Survival prediction model for postoperative hepatocellular carcinoma patients

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Abstract

This study is to establish a predictive index (PI) model of 5-year survival rate for patients with hepatocellular carcinoma (HCC) after radical resection and to evaluate its prediction sensitivity, specificity, and accuracy.

Patients underwent HCC surgical resection were enrolled and randomly divided into prediction model group (101 patients) and model evaluation group (100 patients). Cox regression model was used for univariate and multivariate survival analysis. A PI model was established based on multivariate analysis and receiver operating characteristic (ROC) curve was drawn accordingly. The area under ROC (AUROC) and PI cutoff value was identified.

Multiple Cox regression analysis of prediction model group showed that neutrophil to lymphocyte ratio, histological grade, microvascular invasion, positive resection margin, number of tumor, and postoperative transcatheter arterial chemoembolization treatment were the independent predictors for the 5-year survival rate for HCC patients. The model was $PI = 0.377 \times NLR + 0.554 \times HG + 0.927 \times PRM + 0.778 \times MVI + 0.740 \times NT - 0.831 \times$ transcatheter arterial chemoembolization (TACE). In the prediction model group, AUROC was 0.832 and the PI cutoff value was 3.38. The sensitivity, specificity, and accuracy were 78.0%, 80%, and 79.2%, respectively. In model evaluation group, AUROC was 0.822, and the PI cutoff value was well corresponded to the prediction model group with sensitivity, specificity, and accuracy of 85.0%, 83.3%, and 84.0%, respectively.

The PI model can quantify the mortality risk of hepatitis B related HCC with high sensitivity, specificity, and accuracy.

Abbreviations: AUROC = the area under receiver operating characteristic, HCC = hepatocellular carcinoma, HG = histological grade, MTS = maximum tumor size, MVI = microvascular invasion, NLR = neutrophil-to-lymphocyte ratio, NT = number of tumor, PI = predictive index, PRM = positive resection margin, ROC = receiver operating characteristic, TACE = transcatheter arterial chemoembolization.

Keywords: Cox regression model, hepatocellular carcinoma, postoperative transcatheter arterial chemoembolization, radical resection, survival analysis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the world's most common malignancies, with more than 750,000 new cases each year.[1] It also ranked the third among the mortality rate of all cancers,[2] and more than 55% HCC were in China because of the high rate of hepatic B infection.[3]

HCC resection and liver transplantation is of high efficacy for patients with early HCC.[4,5] Liver transplantation is seldom performed because of limited liver donor, therefore, liver resection remains the most widely used radical HCC treatment. Other treatments, including radiofrequency, interventional therapy, immune enhancement, molecularly targeted therapies, traditional medicine, can serve as complement to further improve the survival rate.[6,7]

Complete removal of the tumor is essential in HCC recurrence reduction and survival improvement. The pathology diagnosis of surgical margin is still the gold standard to determine whether surgical resection is completed. Those with positive resection margin (PRM) usually come with poor prognosis[8] and significantly higher recurrence rate compared with non-PRM patients, probably because of the postoperative residual micrometastases.

Second, HCC histological grade (HG) can reflect the HCC biological characteristics. Poor differentiation indicates high malignancy, that is, patients with poor differentiation usually have lower average disease-free survival and lower overall survival rate compared patients with high differentiation.[9–11]

The HCC survival time is closely related with microvascular invasion (MVI) in resected HCC tissue,[12] and MVI is one of the prediction markers of intrahepatic micrometastases and HCC recurrence.[12] Positive MVI in HCC tissue pathology suggested

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intrahepatic and extrahepatic metastasis that led to poor prognosis.[13–16] It is worth noting that lymph node metastasis is also listed as one of MVI presentations.

Patients with multiple intrahepatic HCC are often of high recurrence rate and postoperative mortality after surgical resection.[17] Even if the pathology of surgical margins are negative, microsatellite lesions, and MVI could be detected.[18,19] Except for only a few cases, multiple HCCs are all intrahepatic metastasis that surgery cannot achieve radical resection.[20–23] Therefore, surgical resection is not recommended for patients with HCC of equal or more than 3 lesions.[24]

HCC is of higher postoperative recurrence rate and metastasis rate, and lower 5-year survival rate.[17] Therefore comprehensive treatment is commonly recommended. However, the effectiveness of various treatments still requires further investigation. For example, whether transcatheter arterial chemoembolization (TACE) should be routinely used as postoperative prevention remains controversial.[25] TACE may cause various degrees of hepatic injury that would lead to poor prognosis.[26] In recent years, TACE is advancing by using safer chemotherapy drugs and highly selective blood clots to optimize the benefits and reduce liver damage of interventional therapy. Currently, there are each time more reports on the benefits of prophylactic TACE treatment after surgery[27–33] for its safe and effective improvement for HCC patients' prognosis. Chen et al[34] showed that prophylactic TACE performed in postoperative 1 or 2 month would reduce recurrence rate; however, multiple TACE may increase liver damage and affect the survival rate.[25] Yang et al[35] showed that TACE could significantly improve the prognosis of HCC patients with Child–Pugh A level. In summary, the benefit of TACE for HCC patients required more evidence-based research.

Lymphopenia would reduce T lymphocyte-mediated tumor cell killing effect,[36] and the increased neutrophils would result in release of systemic cytokines, such as chemokines and interleukin, leading to persistent inflammation, tumor cell proliferation, and angiogenesis.[36] Increased neutrophil-to-lymphocyte ratio (NLR) indicates the imbalance of the immune response to cancer and the body's immune system.[36] Therefore, NLR is widely accepted as marker of poor prognosis.[12] However, there are no quantitative measures for the effects of immune imbalance on HCC prognosis. In this study, prediction model is established to quantify the risk impact on HCC prognosis.

2. Patients and methods

2.1. Subjects

HCC patients admitted in Xinjiang Medical College First Hospital from October 2007 to October 2010 were recruited. Patients with complete clinical recording and follow-up data were included in the final analysis. All patients had HCC on the basis of chronic hepatitis B infection and cirrhosis[37] who underwent surgical resection. Patients were excluded if they had preoperative HCC with extensive intrahepatic or distant metastasis; no major invasions of surrounding organs and vessels; other malignancies; Child–Pugh class C; major diseases, such as cardiovascular diseases, and respiratory diseases. Patients were followed up from surgical resection until 5 years or death. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of the First Affiliated Hospital of Xinjiang Medical University.

2.2. Outcome measurements

The surgical margin is defined positive if any one of the below was positive: microinvasion was detected on surgical margin; abnormal cell growth or precancerous lesions were detected on surgical margin; surgical margins were of less than 0.5 mm from the foci, according to the NCCN (National Comprehensive Cancer Network) Guidelines Version 1.2016 for Hepatobiliary Cancers (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Surgery indicators for HCC were in accordance with the Chinese HCC expert consensus. Clinical and follow-up data were all extracted from their medical records. Pathology was reviewed by 2 blinded professional pathologists.

2.3. Statistical analysis

SPSS19.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Univariate and multivariate Cox regression analysis and maximum likelihood method was used to establish predictive index (PI) model. ROC curve was drawn accordingly. The area under ROC and PI cutoff value was identified, combined with sensitivity, specificity, and accuracy value, to evaluate the predictive value of PI model. $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of patients in the 2 groups

There were 201 patients finally included in the study, and patients were randomly divided into prediction model group (101 patients) and model evaluation group (100 patients). There were 130 males (64.7%) and 71 females (35.3%). Their age ranged from 38 to 69 years, with median age of 45 years. The survival time was 7 to 60 months, with median survival time of 25 months. There were 81 cases (40.3%) died during the 5-year follow-up, including 41 cases (40.6%) in prediction model group and 40 cases (40.0%) in model evaluation group. There were no significant difference between age, sex, and major blood indicators between prediction model group and model evaluation group ($P > .05$) (Table 1).

3.2. Univariate Cox regression analysis

To determine early prediction factors of postoperative HCC survival, univariate Cox regression analysis was performed. Univariate Cox regression analysis showed that 9 factors had significant differences in 5-year survival, namely, NLR, cirrhosis, MVI, maximum tumor size (MTS), number of tumor (NT), HG, tumor capsule, PRM, postoperative TACE ($P < .05$) (Table 2). The results indicate that NLR, cirrhosis, MVI, MTS, NT, HG, tumor capsule, PRM, and postoperative TACE may be used as prediction factors for postoperative HCC survival.

3.3. Multivariate Cox regression analysis

To further determine the independent prediction factors of postoperative HCC survival, multivariate Cox regression analysis was performed. Taken the 9 factors into the multivariate Cox regression model, there were 6 factors that significantly impacted prognosis (Table 3). Among these 6 factors, 5 factors were the independent risk factors, namely NLR, HG, PRM, MVI, and NT with OR of 1.46, 1.74, 2.53, 2.18, and 2.10, respectively. The postoperative TACE was the independent protective factor with

Table 1

Comparison of baseline characteristics of HCC patients between prediction model group and model evaluation group.

	Prediction model group (n=101)	Model evaluation group (n=100)	P
Sex (male/female)	64/37	66/34	.696
Age, y	49	51	.183
Smoking	56/45	43/57	.078
Drinking	53/48	55/45	.720
NLR	4.31±1.03	4.36±1.41	.792
Hb, g/L	113±19	114±22	.718
AFP, ng/mL			.101
>300	66	54	
<300	35	46	
Hepatitis B DNA load, copies/mL			.433
>5.00E+02	52	57	
<5.00E+02	49	43	
Prealbumin, g/L	132±33	140±27	.075
Ccr, μmol/L	83±23	79±18	.212
ALT, U/L	96±57	81±66	.090
AST, U/L	73±25	66±38	.147
ApoA$_1$, g/L	1.24±0.34	1.21±0.33	.530
ApoB, g/L	0.91±0.14	0.93±0.24	.400
TC, mmol/L	2.75±1.97	3.23±1.85	.072
TG, mmol/L	1.36±0.38	1.29±0.35	.170
HDL, mmol/L	1.46±0.23	1.44±0.23	.435
LDL, mmol/L	2.98±0.22	2.95±0.22	.314
TBiL, μmol/L	36.27±9.47	35.85±10.80	.767
PTA, %	90±18	89±14	.510
Albumin, g/L	46.45±8.24	45.23±6.24	.236
GGT, U/L	123±42	130±49	.272
Child Pugh class (A, B)			.858
A level	87	87	
B level	14	13	

AFP = alpha fetal protein, ALT = alanine transaminase, ApoA$_1$ = apolipoprotein A$_1$, ApoB = apolipoprotein, AST = glutamic-oxalacetic transaminease, Ccr = creatinine clearance rate, GGT = gamma-glutamyl transpeptidase, HCC = hepatocellular carcinoma, HDL = high density lipoprotein, LDL = low density lipoprotein, NLR = neutrophil to lymphocyte ratio, PTA = prothrombin time activity percentage, TBiL = total bilirubin, TC = total cholesterol, TG = triglyceride.

Table 2

Univariate Cox regression analysis of 5-year survival rate for postoperative HCC patients.

	β	Standard error	Wald value	Degree of freedom	P	OR	95% CI
NLR	0.51	0.17	9.12	1	.003	1.66	1.20–2.30
Cirrhosis	0.65	0.33	3.85	1	.050	1.91	1.00–3.64
Tumor capsule	0.69	0.32	4.77	1	.029	1.99	1.07–3.69
MTS	0.79	0.32	6.19	1	.013	2.20	1.18–4.10
MVI	0.96	0.31	9.24	1	.002	2.60	1.401 -4.82
NT	0.65	0.31	4.28	1	.038	1.91	1.04–3.53
PRM	0.62	0.32	3.90	1	.048	1.86	1.00–3.46
Postoperative TACE	−0.95	0.35	7.22	1	.007	0.39	0.19–0.77
HG	0.43	0.20	4.78	1	.029	1.53	1.05–2.24

CI = confidence interval, HCC = hepatocellular carcinoma, HG = tumor histological grade, MTS = maximum tumor size, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, NT = number of tumor, OR = odds ratio, PRM = positive resection margin; TACE = transcatheter arterial chemoembolization.

Table 3

Multivariate Cox regression analysis of 5-year survival rate for postoperative HCC patients.

	β	Standard error	Wald value	Degree of freedom	P	OR	95% CI
NLR	0.377	0.19	3.93	1	.047	1.46	1.00–2.12
MVI	0.778	0.36	4.71	1	.030	2.18	1.08–4.39
NT	0.740	0.32	5.34	1	.021	2.10	1.12–3.93
PRM	0.927	0.34	7.53	1	.006	2.53	1.30–4.90
Postoperative TACE	−0.831	0.37	5.13	1	.023	0.44	0.21–0.89
HG	0.554	0.21	6.77	1	.009	1.74	1.15–2.64

CI = confidence interval, HCC = hepatocellular carcinoma, HG = tumor histological grade, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, NT = number of tumor, OR = odds ratio, PRM = positive resection margin; TACE = transcatheter arterial chemoembolization.
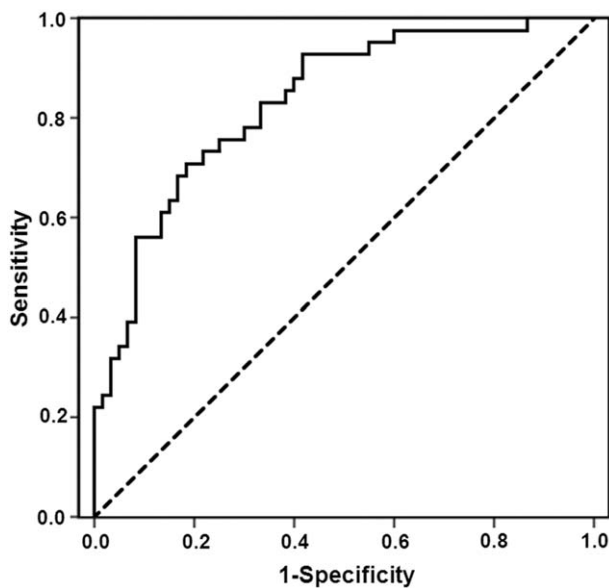
Figure 1. ROC curve for prediction of 5-year survival rate for postoperative HCC patients in prediction model group. The area under ROC (AUROC) was 0.832 (0.753–0.911) with statistical significance ($P < .05$). PI cutoff value was 3.38. HCC = hepatocellular carcinoma, ROC = receiver operating characteristic.
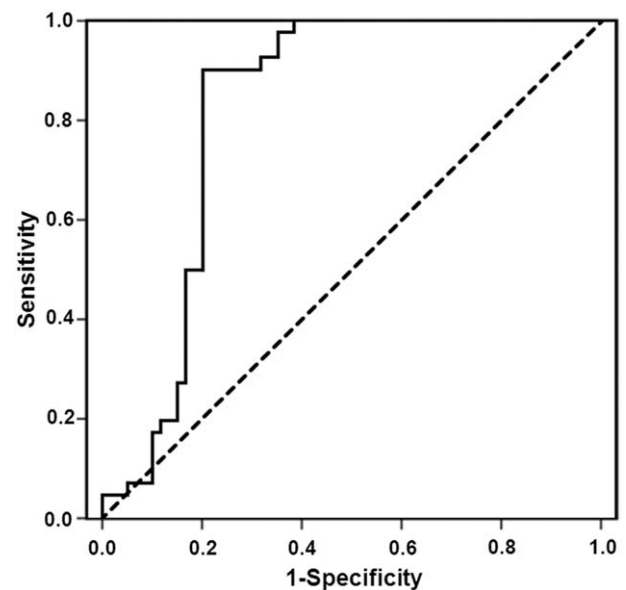

Figure 2. ROC curve for prediction of 5-year survival rate for postoperative HCC patients in model evaluation group. The area under ROC AUROC was 0.822 (0.753–0.909) with statistical significance ($P < .05$). The cutoff value of PI was 3.3. HCC = hepatocellular carcinoma, ROC = receiver operating characteristic.

OR of 0.44 ($P < .05$). There were no significant difference in factors of cirrhosis, MTS, and tumor capsule in the multivariate analysis. Thus, they were not independent factors for the 5-year survival.

3.4. PI model and its predictive value

To determine the weight of independent prediction factors of postoperative HCC survival, PI model was established. The PI model was established based on multivariate analysis: PI = 0.377 × NLR + 0.554 × HG (high = 1, medium = 2, low = 3) + 0.927 × PRM (yes = 1, no = 0) + 0.778 × MVI (yes = 1, no = 0) + 0.740 × NT (single = 0, multiple = 1) − 0.831 × TACE (yes = 1, no = 0). The PI was between 0.73 and 5.65. The greater the PI is, the worse the prognosis would be.

Figure 1 showed that the area under ROC (AUROC) curve in prediction model group was 0.832 (0.753–0.911) with statistical significance ($P < .05$). PI cutoff value was 3.38. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the PI model in prediction model group was 78.0%, 80.0%, 72.7%, 84.2%, and 79.2%, respectively (Table 4). In model evaluation group, AUROC was 0.822 (0.753–0.909) with statistical significance ($P < .05$) (Fig. 2). The cutoff value of PI was 3.31. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 82.5%, 80.0%, 73.3%, 87.3%, and 81.0%, respectively (Table 5). This result indicates that the PI model was of high-prediction value to guide clinical treatment.

4. Discussion and conclusion

There were 201 patients in this study with 5-year survival rate of 59.7% and mortality rate of 40.3%, which was in accordance with that in clinical guide.[38] NLR, HG, PRM, MVI, and NT were independent risk factors for the 5-year survival rate of HCC, and postoperative TACE was the only independent protective factor, which was in line with previous studies.[39] Besides the above consensus, this study is the first to quantify the independent risk factors and protective factors in prediction model.

In univariate analysis, patients with liver cirrhosis of Child-Pugh B level were of lower survival rate than patients of Child–Pugh A level. However, multivariate regression showed that liver function had no significant impact on 5-year survival rate. In China, most HCC patients were receiving HCC surgery and chronic hepatitis B treatment concurrently. Thus, we speculate that the liver cirrhosis of these patients may improve along with the antiviral treatment and that the initial staging may not reflect the liver function during follow-up.

In this study, multivariate statistics showed that MTS was not the independent risk factor for HCC 5-year survival rate with

Table 4

Risk index prediction in prediction model group.

	Number (cases)	Survival (cases)	Death (cases)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	AUROC
≥3.38	44	12	32	—	—	—	—	—	(0.753–0.911)
<3.38	57	48	9	—	—	—	—	—	—
Total	101	60	41	78.0	80.0	72.7	84.2	79.2	0.832

AUROC = the area under receiver operating characteristic

Table 5

Risk index prediction in model evaluation group.

	Number (cases)	Survival (cases)	Death (cases)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	AUROC
≥3.31	45	12	33	—	—	—	—	—	(0.735–0.909)
<3.31	55	48	7	—	—	—	—	—	—
	100	60	40	82.5	80.0	73.3	87.3	81.0	0.822

AUROC = the area under receiver operating characteristic

diameter of 5 cm as the cutoff point. For patients with tumor diameter of more than 5 cm, there were no significant differences in 5-year survival compared with that of diameter less than 5 cm when all other factors were adjusted. However, as tumor diameter increased, MVI, PRM and NLR would accordingly increase, thus tumor diameter may still be an important factor.

In accordance with previous studies,[12,40] MVI, NT, and PRM were independent risk factors for postoperative HCC 5-year survival rate with high weight in the risk prediction model. In fact, HCC with large tumor size is more likely to have MVI and PRM,[22,23] suggesting the importance of surgery optimization.

The increased NLR reflected the body's reduced tumor-specific immune response to cancer and immunity imbalance.[36] Consistently, our result showed that NLR was an independent risk factor for 5-year survival of HCC patients. Multivariate Cox regression showed that postoperative TACE treatment was independent protective factor for the 5-year survival rate with high significance. Therefore, at least 1 TACE is recommended for HCC patients after surgery. If patients with multiple risk factors, such as poorly differentiated HCC, PRM, multiple tumors, MVI, and satisfactory liver function, 3 TACE treatments and more frequent follow-ups are recommended.[40] The OR of TACE was 0.44 in our study, suggesting its great benefit to improve the prognosis.

In our study, NT was also the independent risk factor for 5-year survival rate. Patients with multiple liver tumors are often associated with higher recurrence rate and postoperative mortality.[12,40] Histological tumor microsatellite lesions and MVI are often observed even if postoperative pathology shows negative margins.[18,41] In addition, except for only a few cases, multiple HCCs are all intrahepatic metastasis that surgery cannot achieve radical resection, as reported previously.[20–23]

This study has some limitations. First, we did not include the tumor markers (such as AFP, DCP, and AFP L3%) of HCC in the prediction model. The influences of tumor markers on the prediction model are unknown. Second, the influence of the etiology of underlying liver cirrhosis on the prediction model was not analyzed.

To sum up, based on the PI model above, patients with PI ≥ 3.38 showed poor prognosis and the AUROC were 0.832 and 0.822 for prediction model group and model evaluation group, respectively. Our findings may provide evidence for clinicians to predict 5-year survival rate based on clinical information and to make individualized treatment strategy accordingly.

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