A practical nomogram from the SEER database to predict the prognosis of hepatocellular carcinoma patients with lymph node metastasis

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Abstract

Background: The presence of lymph node metastases is related to poor survival outcomes in hepatocellular carcinoma patients and because of the reported low probability of lymph node metastasis, research into the prognoses of such patients is difficult to conduct. In this study, we aimed to develop a nomogram model to predict the prognosis of HCC patients with lymph node metastasis and provided a reasonable basis for the choice of follow-up treatment.

Methods: HCC patients diagnosed with LN metastasis from 2010 to 2015 were enrolled from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate Cox regression and lasso regression were used to screen prognostic factors. Cox multiple-factor analysis was employed to investigate the independent prognostic factors for survival. The concordance index (C-index) and calibration curve were used to evaluate the predictive performance of our model. The clinical benefit was assessed via decision curve analysis (DCA). The survival was analyzed using Kaplan-Meier method and the differences among survival curves were compared by the log-rank test.

Results: Patients were randomized into the training group (944 patients) and the validation group (402 patients) in a 70:30 ratio. Grade, T stage, surgery to the liver, chemotherapy, radiation recode, AFP, fibrosis score, tumor size group, M stage were selected as independent prognostic factors, and we developed nomograms using these variables. The c-indices of the training and validation groups were 0.70 and 0.73, respectively. The calibration curves for probability of survival showed good agreement. The DCA indicated that the nomogram had positive net benefits. Patients were divided into two risk groups according to our model, survival curves were drawn, and the log-rank test was performed, the p-value of which was <0.001.

Conclusions: The nomogram can accurately predict the prognosis of HCC patients with lymph nodes metastasis and provide a reasonable basis for treatment.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of malignant liver tumor and the seventh most prevalent tumor worldwide with 841,080 new cases occurring every year^[1, 2]. The dominant pathogenic factors vary according to countries and regions, including hepatitis B infection in China^[3], hepatitis C infection in Japan and Africa and alcohol intake in Western countries^[4]. Extrahepatic metastasis occurs in almost 30%-50% of patients during the course of the disease^[5]. The lymph nodes are the second most common site of extrahepatic metastases in HCC^[6] but the incidence of LN metastasis has varied among different reports. The literature reports the incidence range from 1.23% to 7.5% in some studies with large sample sizes^[7-9]. Other research has shown that the incidence might reached approximately 30 percent of the average rate^[10, 11]. Although a large proportion of the data are derived from autopsies, they might reflect that the occurrence of LN metastasis is underestimated, and more patients have lymph node metastasis.

According to the Barcelona staging, patients with lymph nodes metastasis are assigned to the C phase^[12] and the primary treatment for such patients is systemic therapy. The same situation has also been observed in other staging systems, such as the AJCC staging system and the NCCN guidelines^[13]. The main reason for this phenomenon is that HCC patients with lymph nodes metastasis have a poor prognosis. A recent study, including 2043 cases, showed that the median progression-free survival (PFS) time after surgery is 16.3 months for HCC patients without nodal involvement, but only 5.8 months for the group with lymph nodes metastasis^[7]. The 1- and 3-year survival rates of HCC patients who don't have lymph node metastasis were 81% and 62%, respectively. However, the 1- and 3-year overall survival rates were only 62% and 31%, respectively, for HCC patients with nodal involvement^[14]. It is undeniable that lymph node metastasis is a poor prognostic factor for hepatocellular carcinoma^[9, 15]. However, with the development of various treatments and drugs in recent years, the prognosis of HCC patients with lymph node metastases has been improving^[16–18]. Previous studies have shown that patients who were diagnosed with stage IV HCC demonstrated a different prognosis^[18]. The prognosis of HCC patients with lymph node metastases is also different, although they were treated with similar external beam radiotherapy in a study^[19]. The selection of the appropriate treatment should be based on accurate identification of different prognosis groups. Therefore, it is important to distinguish patients' different prognoses. Because of its reported low probability, the grouping of patients requires a large sample size. This situation adds to the difficulty of implementation process of such studies. As far as we know, a study which constructing a prognostic model for the risk assessment of HCC patients with LN metastasis has not yet been reported. Therefore, the aim of our research was to distinguish the different prognostic groups of HCC patients with LN metastasis and to assist and guide clinicians in making treatment decisions.

The nomogram is an efficient statistical tool that represents a graphical method to a predictive model, and it can accurately predict the outcomes of individual patients^[20]. As far as we know, a nomogram model that predicts overall survival in HCC patients with LN metastases does not exist. As previously mentioned, this type of study is difficult because of its reported low probability and the need for a large sample size. To expand the sample size and comprehensively identify the factors affecting the prognosis of HCC patients with LN metastasis, we analyzed medical records from the Surveillance, Epidemiology and End Result (SEER) database. The SEER database collects several types of cancer patient data from electronic pathology reports and is an authoritative source of information on cancer, covering approximately 34.6% of the U.S. population (<http://seer.cancer.gov/>). In the present study, we downloaded data on HCC patients with LNs metastasis from the SEER registry between 2010 and 2015. Then, we divided these patients into a training group and validation group. A nomogram was constructed using the training group, and the validation group was used to evaluate its ability to predict patient survival.

Methods

Ethics statement

This research was exempted by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). Because the data were obtained from the publicly available database, this study was recognized as a retrospective, noninterventional study.

Patient Selection

The data were obtained from the SEER database (SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 sub (1973–2016 varying)). The data were obtained via the SEER*Stat software (version 8.3.6). Because some important prognostic factors were not available before 2010, patients diagnosed with HCC with LN metastases from 2010 to 2015 were finally included in our research.

The inclusion criteria were as follows: (1) hepatocellular carcinoma patients from 2010 to 2015 (histologic type ICD-O-3 = 8170–8175), for whom the site recode ICD-O-3/WHO 2008 was liver and the histologic behavior was malignant; (2) according to the 7th edition of AJCC TNM staging, lymph-node metastasis (N1) patients were enrolled; (3) the patients was older than 18 years old; and (4) follow-up data were available. The exclusion criteria were as follows: (1) survival months were unknown or zero; (2) samples without follow-up time information data; (3) demographic Information was not complete; (4) treatment data were missing; (5) data on vital prognostic factors and tumor staging information were missing; (6) and other cause of death classification was not the first tumor. The patients were randomized into the training group (accounting for 70%) and the validation group (accounting for 30%) using R software. The caret package was used, and the seed was 1988. To acquire more information, the selection process is shown in Fig. 1.

Statistical analysis

The data from the SEER database comprised sex, age group, race, grade, T stage, diagnostic confirmation information, surgery to the liver, surgery to LN, bone metastasis, brain metastasis, liver metastasis, pulmonary metastasis, chemotherapy, radiation, insurance, marital status, AFP, fibrosis score, tumor size group and M stage. The patients were censored as alive or dead of other causes. Categorical variables were compared between different groups using the chi-square test or Fisher's exact test if necessary. Mann-Whitney U-test was used for comparison of numerical variables. Survival curves were generated by Kaplan-Meier method and survival distributions were compared by the log-rank test. Cox univariate and multivariate models were used to screen for prognostic factors associated with survival in the training group. According to the results of multivariate analysis, we developed a nomogram using R software (version 3.4.3, <https://www.r-project.org/>), which was internally validated by bootstrapping in 1000 bootstrap samples. The c-index and area under the receiver operating characteristic curve (AUC) of different time were used to compare the discriminative ability of the nomogram and AJCC 7th system (IVA/IVB) in the training and validation groups. Calibration curves were created to assess the predictive accuracy in the two groups^[21]. Then, we calculated the risk score of each training group patient according to the Cox regression model. The X-tile program (versions 3.6.1) was used to select the optimal cut-off

for the risk score to distinguish the differences in patient survival. The X-tile program is used to find the optimal value of continuous variables, and the application of program has been reported in many studies^[22, 23]. Then, we stratified patients into different risk groups. Survival curves were plotted by the Kaplan-Meier method, and the log-rank test was used to determine significance. Statistical analyses were performed with SPSS software, version 25 (IBM) and R software (version 3.3.4). All of the tests were two-sided, and a P-value of less than 0.05 was considered statistically significant.

Results

Training and validation group patients' characteristics

The flow diagram of the research selection process is depicted in Fig. 1. A total of 40,173 HCC patients from 2010 to 2015 were included in our study, of whom 2,662 cases (6.6%) had LN metastasis and 37,511 cases (94.3%) did not. According to the above exclusion criteria, 1346 patients were finally enrolled. We allocated 944 patients into the training group and the others into the validation group. Table 1 provides details of the patients' clinical information.

Table 1
Comparison of the demographics of the training and validation groups

Variable	All patients	Training group number (%)	Validation group number (%)	p-value
Number of patients	1346	944	402	
Sex				0.731
Male	1099 (81.65%)	773 (81.89%)	326 (81.09%)	
Female	247 (18.35%)	171 (18.11%)	76 (18.91%)	
Age group				0.969
≥ 61	731 (54.31%)	513 (54.34%)	218 (54.23%)	
18–60	615 (45.69%)	431 (45.66%)	184 (45.77%)	
Race				0.277
White	935 (69.47%)	653 (69.17%)	282 (70.15%)	
Black	220 (16.34%)	163 (17.27%)	57 (14.18%)	
Other ^a	191 (14.19%)	128 (13.56%)	63 (15.67%)	
Grade				0.951
Grades I + II	269 (19.99%)	189 (20.02%)	80 (19.90%)	
Grades III + IV	188 (13.97%)	130 (13.77%)	58 (14.43%)	
Unknown	889 (66.05%)	625 (66.21%)	264 (65.67%)	
T stage				0.579
T1	245 (18.20%)	177 (18.75%)	68 (16.92%)	
T2	233 (17.31%)	160 (16.95%)	73 (18.16%)	
T3	748 (55.57%)	518 (54.87%)	230 (57.21%)	
T4	120 (8.92%)	89 (9.43%)	31 (7.71%)	
Diagnostic confirmation				0.123

a:includes American Indian/AK Native, Asian/Pacific Islander

b:positive histology/positive exfoliative cytology

c:clinical diagnosis/direct visualization/positive laboratory test

d:divorced/separated/single (never married)/unmarried or domestic partner/widowed

Variable	All patients	Training group number (%)	Validation group number (%)	p-value
Histology/cytology ^b	829 (61.59%)	594 (62.92%)	235 (58.46%)	
Clinical/radiography/text ^c	517 (38.41%)	350 (37.08%)	167 (41.54%)	
Surgery to the liver				0.902
No surgery	1254 (93.16%)	880 (93.22%)	374 (93.03%)	
Surgery	92 (6.84%)	64 (6.78%)	28 (6.97%)	
Surgery to LNs				0.609
None	1283 (95.32%)	898 (95.13%)	385 (95.77%)	
Yes	63 (4.68%)	46 (4.87%)	17 (4.23%)	
Bone metastasis				0.946
No	1221 (90.71%)	856 (90.68%)	365 (90.80%)	
Yes	125 (9.29%)	88 (9.32%)	37 (9.20%)	
Brain metastasis				0.083
No	1339 (99.48%)	937 (99.26%)	402 (100.00%)	
Yes	7 (0.52%)	7 (0.74%)	0 (0.00%)	
Intrahepatic metastasis				0.196
No	1302 (96.73%)	917 (97.14%)	385 (95.77%)	
Yes	44 (3.27%)	27 (2.86%)	17 (4.23%)	
Pulmonary metastasis				0.046
No	1182 (87.82%)	818 (86.65%)	364 (90.55%)	
Yes	164 (12.18%)	126 (13.35%)	38 (9.45%)	
Chemotherapy				0.573
No	597 (44.35%)	414 (43.86%)	183 (45.52%)	

a:includes American Indian/AK Native, Asian/Pacific Islander

b:positive histology/positive exfoliative cytology

c:clinical diagnosis/direct visualization/positive laboratory test

d:divorced/separated/single (never married)/unmarried or domestic partner/widowed

Variable	All patients	Training group number (%)	Validation group number (%)	p-value
yes	749 (55.65%)	530 (56.14%)	219 (54.48%)	0.13
Radiation recode				
No	1161 (86.26%)	823 (87.18%)	338 (84.08%)	0.194
yes	185 (13.74%)	121 (12.82%)	64 (15.92%)	
Insurance recode				0.102
Insured and any medicaid	1257 (93.39%)	887 (93.96%)	370 (92.04%)	
Uninsured	89 (6.61%)	57 (6.04%)	32 (7.96%)	0.461
Marital status				
Unmarried ^d	662 (49.18%)	478 (50.64%)	184 (45.77%)	0.692
Married	684 (50.82%)	466 (49.36%)	218 (54.23%)	
AFP				0.388
Positive/elevated	999 (74.22%)	707 (74.89%)	292 (72.64%)	
Negative/normal	198 (14.71%)	139 (14.72%)	59 (14.68%)	0.388
Unknown ^a	149 (11.07%)	98 (10.38%)	51 (12.69%)	
Fibrosis score				0.388
0–4	1008 (74.89%)	713 (75.53%)	295 (73.38%)	
5–6	75 (5.57%)	52 (5.51%)	23 (5.72%)	0.388
Unknown ^a	263 (19.54%)	179 (18.96%)	84 (20.90%)	
Tumor size group(mm)				0.388
0–20	60 (4.46%)	41 (4.34%)	19 (4.73%)	
21–50	334 (24.81%)	238 (25.21%)	96 (23.88%)	0.388
51–100	601 (44.65%)	431 (45.66%)	170 (42.29%)	

a:includes American Indian/AK Native, Asian/Pacific Islander

b:positive histology/positive exfoliative cytology

c:clinical diagnosis/direct visualization/positive laboratory test

d:divorced/separated/single (never married)/unmarried or domestic partner/widowed

Variable	All patients	Training group number (%)	Validation group number (%)	p-value
≥ 101	351 (26.08%)	234 (24.79%)	117 (29.10%)	
M stage				0.19
M0	784 (58.25%)	539 (57.10%)	245 (60.95%)	
M1	562 (41.75%)	405 (42.90%)	157 (39.05%)	
Survival months	5.00(2.00–12.00)	5.00 (2.00–12.00)	5.00 (2.00–12.00)	0.637
a:includes American Indian/AK Native, Asian/Pacific Islander				
b:positive histology/positive exfoliative cytology				
c:clinical diagnosis/direct visualization/positive laboratory test				
d:divorced/separated/single (never married)/unmarried or domestic partner/widowed				

Of all the patients, 81.7% were male, and 69.5% were white in race. Patients older than 60 accounted for 54.3%, which were the largest proportion of the population. The AFP level was elevated in 74.82% of patients, and 14.0% of patients were grade III/IV for the Edmondson-Steiner classification. More than half (86.3%) of the patients did not receive radiation treatment. The same trend was observed for surgery to the liver/LN. More than 90% of patients did not undergo surgery or lymph nodes dissection. The median (Q1-Q3) follow-up time of the patients was 5.00(2.00–12.00) months. Finally, we found that there was no significant difference in sex, age group, race, grade, T stage, diagnostic confirmation, surgery to the liver, surgery to LNs, brain metastasis, intrahepatic metastasis, bone metastasis, chemotherapy, radiation recode, insurance recode, marital status, AFP, fibrosis score, tumor size group, M stage, survival months between the training group and validation group. The incidence of pulmonary metastasis was different between the two groups. The incidence was higher in the training group than in the validation group, but there was no significant difference between the training group and the overall population.

Prognostic factors for HCC patients with lymph node metastasis (N1)

As shown in Table 2, in the univariate analysis, grade, T stage ,surgery to the liver, surgery to LN, bone metastasis, brain metastases, pulmonary metastasis, chemotherapy, radiation recode, Insurance recode, AFP, tumor size group, fibrosis score, M stage were associated with overall survival (OS).

Table 2
Univariate analysis of overall survival for the primary group

Variables	Univariate analysis		
	HR	95%CI	P-value
Sex			
Male	1(reference)		
Female	0.92	1.1–0.76	0.3518
Age group			
18–60	1(reference)		
≥ 61	0.91	1.04–0.79	0.1714
Race			
White	1(reference)		
Black	1.01	1.22–0.84	0.8917
Other	0.95	1.18–0.77	0.66
Grade			
Grades I + II	1(reference)		
Grades III + IV	1.66	2.13–1.3	< 0.0001
Unknown	1.22	1.46–1.01	0.0366
T Stage			
T1	1(reference)		
T2	0.98	1.24–0.76	0.8385
T3	1.46	1.77–1.21	0.0001
T4	1.73	2.28–1.32	< 0.0001
Diagnostic confirmation			
Positive histology	1(reference)		
Clinical diagnosis only	0.92	1.06–0.79	0.2353
Surgery to the liver			
No surgery	1(reference)		
Surgery	0.25	0.36 – 0.17	< 0.0001
Surgery to LN			

Variables	Univariate analysis		
	HR	95%CI	P-value
None	1(reference)		
LN removed	0.45	0.65 – 0.31	< 0.0001
Bone metastasis			
No	1(reference)		
Yes	1.5	1.9–1.19	0.0006
Brain metastasls			
No	1(reference)		
Yes	3.4	7.18–1.61	0.0013
Intrahepatic metastasis			
No	1(reference)		
Yes	0.87	1.33–0.57	0.5116
Pulmonary metastasis			
No	1(reference)		
Yes	1.82	2.22–1.49	< 0.0001
Chemotherapy			
No	1(reference)		
Yes	0.64	0.74 – 0.56	< 0.0001
Radiation recode			
No	1(reference)		
Yes	0.79	0.97 – 0.64	0.0271
Insurance Recode			
Insured	1(reference)		
Uninsured	1.43	1.91–1.07	0.0146
Marital status			
Married	1(reference)		
Single (never married)	0.9	1.03–0.78	0.1393
AFP			

Variables	Univariate analysis		
	HR	95%CI	P-value
Positive/elevated	1(reference)		
Negative/normal	0.62	0.76 – 0.5	< 0.0001
Unknown	0.93	1.17–0.73	0.5328
Fibrosis score			
Unknown	1(reference)		
0–4	0.67	0.94 – 0.49	0.0185
5–6	0.9	1.08–0.75	0.2515
Tumor size group(mm)			
0–20	1(reference)		
21–50	1.09	1.59–0.75	0.6545
51–100	1.49	2.15–1.04	0.03
≥ 101	1.74	2.53–1.2	0.0036
M Stage			
M0	1(reference)		
M1	1.69	1.94–1.46	< 0.0001

To reduce the risk of over-fitting our model, we applied the Lasso regression method, which can compress partial factorial regression coefficients to zero^[24]. The glmnet package was used in the R software. 10x cross validation was applied to search for the least partial likelihood deviance which can represent the complexity of the model. A simplified model can avoid overfitting as much as possible. Finally, the variables that we chose when the partial likelihood deviance is least (lambda= -4.37) were age group, grade, T stage, surgery to the liver, surgery to LNs, bone metastasis, brain metastasis, pulmonary metastasis, Intrahepatic metastasis, chemotherapy, radiation recode, Insurance recode, AFP, tumor size group, fibrosis score, M stage .Combined with the results of Cox univariate analysis, we removed the variables of age group and intrahepatic metastasis and 14 variables were included in multivariate analysis. For more details see Fig. 2a-b.

In the multivariate analysis, grade, T Stage, surgery to the liver, chemotherapy, radiation recode, AFP, fibrosis score, tumor size group, M stage remained independently related to OS. The details are summarized in Table 3. Collinearity diagnostics were examined for potential presence of collinearity between independent variables, and VIF (variance inflation factors) ≤ 5 .

Table 3
Multivariate analysis of overall survival for the primary group

Variables	multivariate analysis		
	HR	95%CI	p-value
Grade			
Grades I + II	1(reference)		
Grades III + IV	1.56	1.21- 2.00	0.0006
Unknown	1.15	0.95–1.38	0.1513
T Stage			
T1	1(reference)		
T2	1.1	0.85–1.43	0.4718
T3	1.25	1.02–1.54	0.0328
T4	1.2	0.89–1.60	0.2309
Surgery to the liver			
No surgery	1(reference)		
Surgery	0.3	0.20–0.44	< 0.0001
Surgery to LN			
None	1(reference)		
LN removed	0.76	0.51–1.14	0.1815
Bone metastasis			
No	1(reference)		
Yes	1.26	0.97–1.65	0.0872
Brain metastases			
No	1(reference)		
Yes	1.96	0.92–4.19	0.0823
Pulmonary metastasis			
No	1(reference)		
Yes	1.14	0.91–1.43	0.2593
Chemotherapy			
No	1(reference)		

Variables	multivariate analysis		
	HR	95%CI	p-value
Yes	0.57	0.50–0.66	< 0.0001
Radiation recode			
No	1(reference)		
Yes	0.63	0.50–0.79	< 0.0001
Insurance recode			
Insured	1(reference)		
Uninsured	1.13	0.84–1.51	0.4294
AFP			
Positive/elevated	1(reference)		
Negative/normal	0.66	0.53–0.82	0.0002
Unknown	0.84	0.66–1.07	0.1618
Fibrosis score			
Unknown	1(reference)		
0–4	0.63	0.45–0.89	0.0078
5–6	0.94	0.79–1.14	0.5484
Tumor size group(mm)			
0–20	1(reference)		
21–50	1.21	0.82–1.77	0.3339
51–100	1.45	0.98–2.13	0.0616
≥ 101	1.81	1.21–2.71	0.0037
M stage			
M0	1(reference)		
M1	1.4	1.18–1.67	0.0001

Construction And Validation Of The Nomogram

A nomogram was created based on the significant variables of the multivariate Cox regression analysis, as shown in Fig. 3. In the training group, the Harrell's C-index for OS prediction was 0.70 (95% CI, 0.68 to

0.72), and the area under ROC curve (AUC) for 1 and 2 years was 0.76 and 0.80, respectively. In the validation group, the Harrell's C index for OS prediction was 0.73 (95% CI, 0.70 to 0.76), and the area under ROC curve (AUC) for 1 and 2 year was 0.79 and 0.75. However, in the training and validation groups, the C-index of the AJCC staging system was only 0.58 (95% CI, 0.56 to 0.60) and 0.59 (95% CI, 0.56 to 0.62), respectively. The nomogram model showed better discrimination.

We further assessed the accuracy of our model predictions by calibration plot. The calibration curves were drawn according to the training and validation groups. The calibration plot for the probability of survival at 1 and 2 years showed good agreement between the prediction by nomogram and actual observation. See further details in Fig. 4a-d.

Furthermore, the decision curve analysis (DCA) was plotted to observe the clinical benefits to the patient. The DCA indicated that our nomogram had a positive net benefit with a wide scale of threshold probabilities in the training and validation groups. See further details in Fig. 5a-d.

The establishment of different risk groups according to the model

According to Cox regression model, the risk score of each training group patient in the model was calculated. The risk score ranged from 0.079 to 3.773. The X-tile program was used to select optimal cut-off for risk score to distinguish the difference in patient survival. The point of grouping was 1.12 when the training group was divided into a low-risk group (score ≤ 1.12) and a high-risk group (score > 1.12). The corresponding total points was 261. The survival curves of the training and validation groups were drawn, and the log-rank test was performed, with the p-value < 0.001 . See further details in Fig. 6a-6b.

According to existing reports, the incidence of lymph node metastasis during the treatment of liver cancer is 1.6–5.9%, while it is 25.5% on autopsy, indicating that lymph node metastasis might be neglected^[11]. In our research, 6.6% of all HCC patients had LN metastasis, which were in line the previous studies. Regarding the prognosis of such patients, the emergence of novel treatments, including radiation, ablation, interventional therapy, and sorafenib, has improved the prognosis^[17, 25–27]. Our study also showed that the HCC patients with LN metastasis can benefit from radiation and chemotherapy. In terms of surgical treatment, our study showed that patients with LN metastasis had no benefit from lymphadenectomy, and previous studies have shown similar results^[28–30]. However, our research analysis showed a benefit for surgery at the primary site: the liver. We consider three possible reasons for the finding. First of all, more than 38% of patients included in our study were diagnosed without histology or cytology. Whereas the diagnosis of primary liver cancer can be made by clinical diagnosis, imaging and laboratory examinations^[31–33], we included patients whose diagnoses were established according to clinical diagnostic criteria. In this case, the diagnosis of lymph node metastasis in many patients was based on clinical and radiographic findings and many patients might not actually have had cancerous lymph node metastasis. HCC patients often have chronic inflammation of the liver, such as hepatitis B,

hepatitis C and on-alcoholic fatty liver disease. Inflammation of the liver can also cause enlarged lymph nodes and a study showed that the proportion of enlarged lymph nodes in hepatitis B virus-infected patients reached 9.4%^[34]. According to the above discussion, in the absence of a pathological diagnosis of the lymph node, HCC patients with LN metastasis can be classified with cancerous metastasis and benign perihepatic lymph node enlargement (PLNE). A study showed that PLNE was an independent positive prognostic factor that might improve the prognosis of HCC patients^[35]. In this case, some patients might benefit from surgery on the primary site. Second, only a few patients had their livers operated on, which might have affected the results of our statistical analysis. Third, patients undergoing surgery might have better basic indicators, such as performance status and liver function, than non-surgical patients. These facts might affect the outcome. In summary, Cytological or histological confirmation is recommended to determine whether lymph node metastasis is truly present, especially as to the patients with hepatitis, and we should choose the treatment more carefully for HCC patients without pathological diagnosis of LN metastasis.

The Edmondson-Steiner classification indicates a pathological grade. A higher grade indicates a lower degree of differentiation and a higher degree of malignancy. Some reports in the literature have shown a relationship between Edmondson-Steiner classification and HCC patients' prognosis, and a higher grade indicates that the patients' prognosis is likely to be worse^[36, 37]. Zhang et al reviewed the degree of cirrhosis affecting the prognosis of patients and found that the histological severity of cirrhosis is a vital adverse factor that affects the long-term outcomes of HCC patients undergoing liver surgery^[38]. Similar results have been found in many reports^[39–41]. The effect of AFP levels on patient prognosis is controversial. Some studies have found that elevated AFP levels could worsen HCC patients' prognosis^[42–44]. Other scholars have found that AFP has no significant effect on patient survival^[45], perhaps because the studies are from different populations. In our study, we found that an elevated AFP level is an adverse prognostic factor.

With respect to pathological stage and tumor characteristics, T Stage, M Stage and tumor size group were related to the prognosis of HCC patients with LN metastasis. Wu et al found that tumor size could be used as an independent risk predictor associated with survival in HCC^[46]. In combination with T stage, we grouped the patients according to different tumor sizes and obtained similar conclusions. The effect of M stage on patient prognosis is not in doubt. The previous literature has shown that the prognosis of HCC patients with different metastatic sites is different^[47, 48]. Therefore, we included the following prognostic indicators: bone metastasis, brain metastasis, intrahepatic metastasis, pulmonary metastasis and M Stage. Finally, we found that only M Stage of the above factors was an independent risk factor. This outcome suggests that differences in metastatic site might not be as important in such patients as in those with HCC without LN metastasis. T Stage was also an independent risk factor for worse prognosis. In general, with the increase in T stage, the prognosis of patients became worse. However, in our analysis, T3 stage patients had poorer survival than T4 stage patients. The 7th edition American Joint Committee on Cancer (AJCC) stage was used by SEER in the original data. According to the 7th edition of AJCC staging^[49], T stage includes not only information about the size of the tumor but also

about visceral vessel invasion and number of hepatic tumors. T3a indicates multiple tumors, at least one of which is > 5 cm. T3b indicates that the tumor has invaded the main trunk of the portal vein or/and hepatic vein, which would lead to worse prognosis^[50, 51], and it has been included in stage T4 by the 8th AJCC cancer staging manual. In the 7th edition AJCC staging manual, T4 is defined as the tumor invading adjacent organs except for the gallbladder or penetrating the serous membrane. Therefore, for patients with liver cancer with lymph node metastasis, the prognostic significance of the number of liver tumors and vascular invasion might be greater than that of the invasion of adjacent organs.

As previously mentioned, the prognosis of HCC patients with LN metastasis is improving, and some studies have shown that stage IV HCC patients demonstrated a different prognosis^[16–18]. Therefore, it is important to distinguish the difference in prognosis in such patients.

On the basis of identifying the risk factors, we built the nomogram model and verified it. The model could well distinguish the difference of prognoses of HCC patients with LN metastasis. It could provide a basis for the choice of treatment for such patients. Only under the circumstance of reasonable differentiation of patients with different prognoses can a reasonable treatment plan be put forward. The establishment of the model could help to better distinguish the different prognoses of HCC patients with LN metastasis and provide a basis for follow-up treatment. As far as I concerned, no similar studies have yet been performed. Comparing to other models which need to use some technologies, our model applies a number of clinically accessible indicators. We evaluated predictors that were clinically relevant, so that the model can be easily applied in clinical practice.

However, our research still has some shortcomings. First, bias is inevitable in this type of retrospective study. For example, we removed many patients with lymph node metastasis whose important clinical data were unknown. A number of important prognostic factors were also missing from the enrolled patients. Some significant prognostic values were not recorded in the SEER database, such as liver function tests, hepatitis B or hepatitis C infections, and details of chemotherapy, radiation therapy and surgery. Second, internal validation was used for the model which might affect the accuracy of the models in general HCC patients with LNs metastasis. Next, we should further validate this model with our own clinical data. Prospective, randomized, controlled studies must be further implemented

Conclusion

In summary, we showed that grade, surgery to the liver, T stage, chemotherapy, radiation recode, AFP, fibrosis score, tumor size group and M stage are independent risk factors for the prognosis of HCC patients with LN metastases. We established a nomogram to distinguish between patients with a good prognosis and those with a poor prognosis. Our nomogram proved to be highly accurate and usefulness by internal validation. A reasonable treatment could be devised according to different risk scores. Further studies are warranted.

List Of Abbreviations

HCC, Hepatocellular carcinoma; LN, Lymph node; SEER , Surveillance, Epidemiology, and End Results; C-index, concordance index; DCA, decision curve analysis; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer ; PFS , progression-free survival; OS, overall survival; DCA, decision curve analysis; PLNE ,perihepatic lymph node enlargemen.

Declarations

Acknowledgments

Not applicable

Author Contributions

All authors contributed significantly to this work. Kai Zhang, Changcheng Tao, Weiqi Rong performed the research study and collected the data; Kai Zhang and Jianxiong Wu analyzed the data; Kai Zhang, Jianxiong Wu and Weiqi Rong designed the research study; Kai Zhang wrote the paper; Weiqi Rong prepared all the Tables. All authors reviewed the manuscript. In addition, all authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This research was exempted by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China).

Consent for publication

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Author details

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Figures

Figure 1

The flow diagram of the patients' selection.

Figure 2

Lasso regression search for the optimal coefficient. (a) Lasso regression search for the optimal coefficient when the Lambda was -4.37. (b) 10x cross-validation was applied for search the Lambda when partial likelihood deviance was the least.

Figure 3

Nomogram predicting 1-and 2-year overall survival probability.

Figure 4

Calibration curve for 1 and 2 years in the training and validation group. (a) Calibration curve for 1 year in the training group. (b) Calibration curve for 2 years in the training group. (c) Calibration curve for 1 year in the validation group. (d) Calibration curve for 2 year in the validation group.

Figure 5

Clinical decision curve analysis (DCA) of the traing and validation group in terms of 1 and 2 years. (a) Clinical decision curve analysis (DCA) of the traing group in terms of 1 year. (b) Clinical decision curve analysis (DCA) of the traing group in terms of 2 years. (c) Decision curve analysis (DCA) of the validation group in terms of 1 year. (d) Decision curve analysis (DCA) of the validation group in terms of 2 years.

Figure 6

Survival curves of the training and validation of different groups according to risk score. (a) Survival curves of the training set of different groups according to risk score. (b) Survival curves of validation set of different groups according to risk score.