Original Article

Establishment and validation of a predictive model of recurrence in primary hepatocellular carcinoma after resection

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Background: In recent years, nomogram prediction models have been widely used to evaluate the prognosis of various diseases. However, studies in primary hepatocellular carcinoma (HCC) are limited. This study sought to explore the risk factors of recurrence of patients with primary HCC after surgical resection and establish a nomogram prediction model.

Methods: The data of 424 patients with primary HCC who had been admitted to the Wuhan Third Hospital were retrospectively collected. The patients were followed-up for 5 years after surgery. The patients were divided into the recurrence group (n=189) and control group (n=235) according to whether the cancer recurred after surgery. The differences in the clinical characteristics between the two groups were analyzed. The risk factors of recurrence after surgical resection of primary HCC were also analyzed, and a prediction model was then established using R4.0.3 statistical software.

Results: There were significant statistical differences between the two groups in terms of the tumor size, systemic immune-inflammation (SII) index, the number of lesions, tumor differentiation degree, ascites, vascular invasion, and portal vein tumor thrombus (P<0.05). The multivariate regression analysis showed that multiple foci, poorly differentiated tumors, ascites, vascular invasion, and portal vein tumor thrombus were risk factors for the recurrence of primary HCC in patients after surgical resection (P<0.05). The data set was randomly divided into a training set and verification set. The sample size of the training set was 297, and the sample size of the verification set was 127. The area under the receiver operating characteristic (ROC) curve of the training set was 0.866 [95% confidence interval (CI): 0.824–0.907], and the area under the ROC curve of the validation set was 0.812 (95% CI: 0.734–0.890). The Hosmer-Lemeshow Goodness-of-Fit Test was used to test the model with the validation set (χ^2=11.243, P=0.188), which indicated that the model had high value in predicting the recurrence of primary HCC after surgical resection.

Conclusions: This model had high value in predicting the recurrence of primary HCC in patients after surgical resection. This model could assist clinicians to assess the prognosis of patients. Intensive treatment for high-risk patients might improve the prognosis of patients.

Keywords: Primary hepatocellular carcinoma; operation; recurrence; prediction model

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Introduction

Primary hepatocellular carcinoma (HCC) is a common malignant tumor. Hepatitis B is the main cause of primary HCC in China. Primary HCC is aggressive with a high incidence rate and mortality (1). Postoperative recurrence and metastasis are the most important causes of death. Identifying the risk factors of postoperative recurrence could help clinicians to assess the prognosis of patients. Targeted interventions according to the relevant risk factors could also help to reduce the postoperative recurrence rate.

A previous study confirmed that multiple foci, large tumor size, portal vein tumor thrombus, and vascular invasion are risk factors for the early recurrence of primary HCC within 1 year of surgery (2); however, the follow-up time of the study was insufficient, and thus its value is limited. In addition, single biological indicators have limited predictive value for prognosis. Nomogram model could assist clinicians to assess the prognosis of patients and identify the high risk of recurrence patients. Some scholars have tried to use nomogram prediction models to predict the prognosis of various diseases in recent years, and research have shown that prediction models often have higher diagnostic value than a single biological indicator (3-5). However, studies in primary HCC are limited. Thus, it is necessary to further explore the risk factors of recurrence of primary HCC after surgical resection and establish a prediction model according to the relevant risk factors to assess the prognosis of primary HCC patients after surgery. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1303/rc).

Highlight box

Key findings

- This model had high value in predicting the recurrence of primary hepatocellular carcinoma (HCC) after resection.

What is known and what is new?

- Single biological indicators have limited value in predicting patient prognosis.
- This study aimed to analyze the risk factors of recurrence in patients with primary HCC after surgical resection and establish a prediction model according to the relevant risk factors.

What is the implication, and what should change now?

- This model had high value in predicting the recurrence of primary HCC after surgical resection. This model could assist clinicians to assess the prognosis of patients. Intensive treatments for high-risk patients might improve patient prognosis.

Methods

General information

The data of 424 patients with primary HCC treated at the Wuhan Third Hospital were retrospectively collected. All the patients were treated with surgery. The patients were divided into the recurrence group (n=189) and control group (n=235) according to whether the cancer recurred after surgery. Inclusion criteria: (I) have primary HCC; (II) be aged ≥18 years; (III) have undergone surgical treatment; and (IV) have complete clinical data. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had metastatic liver cancer; (II) had other malignant tumors; (III) had unresectable liver cancer; (IV) had undergone palliative surgical resection for advanced liver cancer; (V) had perioperative liver failure leading to death; and/or (VI) were lost to follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Wuhan Third Hospital (No. 202200172), and the requirement for individual informed consent was waived.

Treatment strategy

The patients were required to undergo hepatectomy within a limited time after admission, and were given symptomatic support treatment, such as liver protection, anti-inflammatory treatment, and nutritional support. The diagnosis of primary HCC was confirmed by postoperative pathology. The patients were followed-up for 5 years after surgery through outpatient visits, and their abdominal computed tomography or magnetic resonance imaging and α-fetoprotein (AFP) results were reviewed regularly to observe whether there was a suspected recurrence after operation. If there is a suspected recurrence, we used liver puncture biopsy to determine whether it was a recurrence or not.

Observation indicators

The observation indicators were as follows: age at the time of diagnosis, gender, body mass index, smoking history, drinking history, tumor size, systemic immune-inflammation (SII) index, number of lesions, tumor

differentiation degree, ascites, vascular invasion, portal vein tumor thrombus, tumor site, liver function Child-Pugh grade, surgical method, the integrity of the tumor capsule, and the preoperative AFP level.

Establishment and verification of the model

This study used R4.0.3 statistical software for the statistical analysis. The data set was randomly divided into the training set and verification set (according to the principle of completely random number table). The sample size of the training set was 297, and the sample size of the verification set was 127. According to the selected independent variables, the prediction model was established, and a decision curve analysis was conducted using the data from the training set. The calibration curve and receiver operating characteristic (ROC) curve were drawn using the data from the validation set. The Hosmer-Lemeshow Goodness-of-Fit Test was used to test the model with the validation set to evaluate the predictive value of the model.

Statistical analysis

R4.0.3 statistical software and SPSS26.0 software were used to complete the data analysis of this study. A 2-tailed P<0.05 indicated that the difference was statistically significant. The data that conformed to a normal distribution are presented as the mean ± standard deviation, and the independent sample *t*-test was used to analyze the differences between the two groups. The data that did not conform to a normal distribution are presented as the median [interquartile range (IQR)], and the non-parametric test was used to analyze the differences between the two groups. The counting data are presented as the number (percentage), and the Chi-Square test was used to analyze the differences between the two groups. The predictive value of different indicators on postoperative recurrence of liver cancer patients was analyzed by using the ROC curve; multivariate logistic regression analysis was used to explore the risk factors of postoperative recurrence in patients with primary HCC.

Results

Comparison of the clinicopathological features

There were significant statistical differences between the two groups in terms of the tumor size, SII index, the number of lesions, tumor differentiation degree, ascites, vascular invasion, and portal vein tumor thrombus (P<0.05) (*Table 1*).

Risk factors for the recurrence of primary HCC after surgical resection

The multivariate regression analysis showed that multiple foci, poorly differentiated tumors, ascites, vascular invasion, and portal vein tumor thrombus were risk factors for the recurrence of primary HCC in patients after surgical resection (P<0.05) (*Table 2*).

Establishment and validation of a model of recurrence of primary HCC after resection

The data set was randomly divided into the training set and the verification set. The sample size of the training set was 297, and the sample size of the verification set was 127. The following factors were included in the model: tumor size, SII index, multiple foci, poorly differentiated tumors, ascites, vascular invasion, and portal vein tumor thrombus. The nomogram was established, and a decision curve analysis was conducted (*Figures 1*,*2*). The calibration and ROC curves were drawn using the data of the validation set (*Figures 3*,*4*). The area under the ROC curve of the training set was 0.866 [95% confidence interval (CI): 0.824–0.907], and the area under the ROC curve of the validation set was 0.812 (95% CI: 0.734–0.890). The Hosmer-Lemeshow Goodness-of-Fit Test was used to test the model with the validation set (χ^2=11.243, P=0.188), and the results indicated that the model had high value in predicting the recurrence of primary HCC after surgical resection.

The value of tumor size and the SII index in predicting the recurrence of primary HCC after surgical resection

Tumor size had certain value in predicting the recurrence of primary HCC after surgical resection, and the area under the curve (AUC) was 0.768 (95% CI: 0.722–0.814, P=0.000). The SII index had certain value in predicting the recurrence of primary HCC after surgical resection, and the AUC was 0.646 (95% CI: 0.593–0.700, P=0.000). Thus, tumor size and the SII index had certain value in predicting the recurrence of primary HCC after surgical resection, but the predictive value was not as good as that of the nomogram model (*Figure 5*).

Table 1 Comparison of the clinicopathological features

Category	Recurrence group (n=189)	Control group (n=235)	$t/\chi^2/Z$ value	P value
Age at the time of diagnosis (years), mean ± SD	50.12±8.31	50.78±9.02	0.775	0.438
Gender, n (%)			0.138	0.711
Male	132 (69.84)	168 (71.49)		
Female	57 (30.16)	67 (28.51)		
Body mass index (kg/m^2), mean ± SD	24.26±2.17	24.62±1.98	1.783	0.075
Smoking history, n (%)	21 (11.11)	25 (10.64)	0.024	0.876
Drinking history, n (%)	18 (9.52)	29 (12.34)	0.843	0.358
Hepatitis B, n (%)	150 (79.37)	180 (76.60)	0.466	0.495
Tumor size (cm), median (25% quantile–75% quantile)	4.61 (2.84–6.32)	2.51 (1.59–3.68)	9.480	0.000
SII index, median (25% quantile–75% quantile)	488.65 (297.65–710.44)	382.67 (236.14–528.26)	5.184	0.000
Number of lesions, n (%)			12.880	0.000
Single lesion	161 (85.19)	224 (95.32)		
Multiple foci	28 (14.81)	11 (4.68)		
Differentiation degree of tumor, n (%)			15.705	0.000
Poorly differentiated	81 (42.86)	58 (24.68)		
Moderately and well differentiated	108 (57.14)	177 (75.32)		
Ascites, n (%)	17 (8.99)	7 (2.98)	7.100	0.008
Vascular invasion, n (%)	20 (10.58)	6 (2.55)	11.731	0.001
Portal vein tumor thrombus, n (%)	18 (9.52)	7 (2.98)	8.087	0.004
Tumor site, n (%)			2.016	0.1561
Left liver	77 (40.74)	80 (34.04)		
Right liver	112 (59.26)	155 (65.96)		
Liver function Child-Pugh grade, n (%)			0.096	0.757
Grade A	126 (66.67)	160 (68.09)		
Grade B	63 (33.33)	75 (31.91)		
Surgery, n (%)			0.034	0.853
Open	23 (12.17)	30 (12.77)		
Laparoscopic	166 (87.83)	205 (87.23)		
Integrity of tumor capsule, n (%)			1.556	0.212
Yes	146 (77.25)	193 (82.13)		
No	43 (22.75)	42 (17.87)		
Preoperative AFP level (μg/L), mean ± SD	462.46±89.46	448.64±90.47	1.571	0.117

SD, standard deviation; SII, systemic immune-inflammation index; AFP, α-fetoprotein.

Table 2 Risk factors for recurrence of primary HCC after surgical resection

Variables	B	S.E.	Wald	P	Relative risk (95% CI)
Multiple foci	1.432	0.385	13.824	0.000	4.187 (1.968–8.906)
Poorly differentiated tumors	0.915	0.222	16.906	0.000	2.496 (1.614–3.860)
Ascites	0.969	0.486	3.977	0.046	2.635 (1.017–6.829)
Vascular invasion	1.686	0.491	11.787	0.001	5.398 (2.062–14.134)
Portal vein tumor thrombus	1.166	0.479	5.937	0.015	3.209 (1.256–8.199)
Constant	–11.466	1.890	36.814	0.000	0.000

HCC, hepatocellular carcinoma; S.E., standard errors; CI, confidence interval.

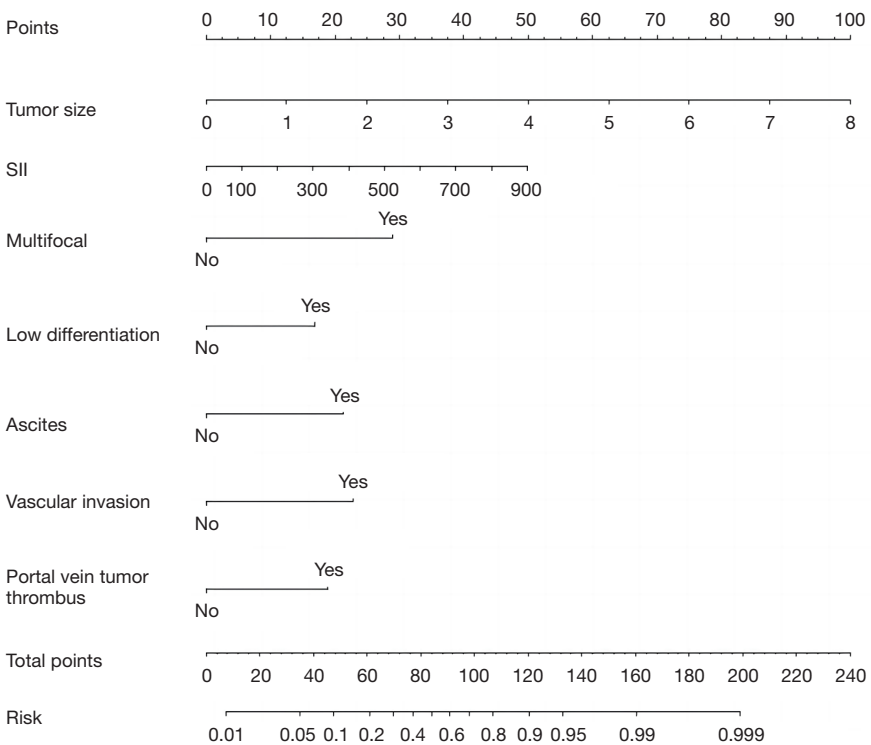

Figure 1 Nomogram of model of recurrence of primary HCC after resection. SII index, systemic immune-inflammation index; HCC, hepatocellular carcinoma.

Discussion

Cancer is a common fatal disease. The effective identification of factors for a poor prognosis would not only help clinicians to assess the prognosis of patients (6-8) but would also help clinicians to identify high-risk patients according to risk factors, and thus reduce mortality (9-12). This study explored the risk factors of recurrence of primary HCC in patients after surgical resection. The results showed that tumor size, the SII index, multiple foci, poorly differentiated tumors, ascites, vascular invasion, and portal vein tumor thrombus were related to recurrence of primary HCC in patients after surgical resection. According to the relevant factors, a prediction model was also established. This prediction model was found to have a high value in predicting the recurrence of primary HCC in patients after surgical resection. The AUC was as high as 0.866 (95% CI: 0.824–0.907), which is higher than the prediction value of single prediction indicators, such as tumor size and the SII

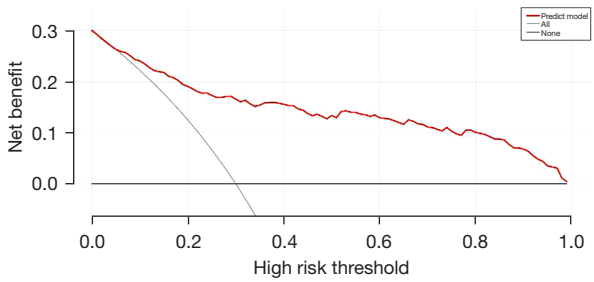

Figure 2 Decision curve analysis of model of recurrence of primary HCC after resection. HCC, hepatocellular carcinoma.

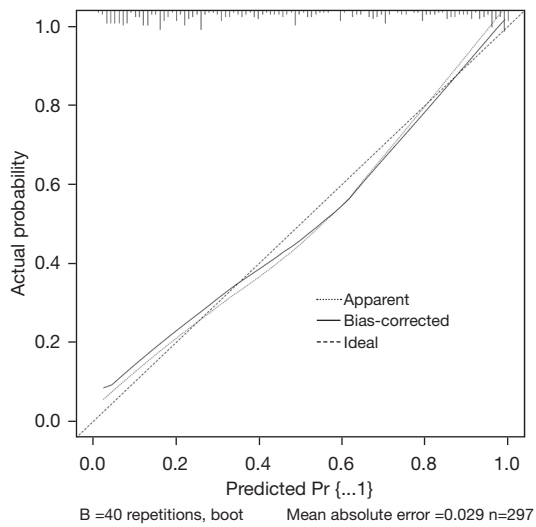

Figure 3 Calibration curve of the model of recurrence of primary HCC after resection. HCC, hepatocellular carcinoma.

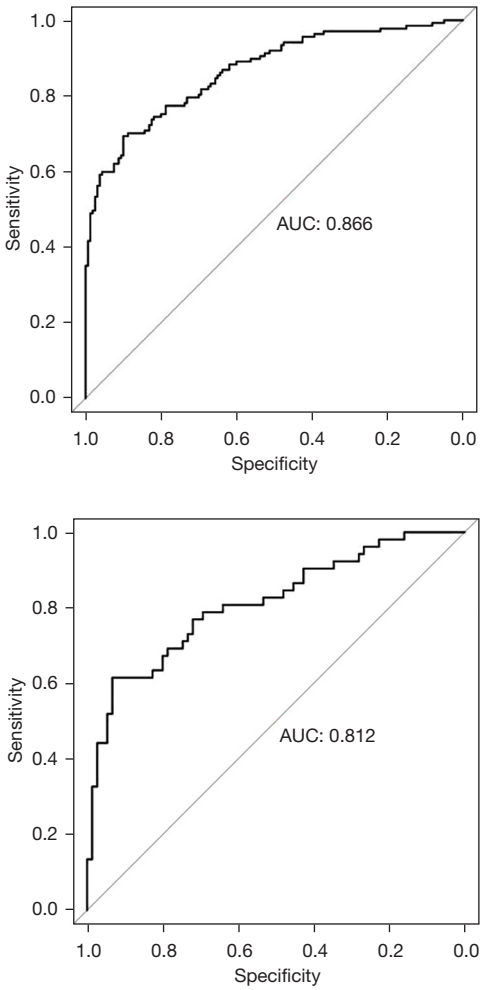

Figure 4 ROC curve of the model of recurrence of primary HCC after resection (the upper figure shows the training set results, and the lower figure shows the verification set results). AUC, area under the curve; ROC, receiver operating characteristic; HCC, hepatocellular carcinoma.

index.

Lymph node metastasis is rare in HCC; thus, in clinical practice, the prognosis of patients is mainly evaluated based on tumor size and number of lesions. At present, tumor size and the number of lesions have been confirmed as risk factors for the postoperative recurrence, metastasis, and death of patients with primary liver cancer (13-15), which is further supported by the findings of this study. The poor differentiation of liver cancer refers to the high degree of malignancy. The higher the degree of malignancy, the faster the growth of liver cancer cells, and the more likely they are to have intrahepatic metastasis and distant metastasis in the early stage, which in turn leads to the poor prognosis of patients (16-18).

The ascites in patients with liver cancer are mainly caused by chronic liver function impairment, which leads to a decrease in albumin synthesis, a decrease in plasma colloid osmotic pressure, or an imbalance in intracellular and extracellular water metabolism caused by portal hypertension. The flow of intracellular fluid out of the cell causes ascites. Ascites in patients with liver cancer generally indicates that the tumor has reached an advanced stage and that patient prognosis is poor (19,20).

Liver cancer patients with vascular invasion and portal vein tumor thrombus are more likely to have intrahepatic metastasis. As liver cancer cells are not sensitive to chemotherapy, such patients are more likely to have

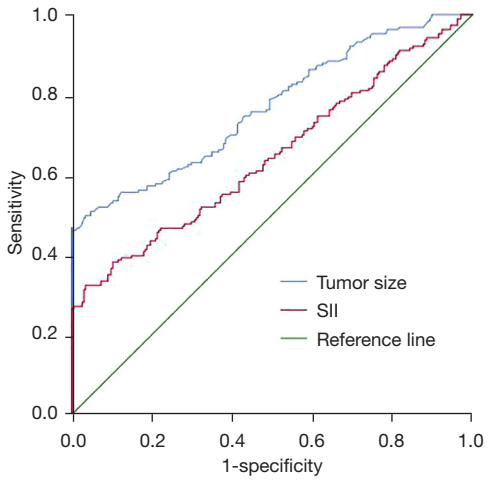

Figure 5 The value of tumor size and the SII index in predicting the recurrence of primary HCC after surgical resection. SII, systemic immune-inflammation index; HCC, hepatocellular carcinoma.

recurrence and metastasis (21-23). In addition, this study found that the SII index was also valuable in predicting recurrence in patients with primary HCC after surgical resection. The SII index is calculated using the following formula: SII index = (the platelet count + neutrophil count)/ the lymphocyte count.

Neutrophils are inflammatory cells. An increase in the level of neutrophils means that the level of systemic inflammation is increased. An inflammatory state is conducive to tumor angiogenesis and promotes the proliferation and metastasis of liver cancer cells. Lymphocytes are immune cells of the body, and mainly include T lymphocytes, B lymphocytes and natural-killer cells, which are the main cells of the body that kill tumor cells. When the number of lymphocytes decreases, it indicates that the patient's immune function is low. Platelets participate in the development of tumor growth, tumor cell exosmosis, and tumor metastasis. Thus, an increase in the SII index suggests that the internal environment is conducive to the growth and metastasis of tumor cells. The SII index has been proven to be associated with the long-term prognosis of colorectal cancer patients with liver metastasis (24,25). However, there is still a lack of relevant research in patients with primary liver cancer. This study found that the SII index is a new marker of poor prognosis in patients with liver cancer.

In addition, this study found that single biological indicators, such as tumor size and the SII index, had some value in predicting the recurrence of primary HCC in patients after surgical resection, but their predictive value was not high. Nomogram models integrate multiple related indicators. Nomogram prediction models have been shown to successfully predict the prognosis of many diseases (26-30). This study established a prediction model and found that the prediction value of this model was high. The model had an AUC as high as 0.866 (95% CI: 0.824–0.907), which was higher than the prediction value of any single prediction indicators, such as tumor size and the SII index.

Limitations

First, it was a single-center retrospective clinical study. Second, the verification of the model was completed using an internal validation method.

Conclusions

Our model was shown to have high value in predicting the recurrence of primary HCC after surgical resection. The model might assist clinicians to assess the prognosis of patients. Intensive treatments for high-risk patients might also improve patient prognosis.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1303/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1303/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1303/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). The study was approved by the Ethics Committee of the Wuhan Third Hospital (No. 202200172), and the requirement for individual informed consent was waived.

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