± standard error	48.0±55.0	45.6±52.4	0.54
AST (U/L), mean ± standard error	50.1±48.0	58.6±59.0	0.03
GGT (U/L), mean ± standard error	80.4±86.4	96.4±82.7	<0.01
ALP (U/L), mean ± standard error	91.5±41.0	110.4±55.5	<0.01
Dbil (μmol/L), mean ± standard error	4.4±4.6	5.6±7.2	0.08
APTT (seconds), mean ± standard error	38.0±4.6	39.7±7.0	0.03
INR, mean ± standard error	1.1±0.2	1.1±0.1	0.04
WBC (10^9/L), mean ± standard error	6.4±2.4	7.0±2.4	0.03
Hemoglobin (g/L), mean ± standard error	135.6±18.0	133.8±21.9	0.63
Platelet (10^9/L), mean ± standard error	188.3±70.8	206.8±85.8	0.04
Tumor size (cm), mean ± standard error	4.9±3.26	7.15±3.78	<0.01

ALT, alanine transaminase; AST, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALB, albumin; Tbil, total bilirubin; Dbil, direct bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; APF, alpha-fetoprotein; HbsAg, hepatitis B surface antigen; HbeAg, hepatitis B e-antigen; HbcAb, hepatitis B core antibody; HBV-DNA, hepatitis B DNA; HCV; hepatitis C virus; WBC, white blood cell.

rGGT (P<0.01), ALP (P<0.01), APTT (P=0.03), INR (P=0.04), WBC (P=0.03), and PLT (P=0.04) were all associated with early HCC recurrence status after curative hepatectomy within 1 year.

Construction of the logistic regression model using the training data set

Not all the independent variables identified in the univariate analyses were significant risk factors (*Table 3*). Based on the AIC of 310.87, the independent prognostic factors were determined to be age, tumor number, tumor capsular, portal vein tumor thrombi, pathological grade, vascular tumor emboli, APTT, and tumor size. These independent prognostic factors comprised the final regression model, and the related parameters are listed in *Table 4*. The results of the regression model likelihood-ratio test and analysis of variance (ANOVA) showed a P value <0.05. The ROC curve of the prognostic model showed an AUC value of 0.806 [95% confidence interval (CI): 0.755 to 0.857; P<0.001; *Figure 1*]. The nomogram was constructed using the above-mentioned eight significant prognostic factors to predict the risk of HCC early recurrence after curative hepatectomy (*Figure 2*).

Prognostic model validation

The prognostic model ROC curve for the validation set,

Table 3 Related risk factor-related parameters (P<0.05) associated with hepatocellular carcinoma early recurrence after curative hepatectomy in the training set

Factors	Beta	SE	Z value	Probability (>|Z|)
Age	–0.42	0.24	–1.75	0.08
TMN stage	0.03	0.20	0.15	0.88
AFP	0.14	0.17	0.84	0.40
Tumor number	0.55	0.19	2.88	<0.01
Tumor capsule	0.94	0.43	2.20	0.03
Tumor size	0.16	0.06	2.93	<0.01
Portal vein tumor thrombi	–1.44	0.73	–1.97	0.05
Pathological grade	0.47	0.29	1.64	0.10
Vascular tumor emboli	–0.86	0.35	–2.58	0.01
Preoperative neo-adjuvant chemotherapy	0.73	0.67	1.08	0.28
Modus operandi	0.19	0.35	0.56	0.58
Postoperative complication	–0.28	0.21	–1.34	0.18
Postoperative adjuvant therapy	–0.01	0.14	–0.10	0.92
AST	>–0.01	<0.01	–1.05	0.29
rGGT	>–0.01	<0.01	–0.33	0.74
ALP	<0.01	<0.01	1.49	0.14
APTT	0.08	0.03	2.30	0.02
INR	–0.34	1.16	–0.29	0.77
WBC	0.04	0.07	0.59	0.56
PLT	>–0.01	<0.01	–0.85	<0.01

Beta represents the standardized coefficient. SE, standard error; AFP, alpha-fetoprotein; AST, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; INR, international normalized ratio; WBC, white blood cell; PLT, platelet.

Table 4 Independent prognostic factor-related parameters associated with hepatocellular carcinoma early recurrence after curative hepatectomy in the training set

Factors	Beta	SE	Z value	Probability (>|Z|)
Age	–0.36	0.23	–1.48	0.14
Tumor number	0.57	0.16	3.50	<0.01
Tumor capsule	0.87	0.41	2.14	<0.01
Tumor size	0.16	0.04	3.85	<0.01
Portal vein tumor thrombi	–1.54	0.54	–2.89	<0.01
Pathological grade	0.45	0.27	1.67	0.09
Vascular tumor emboli	–0.82	0.31	–2.67	<0.01
APTT	0.08	0.04	2.85	<0.01

Beta represents the standardized coefficient. SE, standard error; APTT, activated partial thromboplastin time.

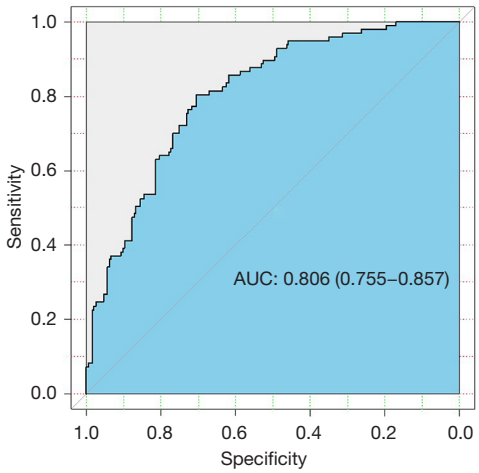

Figure 1 Prognostic model receiver operating characteristic curve for the training set.

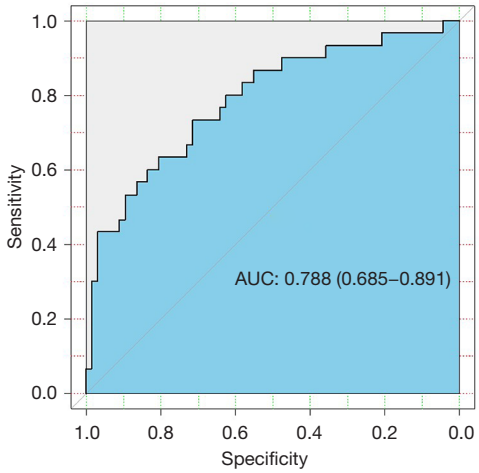

Figure 3 Prognostic model receiver operating characteristic curve for the validation set.

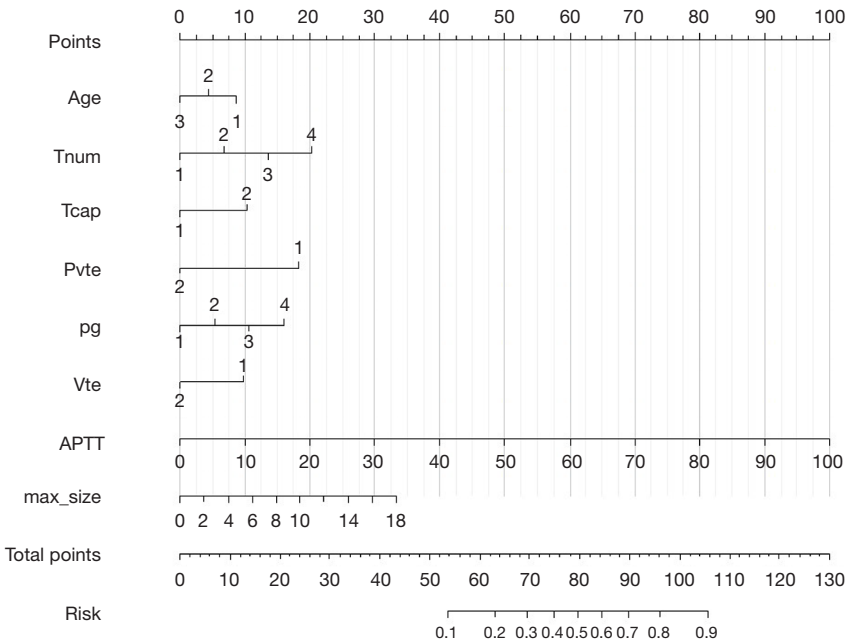

Figure 2 Nomogram for predicting the risk of hepatocellular carcinoma early recurrence after curative hepatectomy. Tnum, tumor number; Tcap, tumor capsule; Pvte, portal vein tumor thrombi; pg, pathological grade; Vte, vascular tumor emboli; APTT, activated partial thromboplastin time; max_size, tumor maximum size.

based on the prognostic index, is shown in *Figure 3*. The AUC was 0.788 (95% CI: 0.685 to 0.891; P<0.001). The DeLong's test for the two ROC curves showed a P value >0.05, indicating that the AUC/ROC of the training set and the validation set were not statistically different.

Discussion

Early HCC recurrence is a serious and common complication affecting patient survival after curative hepatectomy. Thus, identifying the risk factors and

developing a novel prognostic model for HCC early recurrence after hepatectomy would be beneficial for the timely implementation of therapeutic strategies and clinical management such as increased follow-up frequency. Previous studies reported that early recurrence is mainly associated with the aggressive characteristics of the resected tumor, such as tumor size, tumor number, and vascular invasion (18). In contrast, late recurrence is primarily related to background liver disease conditions, such as hepatic inflammation and cirrhosis (18,19). In agreement with previous reports (5-8), this current study demonstrated that tumor multifocality, tumor size, and portal vein tumor thrombus are independent risk factors for HCC recurrence within 1 year after curative hepatectomy. This study further identified age, tumor number, tumor capsular, portal vein tumor thrombi, pathological grade, vascular tumor emboli, APTT, and tumor size as independent risk factors for early HCC recurrence.

Aggressive pathological tumor factors such as tumor size, tumor number, tumor capsule, and vascular infiltration are mainly associated with intrahepatic recurrence (20-24). Jung *et al.* (19) reported that tumor size (>3 cm) was associated with early recurrence after hepatectomy for solitary HCC. Cheng *et al.* (13) considered that tumor diameter (>5 cm) was an independent potential risk factor for early recurrence after hepatectomy. However, other studies have shown that tumor size is a risk for vascular invasion and dissemination which increases with diameter, instead of a definite limiting factor (25,26). In an analysis of 224 patients with HCC, multiple tumors were indicated as a risk factor of early HCC recurrence (<1 year) (27). Du and colleagues (23) also reported that multiplicity of tumors and venous infiltration were independent risk factors for early recurrence of HCC (<2 years). Tumor number may indicate the number of intrahepatic metastases or multicentric HCC. Moreover, the presence of an intact tumor capsule provides a protective effect, especially for large tumors (24), and may prevent local and vascular invasion (28,29). In order to ensure an intact tumor capsule, R0 resection (with no cancer cells found in the surgical margin) is a relatively ideal surgical resection margin status, which may improve the prognosis of patients with HCC (30,31).

Vascular invasion of HCC mainly involves microvascular and portal vein invasion (32). The incidence of tumor thrombus in patients with HCC is approximately 14–65% (20,33). Portal vein invasion may result in intrahepatic tumor metastasis, tumor recurrence, and postoperatively tumor-related death (34,35). It was also suggested that hepatic vein tumor thrombus is a highly independent risk factor for increased extrahepatic recurrence (36,37). Many studies have reported that microvascular invasion, identified above as vascular tumor emboli, is related to early recurrence after hepatectomy (14,27,35,38,39), and this is consistent with our findings. Lim *et al.* (40) demonstrated that patients with microvascular invasion have an increased risk of early recurrence within the first 30 months after hepatectomy compared to patients without microvascular invasion. Although microvascular invasion can only be determined postoperatively based on histological specimens (40), it may be a good predictor of early HCC recurrence.

Pathological grade, determined after resection, has be shown to be associated with the recurrence rate and disease-free survival after liver resection, as well as poor tumor differentiation (41,42). Even so, few studies have demonstrated a numerical correlation between pathological grade and early HCC recurrence. In our study, pathological grade [odds ratio (OR) 1.48; 95% CI: 1.02 to 2.14; P=0.038] was identified as an independent risk factor for early HCC recurrence status after curative hepatectomy within 1 year. Indeed, it may represent an effective predictive risk factor of postoperative HCC recurrence.

Effective therapeutic approaches for patients with HCC recurrence are available in clinical application, such as radiofrequency ablation, transarterial chemoembolization (TACE), surgical resection and transplantation, while the immunotherapy for HCC is considered effective as well recently (43). As a dynamic system, the HCC tumor immune microenvironment comprises cancer cells, the intricate cytokine environment, extracellular matrix, immune cell subsets and other components (44). HCC is an inflammation-related tumor with tumor immune microenvironment promoting immune tolerance through diverse pathways (45). There have been a series of approaches in immunotherapy that activates the tumors pecific immune response brings new opportunities for the HCC therapeutics (46-48). Although lack of sufficient evidence to confirm that immunotherapy could reduce the probability of recurrence after curative hepatectomy, immunotherapy applied to the prevention and treatment of early HCC recurrence postoperatively has the foreseeable future to look forward to.

In conclusion, age, tumor number, tumor capsular, portal vein tumor thrombi, pathological grade, vascular tumor emboli, APTT, and tumor size were identified as independent risk factors for early HCC recurrence status after curative hepatectomy within 1 year. A predictive

nomogram was developed and validated to allow individualized assessment of recurrence risk after curative hepatectomy within 1 year in HCC patients. Although, this study has limitations since it is a retrospective study from a single medical center and further multi-center clinical trials may be needed. The predictive ability of this nomogram may be beneficial for the timely management of HCC patients postoperatively.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019191H). Individual consent for this retrospective analysis was waived.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010;28:2437-44.
3. Singh AK, Kumar R, Pandey AK. Hepatocellular Carcinoma: Causes, Mechanism of Progression and Biomarkers. Curr Chem Genom Transl Med 2018;12:9-26.
4. Sun W, Cabrera R. Systemic Treatment of Patients with Advanced, Unresectable Hepatocellular Carcinoma: Emergence of Therapies. J Gastrointest Cancer 2018;49:107-15.
5. Kow AW, Kwon CH, Song S, et al. Risk factors of peritoneal recurrence and outcome of resected peritoneal recurrence after liver resection in hepatocellular carcinoma: review of 1222 cases of hepatectomy in a tertiary institution. Ann Surg Oncol 2012;19:2246-55.
6. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000;32:1224-9.
7. Roayaie S, Jibara G, Taouli B, et al. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol 2013;20:3754-60.
8. Toyoda H, Kumada T, Kiriyama S, et al. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC, and JIS) in Japan. Am J Gastroenterol 2005;100:1764-71.
9. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
10. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
11. Xu W, Li R, Liu F. Novel Prognostic Nomograms for Predicting Early and Late Recurrence of Hepatocellular Carcinoma After Curative Hepatectomy. Cancer Manag Res 2020;12:1693-712.
12. Poon RT. Differentiating early and late recurrences after

resection of HCC in cirrhotic patients: implications on surveillance, prevention, and treatment strategies. Ann Surg Oncol 2009;16:792-4.
13. Cheng Z, Yang P, Qu S, et al. Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection. HPB (Oxford) 2015;17:422-7.
14. Poon RT, Fan ST, Ng IO, et al. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-7.
15. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.
16. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462-503.
17. Xing H, Zhang WG, Cescon M, et al. Defining and predicting early recurrence after liver resection of hepatocellular carcinoma: a multi-institutional study. HPB (Oxford) 2020;22:677-89.
18. Chan AWH, Zhong J, Berhane S, et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018;69:1284-93.
19. Jung SM, Kim JM, Choi GS, et al. Characteristics of Early Recurrence After Curative Liver Resection for Solitary Hepatocellular Carcinoma. J Gastrointest Surg 2019;23:304-11.
20. Tsai TJ, Chau GY, Lui WY, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery 2000;127:603-8.
21. Cha C, Fong Y, Jarnagin WR, et al. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197:753-8.
22. Nagano Y, Shimada H, Takeda K, et al. Predictive factors of microvascular invasion in patients with hepatocellular carcinoma larger than 5 cm. World J Surg 2008;32:2218-22.
23. Du ZG, Wei YG, Chen KF, et al. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients. Hepatobiliary Pancreat Dis Int 2014;13:153-61.
24. Arnaoutakis DJ, Mavros MN, Shen F, et al. Recurrence patterns and prognostic factors in patients with hepatocellular carcinoma in noncirrhotic liver: a multi-institutional analysis. Ann Surg Oncol 2014;21:147-54.
25. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
26. Fuks D, Dokmak S, Paradis V, et al. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology 2012;55:132-40.
27. Zhu WJ, Huang CY, Li C, et al. Risk factors for early recurrence of HBV-related hepatocellular carcinoma meeting milan criteria after curative resection. Asian Pac J Cancer Prev 2013;14:7101-6.
28. Lee JI, Lee JW, Kim YS, et al. Analysis of survival in very early hepatocellular carcinoma after resection. J Clin Gastroenterol 2011;45:366-71.
29. Ng IO, Lai EC, Ng MM, et al. Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases. Cancer 1992;70:45-9.
30. Lee SG, Hwang S, Jung JP, et al. Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. Br J Surg 2007;94:320-6.
31. Dong S, Wang Z, Wu L, et al. Effect of surgical margin in R0 hepatectomy on recurrence-free survival of patients with solitary hepatocellular carcinomas without macroscopic vascular invasion. Medicine (Baltimore) 2016;95:e5251.
32. Zhang TT, Zhao XQ, Liu Z, et al. Factors affecting the recurrence and survival of hepatocellular carcinoma after hepatectomy: a retrospective study of 601 Chinese patients. Clin Transl Oncol 2016;18:831-40.
33. Nakashima T, Okuda K, Kojiro M, et al. Pathology of hepatocellular carcinoma in Japan. 232 Consecutive cases autopsied in ten years. Cancer 1983;51:863-77.
34. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int 2009;29:502-10.
35. Sumie S, Kuromatsu R, Okuda K, et al. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. Ann Surg Oncol 2008;15:1375-82.
36. Tanaka K, Shimada H, Matsuo K, et al. Clinical features of hepatocellular carcinoma developing extrahepatic recurrences after curative resection. World J Surg 2008;32:1738-47.
37. Zhang T, Huang JW, Bai YN, et al. Recurrence and survivals following hepatic resection for hepatocellular carcinoma with major portal/hepatic vein tumor thrombus. Hepatol Res 2014;44:761-8.

38. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-82.
39. Kim H, Park MS, Park YN, et al. Preoperative radiologic and postoperative pathologic risk factors for early intra-hepatic recurrence in hepatocellular carcinoma patients who underwent curative resection. Yonsei Med J 2009;50:789-95.
40. Lim KC, Chow PK, Allen JC, et al. Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg 2011;254:108-13.
41. Wang GZ, Guo LF, Gao GH, et al. Magnetic Resonance Diffusion Kurtosis Imaging versus Diffusion-Weighted Imaging in Evaluating the Pathological Grade of Hepatocellular Carcinoma. Cancer Manag Res 2020;12:5147-58.
42. Court CM, Harlander-Locke MP, Markovic D, et al. Determination of hepatocellular carcinoma grade by needle biopsy is unreliable for liver transplant candidate selection. Liver Transpl 2017;23:1123-32.
43. Rimassa L, Danesi R, Pressiani T, et al. Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma. Cancer Treat Rev 2019;77:20-8.
44. Chew V, Lai L, Pan L, et al. Delineation of an immunosuppressive gradient in hepatocellular carcinoma using high-dimensional proteomic and transcriptomic analyses. Proc Natl Acad Sci U S A 2017;114:E5900-9.
45. Chen Y, Wang X, Deng X, et al. DNA Damage Repair Status Predicts Opposite Clinical Prognosis Immunotherapy and Non-Immunotherapy in Hepatocellular Carcinoma. Front Immunol 2021;12:676922.
46. Sprinzl MF, Galle PR. Current progress in immunotherapy of hepatocellular carcinoma. J Hepatol 2017;66:482-4.
47. Finkelmeier F, Waidmann O, Trojan J. Nivolumab for the treatment of hepatocellular carcinoma. Expert Rev Anticancer Ther 2018;18:1169-75.
48. Siu LL, Ivy SP, Dixon EL, et al. Challenges and Opportunities in Adapting Clinical Trial Design for Immunotherapies. Clin Cancer Res 2017;23:4950-8.

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