JBUON 2019; 24(4): 1420-1428
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Establishment and validation of a prognostic model for hepatocellular carcinoma after radical liver resection

Yan Xue[1]*, Jianxian Zhang[2]*, Yuhuan Bai[1], Changchun Jing[1], Zhifeng Zhang[3], Xiaoyu Sun[3], Dong Yang[3], Zhijun Duan[3]

[1]Department of Gastroenterology, The Second People's Hospital of Liaocheng, Liaocheng 252600, China. [2]Department of Gastrointestinal Surgery, The Second People's Hospital of Liaocheng, Liaocheng 252600, China. [3]Department of Gastroenterology, The First Affiliated Hospital of Dalian Medical University, Dalian 116011, China.

*Yan Xue and Jianxian Zhang contributed equally to this work

Summary

Purpose: *The prognostic factors related to survival of primary hepatocellular carcinoma (HCC) after radical resection were analyzed in order to establish a new prognostic model for HCC patients and to shed light on personalized treatments.*

Methods: *141 patients pathologically diagnosed as HCC were enrolled. The independent prognostic factors affecting overall survival were identified, and a prognostic mathematical model was established. Independent samples of 21 cases were used to validate the model's ability to predict prognosis of HCC patients.*

Results: *The median survival time was 34 months, and the 1-, 3-, and 5-year overall survival rates were 93.2%, 80%, and 68.9%, respectively. Univariate analysis showed that alpha fetoprotein (AFP) serum level, tumor size, tumor capsule, liver cirrhosis, neutrophil-to-lymphocyte ratio (NLR), and total bilirubin (TBIL) were significantly correlated with overall survival ($p<0.05$). Cox multivariate analysis indicated that the independent prognostic factors were AFP serum level, liver cirrhosis, tumor size, tumor capsule, and NLR. The prognostic mathematical model was: Prognostic Index (PI)=1.725 * liver cirrhosis + 0.783 * NLR + 1.046 * AFP + 0.595 * tumor size - 0.811 * tumor capsule. Based on the PI quartiles, 3.933 (25%), 4.716 (50%), and 5.195 (75%), the patients were divided into 4 groups: low risk ($PI<3.933$), moderate-risk ($3.933 \leq PI < 4.716$), high-risk ($4.761 \leq PI < 5.195$), and very high-risk ($PI \geq 5.195$) group. The median survival times were 60, 34, 32, and 20 months, respectively. The 1-, 2-, 3-, and 5-year cumulative survival rates were 100%, 96%, 96%, 86%; 89%, 75%, 68%, 68%; 77%, 68%, 57%, 44%; 50%, 34%, 29%, 29%, separately. The predictions of the prognostic model demonstrated good consistency with the actual results. The total accuracy rate was 80.9%, and the Kappa consistency coefficient was 0.571 ($p=0.009$).*

Conclusions: *The higher the PI, the lower the postoperative cumulative survival rate and the worse the prognosis. This model can be used as an effective method to assess the prognosis of HCC patients after resection.*

Key words: *hepatocellular carcinoma (HCC), radical liver resection, survival analysis, Cox regression analysis, prognostic model*

Introduction

Hepatocellular carcinoma (HCC) is a serious threat to human life. It is the fifth most common malignant tumor and the third cancer-related cause of death worldwide. More than 600,000 people die every year of HCC [1,2], and its incidence is increasing rapidly [3]. At present, there are many available treatment methods for HCC, among which surgical resection is preferred [4,5]. However, recurrence

Corresponding author: Zhijun Duan, MD. Department of Gastroenterology, The First Affiliated Hospital of Dalian Medical University, No. 222 Zhongshan Rd, 116011 Dalian, Liaoning, China.
Tel: +86 018264521207, Email: cathydoctor@sina.com
Received: 11/02/2019; Accepted: 04/03/2019

and distant metastasis often occur after surgery and reduce the overall survival of patients, affecting the long-term prognosis of surgical treatment [6]. For clinicians, appropriate clinical decision-making is more urgent than the specific treatment regimen. Therefore, a standard for prognosis evaluation is needed. Nowadays, the CLIP, BCLC, and JIS staging systems are used for the prognosis evaluation of HCC patients [7, 8]. However, these systems cannot be widely used due to different population and statistical methods, and/or different inclusion and exclusion criteria. In the present study, a comprehensive model for the prediction of prognosis of HCC patients after radical resection, based on 27 clinical indicators including clinical imaging, serological parameters, and pathological characteristics was developed. The proposed prognosis model can provide a reference for choosing the proper operation, clinical comprehensive treatment, and prognosis of HCC patients, which will contribute to increasing the overall survival of HCC patients.

Methods

Patients

In total, 141 HCC patients pathologically diagnosed and treated in the First Affiliated Hospital of Dalian Medical University from January 2001 to March 2010, were enrolled in this retrospective study. Postoperative follow-up data was collected using the Dalian Centers for Disease Control query, telephone follow-up, and all medical record systems of big Dalian hospitals. The endpoint was defined as death due to liver cancer, the censored data as death due to other diseases, and those surviving during follow-up or lost to follow-up. The survival time was calculated on a monthly basis, and was defined as the period from operation to death or to the deadline of March 2015. This study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. Signed written informed consents were obtained from all participants before the study entry.

Clinical data

On the basis of literature review, a total of 27 indicators were summarized and selected including gender,

Table 1. Clinicopathological variables

No	*Variables*	*Value assignments*			
X1	Sex	Male (1)		Female (2)	
X2	Age	<40 (1)	40-60 (2)		>60 (3)
X3	Blood type	O (0)	A (1)	B (2)	AB (3)
X4	Smoking history	Yes (1)		No (2)	
X5	History of diabetes	Yes (1)		No (2)	
X6	HBsAg	Positive (1)		Negative (0)	
X7	ALT	≤50 (1)		>50 (2)	
X8	AST	≤40 (1)		>40 (2)	
X9	ALB	≤40 (1)		>40 (2)	
X10	γ-GT	≤60 (1)		>60 (2)	
X11	ALP	≤125 (1)		>125 (2)	
X12	TBIL	≤19 (1)		>19 (2)	
X13	PT	≤13 (1)		>13 (2)	
X14	INR	≤1.08 (1)		>1.08 (2)	
X15	PLT	≤133 (1)		>133 (2)	
X16	NLR	≤2.8 (1)		>2.8 (2)	
X17	CEA	≤5 (1)		>5 (2)	
X18	AFP	≤20 (1)		>20 (2)	
X19	Tumor size (cm)	≤3 (1)	3-10 (2)		>10 (3)
X20	Tumor capsule	Yes (1)		No (0)	
X21	Tumor location	Left lobe (1)		Right lobe (2)	
X22	Number of tumors	Single shot (1)		Multiple shots (2)	
X23	Child-Pugh classification	A (1)	B (2)		C (3)
X24	TNM stage	I (1)	II (2)		III (3)
X25	Intraoperative blood transfusion	Yes (1)		No (0)	
X26	Cirrhosis	Yes (1)		No (0)	
X27	Portal vein thrombus	Yes (1)		No (0)	
Y	Survival result	Dead (1)		Survived, lost, dead of other diseases (0)	

age, blood type, smoking history, diabetes mellitus history, HBsAg, AST, ALT, ALB, γ-GT, alkaline phosphatase (ALP), total bilirubin (TBIL), prothrombin time (PT), international normalized ratio (INR), alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), platelet count (PLTx10^9 /L), neutrophil-to-lymphocyte ratio (NLR), tumor size, number of tumors, tumor location, tumor capsule, TNM stage, Child-Pugh classification, liver cirrhosis, portal vein tumor thrombus, and intraoperative blood transfusion. The data of 120 patients from January 2001 to March 2009 were used for the establishment of the model, while the data of 21 patients from March 2009 to March 2010 were used in the validation of the model. Statistical analysis was performed using the SPSS statistical package version 19.0, and $p<0.05$ was considered statistically significant. A total of 27 clinicopathological variables were recorded (Table 1).

Prognostic model establishment

Univariate analysis and multivariate analysis were used to identify the independent prognostic factors of HCC patients after radical resection. Survival curves were generated using Kaplan-Meier method and the log rank test was used to assess the significance of differences in the classification of the factors, and build a Cox regression model and a prognostic index model.

For the prognostic index (PI) classification, the PI of each patient was calculated, and the patients were divided into 4 groups (low risk group, medium risk group, high risk group, and very high risk group). Then, the median survival time and the 1-, 3-, and 5-year overall survival were evaluated by Kaplan-Meier analysis.

Receiver operating characteristic curve (ROC) curve analysis was used to evaluate the prognostic model, where the PI was considered as the test variable, the 3-, and 5-year survival outcomes (survival or death) as the state variable, and the calculated area under the ROC curve (AUC) was used to evaluate the ability of the model to predict the 3-, and 5-year survival outcomes.

For the validation of the model, the ROC curve was used to obtain the optimal risk value, which was used as a PI cut-off value, where PI < cut-off indicated survival, and PI > cut-off indicated death. In addition, Kappa-consistency analysis, specificity, sensitivity, and accuracy were used to evaluate the ability of the model to predict outcomes.

Results

General information

The data of 120 HCC patients were used for the establishment of the model. There were 94 males and 26 females with a mean age of 53.7 ± 9.9 years (range, 31-79). The median survival time of all patients was 34 months and the 1-, 3-, and 5-year overall survival rates were 93.2%, 80%, and 68.9%, respectively.

Prognostic mathematical model

A total of 27 clinicopathological variables were recorded and assigned a value (Table 1). Univariate analysis revealed that AFP, tumor size, tumor capsule, cirrhosis, NLR, and TBIL had a significant impact on the prognosis of HCC ($p<0.05$) (Table 2). On the other hand, sex, age, blood type, smoking

Table 2. Univariate analysis of HCC risk factors

Variables	*Number of cases (%)*	x^2	*p*
AFP (IU/ml)		5.800	0.016
≤20	42 (35.0)		
>20	78 (65.0)		
Cirrhosis		11.414	0.001
With	91 (75.8)		
Without	29 (24.2)		
Total bilirubin (μmol/L)		4.190	0.041
≤19	68 (56.7)		
>19	52 (43.3)		
Tumor size (cm)		9.556	0.008
≤3	48 (40.0)		
3<Tumor size ≤10	64 (53.3)		
>10	8 (6.7)		
Tumor capsule		9.007	0.003
Envelope	94 (78.3)		
Without envelope	26 (21.7)		
Neutrophil lymphocyte ratio		4.903	0.027
≤2.8	70 (58.3)		
>2.8	50 (41.7)		

Table 3. Cox multivariate analysis results

Selected variable	*Regression Coefficient (B)*	*Standard error (SE)*	*Wald* x^2	*Standard deviation*	*p value*	*Relative risk*	*Relative risk CI 95.0%*	
							Lower	*Upper*
AFP	1.046	.388	7. 281	1	0.007	2.845	1.331	6.081
Tumor size	0.595	.251	5.605	1	0.018	1.813	1.108	2.967
Tumor capsule	-0.811	.340	5.686	1	0.017	0.444	0.228	0.866
Cirrhosis	1.725	.531	10.548	1	0.001	5.615	1.982	15.907
NLR	0.783	.314	6.194	1	0.013	2.187	1.181	4.050

Table 4. Cumulative survival rate of different PI levels (%)

Prognostic index.	*Cumulative survival rate (%)*			
	1-year	*2- year*	*3- year*	*5- year*
Low-risk group 60 (PI<3.933)	100	96	96	86
Medium-risk group 34 (3.93 3 ≤ PI < 4.716)	89	75	68	68
High-risk group 32 (4.716 ≤ PI < 5.195)	77	68	57	44
Very high-risk group 20 (PI ≥ 5.195)	50	34	29	29

Table 5. Determination of most dangerous PI values

Prognostic index	*Sensitivity*	*Specificity*
0.61300	1.000	1.000
3.86750	0.848	0.464
3.98500	0.783	0.429
4.05100	0.772	0.393
4.09300	0.750	0.357
4.13500	0.696	0.321
4.26650	0.685	0.321
4.50800	0.609	0.250
6.23950	0.065	0.000
7.57300	0.000	0.000

history, history of diabetes, HBsAg-positive or not, AST, ALT, ALB, r-GT, ALP, PT, INR, CEA, PLT, number of tumors, tumor location, TNM stage, portal vein tumor thrombus, with or without intraoperative blood transfusion, liver function, and Child-Pugh classification had not impact on the prognosis of liver cancer (p>0.05).

Cox multivariate analysis shows that AFP, tumor size, tumor capsule, cirrhosis, NLR were independent prognostic factors in HCC after curative resection (p<0.05) (Table 3). The Cox regression model was: h (t,x) = h0 (t) exp (1.725 × cirrhosis + 0.783 × NLR + 1.046 × AFP + 0.595 ×tumor size + (-0.811) × tumor capsule). The x^2 test was used for the hypothesis testing, and the overall model was statistically significant (p<0.01). The mathematical model for HCC prognosis after radical resection was PI=1.725 × cirrhosis + 0.783 × NLR + 1.046 × AFP + 0.595 × tumor size + (-0.811) × tumor capsule.

Table 6. Predictions and actual situations of 21 validation samples

Model prediction	*Actual result*		
	Death	*Survival*	*Total*
Death	5	2	7
Survive	2	12	14
Total	7	14	21

Survival reference table

Each patient's prognostic index was calculated, and according to the PI quartiles, the patients were divided into 4 groups, which were the low-risk (PI < 3.933), the medium-risk (3.933 ≤ PI < 4.716), the high-risk (4.716 ≤ PI < 5.195), and the very high-risk group (PI ≥ 5.195). The 1-, 2-, 3-, and 5-year cumulative survival rates of patients in the different groups can be seen in Table 4.

Most dangerous PI values (cut-off)

The cut-off value for predicting the risk of 5-year survival outcome was calculated using the ROC curve and was found to be 4.093 (with sensitivity 75%, specificity 64.3%, Youden index (YI) = 0.393) (Table 5), meaning that if PI ≤ 4.093, the model predicts survival after 5 years, while if PI > 4.093, it predicts death after 5 years.

Comparison between model predictions and actual results

Between March 2009 and March 2010, 21 cases (19 males and 2 females; 7 deaths, 14 sur-

vived) were set apart to be used as the independent sample (Table 6). The 5-year survival outcomes of the model predictions were compared with the actual results based on the 5-year follow-up. The total prediction accuracy was 80.9% and the Kappa=0.571 (p=0.009). The results revealed that the model prediction and the consistency with the actual outcomes were statistically significant with good consistency.

Discussion

Both outcome quality and time length, which can be called survival data, should be considered when assessing the effect of treatment or prognosis, and this statistical method is called survival analysis. Univariate analysis results have a significant impact on the prognosis. However, this type of analysis cannot fully reflect the complexity of the disease, due to the interaction of a single factor, and thus the prognosis is prone to bias. As medical statistics develop, multivariate analysis has become a hot topic, and is carried out through the establishment of prognostic models. Consequently, logistic regression and Cox regression analysis should be applicable. Logistic regression is mainly used for binary or multiple data classification. In this study, the Cox regression model, which was developed by Dr. Cox, a British statistical expert, in 1972, is a commonly used semi-parametric regression model. There are no special requirements for survival distribution, and compared to other analysis methods, it has a unique ability to evaluate the prognosis. This more flexible model can successfully integrate a number of factors, effectively control confounding factors affecting the strength and direction of observation indicators, and fully utilize the "censored data". Therefore, the prognostic model outcomes are more consistent with the objective results. Both CLIP and CUPI staging systems are established based on Cox models. In addition, in the present study the model prognostic index was applied in order to obtain a ROC curve for preliminary evaluation. ROC curve evaluation is more accurate, effective, and comprehensive in diagnostic tests. An AUC between 0.5-0.7 indicates a low diagnostic value, while between 0.7-0.9 indicates a moderate diagnostic value. When AUC is >0.9, a diagnostic test is considered of high accuracy [9]. However, the ROC curve is less sensitive in individual prediction evaluation. Therefore, further validation is necessary, and this can be achieved with Kappa consistency test. The Kappa value is an important indicator of the reliability of clinical diagnostic evaluation. The larger the k-factor, the higher the matching degree. In practice, $k \geq 0.7$ represents strong goodness of fit, $0.4 \leq k < 0.7$ general goodness of fit, and $k < 0.4$ weak goodness of fit.

In general, HCC is associated with both high incidence and mortality rates, and poor prognosis with short overall survival. Its prognosis includes many factors which are extensive at home and abroad. Widely recognized factors include tumor, non-tumor, and surgical procedure factors. Following univariate analysis of 27 clinical indicators affecting HCC prognosis after radical resection, it was found that serum AFP level, tumor size, tumor capsule, cirrhosis, NLR, and TBIL were significantly correlated with the prognosis of HCC ($p<0.05$). However, in multivariate analysis, TBIL was excluded, indicating that it has poor prognostic sensitivity. Tumor size, tumor capsule, NLR, AFP, and cirrhosis were independent survival prognostic factors of HCC after hepatectomy. Compared to previous results of several large studies, the significant prognostic indicators were basically the same. In northeast China, the HCC prognosis model following radical resection provides a comprehensive plan for treatment.

It remains controversial if AFP can be used as an independent prognostic factor. Some authors believe that AFP is an independent prognostic factor affecting the long-term survival of HCC patients [10-13]. In a prospective study of 189 HBV-HCC cases, Blank et al. [10] stratified the different AFP levels, and found that as the AFP level increased, the postoperative cumulative survival rate dropped. While AFP is taken into account in the CLIP [7], CUPI [14], BALAD [15], and CIS staging systems [16], Gomaa et al. [8] suggested that AFP should be also added to the BCLC staging system, in order to increase the selectivity of HCC patients. On the other hand, there is the opposite view that preoperative serum AFP levels have no effect on the prognosis of liver cancer [17,18]. Shim et al. [19] divided the patients after surgical resection into two groups: one with AFP≥20 ng/mL and the other with AFP<20 ng/mL. No significant difference ($p>0.05$) in the recurrence rates was found, indicating that the preoperative AFP level has no effect on overall survival. In this study, it was found that the AFP-positive group had a significantly worse prognosis than the AFP-negative group ($p=0.016$), and the 1, 3, and 5-year survival rates of the AFP-negative group were 90%, 76%, and 71%, respectively, while those of the AFP-positive group were 72%, 56%, and 49%, respectively. Higher AFP levels indicate poorer liver function, higher operative risk and difficulty, more blood loss, and need for more blood transfusion [20]. Moreover, we believe that high AFP levels increase the grade of malignancy,

which facilitates vascular invasion and promotes tumor invasion and metastasis, leading to a poor prognosis.

Many studies have shown that the different degrees of liver fibrosis and cirrhosis are important factors affecting postoperative long-term survival and recurrence of HCC [21,22]. Nanashima et al. [13] found that liver cirrhosis is an independent risk factor for long-term survival of patients with HBV-HCC. Yamashita et al. [23] indicated that liver cirrhosis is worse than useless for the long-term prognosis of HCC patients. Bilimoria et al. [24] studied 145 HCC patients whose survival time was longer than 5 years. They found that, compared to patients with cirrhosis and high degree of liver fibrosis, those with mild hepatic fibrosis had longer survival times. Furthermore, they found that liver fibrosis has a major impact on postoperative long-term survival, and suggested that liver fibrosis/cirrhosis should be included in TNM staging. In the present study, patients were divided into two groups: a cirrhosis group and a non-cirrhosis group. For the cirrhosis group, the 1-, 3- and 5-year cumulative survival rates after surgery were 73%, 53%, and 45%, respectively, while for the non-cirrhosis group were 97%, 89%, and 84%, respectively. This result was consistent with results reported by most researchers.

Tumor size reflects the degree of tumor load, and is also the biological indicator of tumor growth. Several reports have concluded that tumor size is a risk factor for survival and prognosis of HCC patients after hepatectomy [25,26]. Zhou et al. [27] divided 396 HCC cases into two groups: a group with survival time ≥20 years and another with survival time <20 years. The comparative study demonstrated that in the ≥ 20 years group, the proportion of patients with tumor diameter ≤5 cm was higher than that in the <20 years group (p<0.000). The patients with tumor diameter >5cm had a lower cumulative survival rate. In other studies, it was suggested that tumor size is not associated with the prognosis of HCC patients [28,29]. In this paper, it was concluded that tumor size is an independent prognostic factor of liver cancer (p=0.008), where the larger the tumor diameter, the lower the postoperative cumulative survival. This can be attributed to the following reasons: (1) the larger the tumor diameter, the higher the possibility of liver metastasis and vascular invasion, distant metastasis, and thus the survival rate decreases and leads to worse prognosis; (2) the larger the tumor diameter, the more important vascular system can be compressed, which increases the operative risk; (3) most liver cancer patients have liver cirrhosis, and their liver function reserve is poor, thus a larger diameter leads to a larger affected area, which increases the possibility of postoperative tumor residuals. Moreover, it easily causes liver metastasis and recurrence, which affects patient survival.

More and more studies have focused on the relationship between tumor capsule and prognosis of liver cancer. In most cases, it is believed that tumor capsule is the interaction between tumor and host, which inhibits tumor invasion and growth [30,31]. It has been reported, from the pathological standpoint, that the presence of tumor capsule seems to decrease vascular invasion and prevent potential violations [32]. Lee et al. [33] found that the postoperative median survival time was 50 months and 34 months for envelope and no envelope, respectively, and suggested that no envelope is a risk factor. On the other hand, Abdel-Wahab et al. [34] suggested that the capsule had no effect on the long-term survival of patients, while another study suggested that the total survival rate of HCC patients after surgery with capsule was worse than those without capsule (p=0.0022), with a lower grade of tumor differentiation and higher vascular invasion [35]. The results of the present study showed that the 1-, 3-, and 5-year cumulative survival rates of patients with HCC were 84%, 70%, and 62% (envelope), respectively, and 60%, 40%, and 40% (no envelope), respectively (p=0.003). In conclusion, we believe that tumor envelope is highly differentiated, which reflects the ability of tumor metastasis and potential recurrence, and limits tumor development. Furthermore, it is a barrier to tumor cell proliferation and invasion. The difference of surgical effect and prognosis was caused by tumor's biological behavior. A large part of liver cancer without capsule indicates tumor invasive growth, unclear boundary, and thus it restricts to some degree the scope of surgical resection. It is not surprising that there are residual lesions after liver resection, which can lead to recurrence.

In recent years, the relationship between tumor progression and inflammatory response is a hot and difficult research topic. NLR is one of the evaluation indexes of systemic inflammatory response and immune system. Zhou et al. [36] found that in malignant solid tumors, the inflammatory reaction usually occurs before the malignant tissue. Recent studies have shown that elevated preoperative NLR is a risk factor in the prognosis of a variety of malignant tumors of the digestive system such as gastric, esophageal, pancreatic, and colon cancer [37-40]. The prognosis of liver cancer has been also reported [41-43]. After studying 318 HCC cases, Oh et al. (2013) found that NLR is an independent risk factor for HCC prognosis [44]. In the present study, it was also found that the survival

rate of patients with NLR ≥ 2.8 was significantly lower than NLR < 2.8 (p=0.027). Thus, NLR ≥ 2.8 was considered as prognostic risk factor. Elevated NLR means that either neutrophils increase or lymphocytes decrease. On the one hand, the increase of neutrophils provides a good microenvironment for tumor development. VEGF is recognized as a major factor in promoting tumor angiogenesis and increasing vascular permeability. Tumor cells acquire sufficient nutrition, proliferate rapidly, and can enter the blood through vascular endothelial cells, in order to develop a distant metastasis. On the other hand, relative reduction of lymphocytes is mediated by cytotoxic cell death and inhibits tumor proliferation, decreases immune function, and increases tumor malignancy. Both conditions can lead to shorter survival, higher mortality, and poorer prognosis.

In this paper, 27 indexes that may affect HCC prognosis were collected, Cox's multivariate regression analysis was performed, HCC independent factors associated with postoperative prognosis were screened, and a prognostic mathematical model was established. The preliminary assessment showed that the ROC curve model provides better evaluation and stronger verification. Meanwhile, the indexes of the model were simple and easy to calculate. This study was conducted mainly in Liaoning province of China, and has a certain reference value for prognosis prediction in northeast China. Therefore, it can be used in determining survival prognosis, which can help clinicians choose and develop comprehensive treatment plans, and provide scientific assistance for the screening of surgical cases, surgical treatment preliminary judgment, and even a basis for adjuvant therapy. It has clinical value for prediction of prognosis and personalized treatments of HCC patients.

In addition, the present research has also several limitations. Firstly, it was a retrospective study. Limited data and subjective factors, such as tumor size and patient's disease state, may lead to conflicting judgments, which decrease the accuracy of staging. Secondly, it was a single-center study. The small sample size, censored data, same sample source, and other factors may have caused bias in the results. In recent years, with the development of molecular detection methods, an increasing number of studies are focusing on molecular markers of prognosis, expanding into genomics [45,46] and proteomics [47,48]. It becomes more significant in prognostic indicators for HCC postoperative prognosis, and further expands the sample size. Additionally, it provides more effective and reliable prognostic models through multi-center prospective studies, and is promising for future clinical applications

Conclusions

The prognosis of HCC patients after radical liver resection depends on many factors. A mathematical model for prognosis based on liver cirrhosis degree, AFP serum level, NLR, tumor size, and tumor capsule (PI=1.725 * liver cirrhosis + 0.783 * NLR + 1.046 * AFP + 0.595 * tumor size - 0.811 * tumor capsule) was developed. The higher the PI, the lower the postoperative cumulative survival rate and the worse the prognosis. The developed model can be used as an effective method to assess the prognosis of HCC patients after liver resection.

Conflict of interests

The authors declare no conflict of interests.

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-4.
2. Wang JT, Wang ZH. Role of miR-193a-5p in the proliferation and apoptosis of hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:7233-9.
3. Sotiropoulos GC, Prodromidou A, Machairas N. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma: The European experience. JBUON 2017;22:1160-71.
4. Chen L, Ma X, Liu X, Cui X. Sorafenib combined with radiofrequency ablation as treatment for patients with hepatocellular carcinoma: a systematic review and meta-analysis. JBUON 2017;22:1525-32.
5. Li GL, Yuan JH, Zhuang GD, Wu DQ. miR-199b exerts tumor suppressive functions in hepatocellular carcinoma by directly targeting JAG1. Eur Rev Med Pharmacol Sci 2018;22:7679-87.
6. Lee SG, Hwang S, Jung JP, Lee YJ, Kim KH, Ahn CS. Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. Br J Surg 2007;94:320-6.
7. Liu B, Yang XF, Liang XP et al. Expressions of MiR-132 in patients with chronic hepatitis B, posthepatitic cirrhosis and hepatitis B virus-related hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:8431-7.
8. Gomaa AI, Hashim MS, Waked I. Comparing staging

systems for predicting prognosis and survival in patients with hepatocellular carcinoma in Egypt. PLoS One 2014;9:e90929.

9. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561-77.
10. Blank S, Wang Q, Fiel MI et al. Assessing prognostic significance of preoperative alpha-fetoprotein in hepatitis B-associated hepatocellular carcinoma: normal is not the new normal. Ann Surg Oncol 2014;21:986-94.
11. Jin XL, Lian JR, Guan YH. Overexpression of long noncoding RNA MINCR contributes to progressive clinicopathological features and poor prognosis of human hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:8197-202.
12. Li GL, Yuan JH, Zhuang GD, Wu DQ. miR-199b exerts tumor suppressive functions in hepatocellular carcinoma by directly targeting JAG1. Eur Rev Med Pharmacol Sci 2018;22:7679-87.
13. Chen Z, Zhou ZY, He CC, Zhang JL, Wang J, Xiao ZY. Down-regulation of LncRNA NR027113 inhibits cell proliferation and metastasis via PTEN/PI3K/AKT signaling pathway in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:7222-32.
14. Chan SL, Mo FK, Johnson PJ et al. Prospective validation of the Chinese University Prognostic Index and comparison with other staging systems for hepatocellular carcinoma in an Asian population. J Gastroenterol Hepatol 2011;26:340-7.
15. Toyoda H, Kumada T, Osaki Y et al. Staging hepatocellular carcinoma by a novel scoring system (BALAD score) based on serum markers. Clin Gastroenterol Hepatol 2006;4:1528-36.
16. Maida M, Orlando E, Camma C, Cabibbo G. Staging systems of hepatocellular carcinoma: a review of literature. World J Gastroenterol 2014;20:4141-50.
17. Sasaki K, Matsuda M, Ohkura Y et al. Implication of an extremely high preoperative alpha-fetoprotein value (>4,000 ng/mL) for the long-term outcomes of hepatectomy for resectable hepatocellular carcinoma. Surgery 2015;157:223-30.
18. Giannini EG, Marenco S, Borgonovo G et al. Alpha-fetoprotein has no prognostic role in small hepatocellular carcinoma identified during surveillance in compensated cirrhosis. Hepatology 2012;56:1371-9.
19. Shim JH, Yoon DL, Han S et al. Is serum alpha-fetoprotein useful for predicting recurrence and mortality specific to hepatocellular carcinoma after hepatectomy? A test based on propensity scores and competing risks analysis. Ann Surg Oncol 2012;19:3687-96.
20. Bi X, Yan T, Zhao H et al. [Correlation of alpha fetoprotein with the prognosis of hepatocellular carcinoma after hepatectomy in an ethnic Chinese population]. Zhonghua Yi Xue Za Zhi 2014;94:2645-9.
21. Wang Q, Blank S, Fiel MI et al. The Severity of Liver Fibrosis Influences the Prognostic Value of Inflammation-Based Scores in Hepatitis B-Associated Hepatocellular Carcinoma. Ann Surg Oncol 2015;22 (Suppl 3):S1125-32.
22. Wang Q, Fiel MI, Luan W et al. Impact of intrahepatic hepatitis B DNA and covalently closed circular DNA on survival after hepatectomy in HBV-associated hepatocellular carcinoma patients. Ann Surg Oncol 2013;20:3761-70.
23. Yamashita Y, Taketomi A, Itoh S et al. Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. J Am Coll Surg 2007;205:19-26.
24. Vauthey JN, Chaoui A, Do KA et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-9.
25. Yeh CN, Chen MF, Lee WC, Jeng LB. Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. J Surg Oncol 2002;81:195-202.
26. Lu XY, Xi T, Lau WY et al. Pathobiological features of small hepatocellular carcinoma: correlation between tumor size and biological behavior. J Cancer Res Clin Oncol 2011;137:567-75.
27. Zhou XD, Tang ZY, Ma ZC et al. Twenty-year survivors after resection for hepatocellular carcinoma-analysis of 53 cases. J Cancer Res Clin Oncol 2009;135: 1067-72.
28. Yang LY, Fang F, Ou DP, Wu W, Zeng ZJ, Wu F. Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 2009;249:118-23.
29. Kobayashi K, Nakao K, Kawai K et al. Tumor-induced osteomalacia originating from the temporal bone: a case report. Head Neck 2011;33:1072-5.
30. Liang F, Cui ZJ, Liu JD, Liu KP, Li L, Chen YL. Downregulated miR-328 suppressed cell invasion and growth in hepatocellular carcinoma via targeting PTEN. Eur Rev Med Pharmacol Sci 2018;22:6324-32.
31. Huang J, Li BK, Chen GH et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastrointest Surg 2009;13:1627-35.
32. Lockwood DS, Yeadon TM, Clouston AD et al. Tumor progression in hepatocellular carcinoma: relationship with tumor stroma and parenchymal disease. J Gastroenterol Hepatol 2003;18:666-72.
33. Lee WC, Jeng LB, Chen MF. Estimation of prognosis after hepatectomy for hepatocellular carcinoma. Br J Surg 2002;89:311-6.
34. Abdel-Wahab M, El-Husseiny TS, El HE, El SM, Hamdy E. Prognostic factors affecting survival and recurrence after hepatic resection for hepatocellular carcinoma in cirrhotic liver. Langenbecks Arch Surg 2010;395:625-32.
35. Iguchi T, Aishima S, Sanefuji K et al. Both fibrous capsule formation and extracapsular penetration are powerful predictors of poor survival in human hepatocellular carcinoma: a histological assessment of 365 patients in Japan. Ann Surg Oncol 2009;16:2539-46.
36. Zhou L, Rui JA, Wang SB, Chen SG, Qu Q. Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. Eur J Surg Oncol 2011;37:521-5.
37. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte

ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg 2011;35:868-72.

38. Zhang Y, Mi L, Xuan Y et al. LncRNA HOTAIRM1 inhibits the progression of hepatocellular carcinoma by inhibiting the Wnt signaling pathway. Eur Rev Med Pharmacol Sci 2018;22:4861-8.
39. Hamed MO, Roberts KJ, Smith AM, Morris SG. Elevated pre-operative neutrophil to lymphocyte ratio predicts disease free survival following pancreatic resection for periampullary carcinomas. Pancreatology 2013;13:534-8.
40. Perisanidis C, Kornek G, Poschl PW et al. High neutrophil-to-lymphocyte ratio is an independent marker of poor disease-specific survival in patients with oral cancer. Med Oncol 2013;30:334.
41. Wang GY, Yang Y, Li H et al. A scoring model based on neutrophil to lymphocyte ratio predicts recurrence of HBV-associated hepatocellular carcinoma after liver transplantation. PLoS One 2011;6:e25295.
42. Zhang YT, Li BP, Zhang B et al. LncRNA SBF2-AS1 promotes hepatocellular carcinoma metastasis by regulating EMT and predicts unfavorable prognosis. Eur Rev Med Pharmacol Sci 2018;22:6333-41.
43. Chen L, Zhang Q, Chang W, Du Y, Zhang H, Cao G. Viral and host inflammation-related factors that can predict the prognosis of hepatocellular carcinoma. Eur J Cancer 2012;48:1977-87.
44. Oh BS, Jang JW, Kwon JH et al. Prognostic value of C-reactive protein and neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma. BMC Cancer 2013;13:78.
45. Gao Y, Li Z, Guo X, Liu Y, Zhang K. DLX4 as a prognostic marker for hepatocellular carcinoma. Neoplasma 2014;61:318-23.
46. Hou X, Peng JX, Hao XY et al. DNA methylation profiling identifies EYA4 gene as a prognostic molecular marker in hepatocellular carcinoma. Ann Surg Oncol 2014;21:3891-9.
47. Luo RZ, Cai PQ, Li M et al. Decreased expression of PTPN12 correlates with tumor recurrence and poor survival of patients with hepatocellular carcinoma. PLoS One 2014;9:e85592.
48. Ilboudo A, Nault JC, Dubois-Pot-Schneider H et al. Overexpression of phosphatidylinositol 4-kinase type IIIalpha is associated with undifferentiated status and poor prognosis of human hepatocellular carcinoma. BMC Cancer 2014;14:7.