Original Article

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

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Background: The presence of lymph node (LN) metastases is associated with poor survival outcomes in hepatocellular carcinoma (HCC) patients. Because of the low probability of LN metastasis, research into the prognoses of these patients is difficult. The present study developed a nomogram model to predict the prognosis of HCC patients with LN metastasis.

Methods: This retrospective, noninterventional study enrolled patients from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. The following inclusion criteria were used: (I) site recode ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) of 8170–8175 and malignant histological behavior; (II) seventh edition American Joint Committee on Cancer (AJCC) stage N1; (III) older than 18 years; and (IV) available information. Potential prognostic factors were collected from the SEER database; the primary outcomes of interest were overall survival (OS) and disease status. Cox and Lasso regression were used to investigate independent prognostic factors for survival. A prognostic nomogram using these independent risk factors was constructed. The concordance index (C-index) and calibration curves were used to evaluate the model's predictive performance. The clinical benefit was assessed via decision curve analysis (DCA).

Results: Patients were randomized into a training group (944 patients) and a validation group (402 patients) in a 70:30 ratio. Grade, T stage, liver surgery, chemotherapy, radiation recode, alpha-fetoprotein level, fibrosis score, tumor size group, and M stage were selected as independent prognostic factors, and a nomogram was developed using these variables. The C-indices of the training and validation groups were 0.70 and 0.73, respectively. Calibration curves for the probability of survival showed good agreement. DCA indicated that the nomogram had positive net benefits.

Conclusions: The constructed nomogram may assist clinicians in predicting the prognosis of HCC patients with LN metastasis and may provide a rationale for treatment options.

Keywords: Hepatocellular carcinoma (HCC); prognosis; lymph nodes metastasis; prediction model; nomogram

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the seventh most prevalent tumor worldwide, with 841,080 new cases annually (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 30–50% of patients during the course of the disease (5). The lymph nodes (LN) are the second most common site of extrahepatic metastases in HCC (6), but the incidence of LN metastasis varies. In some studies with large sample sizes, an incidence ranging from 1.23% to 7.5% has been reported (7-9). Other studies have shown that this incidence may reach approximately 30% of the average rate (10,11). Although a large proportion of the data were derived from autopsies, the occurrence of LN metastasis may be underestimated, and more patients may have LN metastasis.

The Barcelona staging assigns patients with LN metastasis to the C phase (12), and the primary treatment for these patients is systemic therapy. The same situation is also observed in other staging systems, such as the AJCC staging system and the National Comprehensive Cancer Network (NCCN) guidelines (13), which may be due the fact that HCC patients with LN metastasis have a poor prognosis. A recent study of 2,043 cases showed that the median progression-free survival (PFS) after surgery was 16.3 months for HCC patients without nodal involvement, but only 5.8 months for the group with LN metastasis (9). The 1- and 3-year survival rates of HCC patients who do not have LN metastasis were 81% and 62%, respectively. However, the 1- and 3-year overall survival (OS) rates were only 62% and 31%, respectively, for HCC patients with nodal involvement (14). It is undeniable that LN metastasis is a poor prognostic factor for HCC (8,15). Nevertheless, the prognosis of HCC patients with LN metastases has improved with the development of various treatments and drugs in recent years (16-18). Previous studies have shown that patients diagnosed with stage IV HCC had a different prognosis (17). The prognosis of HCC patients with LN metastases was different in one study, although all HCC patients were treated with similar external beam radiotherapy (19). Selection of the appropriate treatment should be based on accurate identification of different prognostic groups. Therefore, it is essential to accurately stratify patients according to different prognoses. Because of LN metastasis low probability, grouping of patients requires a large sample size, which contributes to the difficulty of the implementation process of these studies. In summary, no study to date has constructed a prognostic model for risk assessment of HCC patients with LN metastasis despite evidence supporting different prognostic outcomes of HCC patients with LN metastases. Accordingly, it is essential to distinguish the different prognostic groups of HCC patients with LN metastasis to allow clinicians to make reasonable treatment decisions.

The nomogram is an efficient statistical tool that uses a graphical method to achieve a model that accurately predicts the outcomes of individual patients (20). To the best of our knowledge, a nomogram model that predicts OS in HCC patients with LN metastases does not exist. As previously mentioned, this type of study is difficult because of the reported low incidence of LN and the need for a large sample size. To obtain an expanded 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. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1876).

Methods

Ethics statement

This study was exempted by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because the data were obtained from a publicly available database, this study was recognized as a retrospective, non-interventional 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 SEER database collects several types of data from electronic pathology reports of cancer patients and is an authoritative source of information on cancer, covering approximately 34.6% of the population in the United States of America (http://seer.cancer.gov/). The data were obtained using the SEER*Stat software (version 8.3.6). Because some essential prognostic factors were not available before 2010, patients diagnosed

with HCC with LN metastases from 2010 to 2015 were finally included in our study. We divided these patients into a training group and a validation group.

The following inclusion criteria were used: (I) HCC patients from 2010 to 2015 (histological type ICD-O-3=8170-8175), for whom the site recode ICD-O-3/WHO 2008 was liver, and the histological behavior was malignant; (II) lymph-node metastasis (N1) patients were enrolled based on the seventh edition of the AJCC TNM staging; (III) patients older than 18 years old; and (IV) follow-up data were available. The following exclusion criteria were used: (I) survival months were unknown or zero; (II) samples without follow-up information data; (III) demographic information was not complete; (IV) treatment data were missing; (V) data on vital prognostic factors and tumor staging information were missing; and (VI) cause of death classification was not the primary tumor. Patients were randomized into a training group (accounting for 70%) and validation group (accounting for 30%) using the caret package and the seed was set at 1988. Additional details are shown in *Figure 1*. The primary outcomes in our study were OS and clinical status. Nineteen potential prognostic factors for HCC were included in the present study, comprising the following three aspects: (I) the general condition of the patient (e.g., sex, age, marital status, race, and liver fibrosis score); (II) tumor-specific factors (e.g., tumor size, tumor grade, alpha-fetoprotein (AFP) level, metastasis status); and (III) treatment factors (e.g., surgery to the liver or LN and whether chemotherapy and/or radiotherapy was administered). Detailed information on potential prognostic factors is listed in *Table 1*. The SEER database is an authoritative source of follow-up information for cancer patients. Clinical follow-up was obtained from the hospital electronic records.

Statistical analysis

The data from the SEER database comprised information on 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 due to other causes. Categorical variables were compared between different groups using the chi-squared test or Fisher's exact test when necessary. The Mann-Whitney U-test was used for comparisons of numerical variables. Survival curves were generated using the Kaplan-Meier method, and survival distributions were compared using the log-rank test. Univariate and multivariate Cox regression models were used to screen for prognostic factors associated with survival in the training group. According to the multivariate analysis results, 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 times were used to compare the discriminative ability of the nomogram and the AJCC seventh edition (IVA/IVB) in the training and validation groups. Calibration curves were created to assess the predictive accuracy in the two groups (21). Statistical analyses were performed using 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

Patient characteristics in the training and validation groups

The flow diagram of the research selection process is shown in *Figure 1*. A total of 40,173 HCC patients from 2010 to 2015 were included in our study, including 2,662 cases (6.6%) with LN metastasis, and 37,511 cases (94.3%) without LN metastasis. According to the exclusion criteria, 1,346 patients were ultimately enrolled. We allocated 944 patients to the training group, and the other patients to the validation group. *Table 1* summarizes the clinical information of the enrolled patients.

Among all the 1,346 patients, 81.7% were male, and 69.5% were white. Patients older than 60 years accounted for 54.3%, which was the largest proportion of the population. The AFP level was increased in 74.8% of patients, and 14.0% were grade III/IV based on the Edmondson-Steiner classification. A total of 86.3% of the patients did not receive radiation treatment. The same trend was observed for surgery to the liver/LNs. More than 90% of patients did not undergo surgery or LN dissection. The median (Q1–Q3) follow-up time of the patients was 5 [2–12] months. We found no significant differences 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,

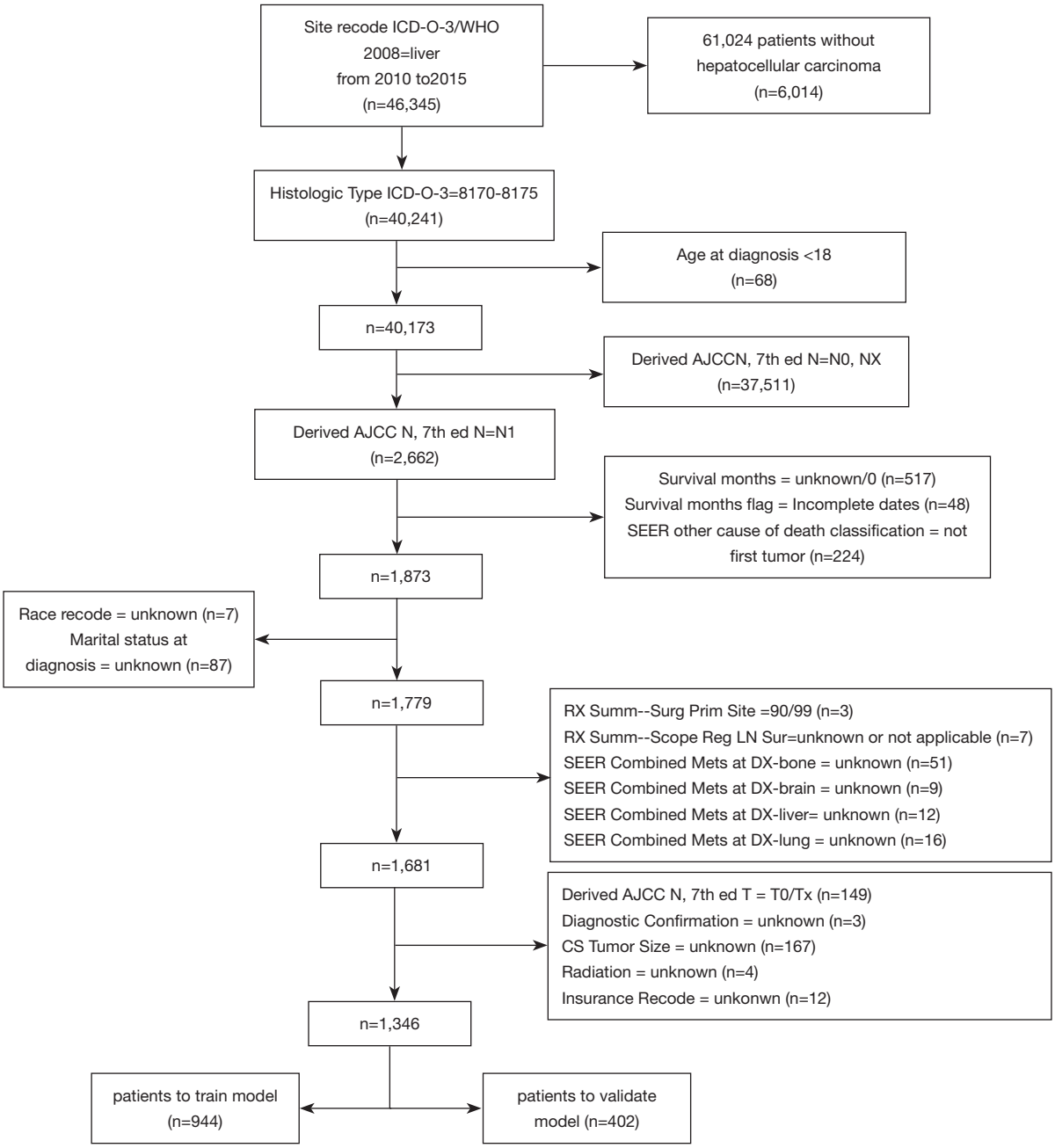

Figure 1 The flow diagram of the research selection process.

tumor size group, M stage, or survival months between the training group and validation group. The incidence of pulmonary metastasis was different between the two groups and was higher in the training group than the validation group, although 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*, univariate analysis revealed that grade, T stage, surgery to the liver, surgery to LN, bone metastasis, brain metastases, pulmonary metastasis, chemotherapy,

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

Variable	All patients	Training group	Validation group	P value
Number of patients	1,346	944	402	
Sex				0.731
Male	1,099 (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
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%)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All patients	Training group	Validation group	P value
Intrahepatic metastasis				0.196
No	1,302 (96.73%)	917 (97.14%)	385 (95.77%)	
Yes	44 (3.27%)	27 (2.86%)	17 (4.23%)	
Pulmonary metastasis				0.046
No	1,182 (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%)	
yes	749 (55.65%)	530 (56.14%)	219 (54.48%)	
Radiation recode				0.13
No	1,161 (86.26%)	823 (87.18%)	338 (84.08%)	
yes	185 (13.74%)	121 (12.82%)	64 (15.92%)	
Insurance recode				0.194
Insured and any medicaid	1,257 (93.39%)	887 (93.96%)	370 (92.04%)	
Uninsured	89 (6.61%)	57 (6.04%)	32 (7.96%)	
Marital status				0.102
Unmarried[d]	662 (49.18%)	478 (50.64%)	184 (45.77%)	
Married	684 (50.82%)	466 (49.36%)	218 (54.23%)	
AFP				0.461
Positive/elevated	999 (74.22%)	707 (74.89%)	292 (72.64%)	
Negative/normal	198 (14.71%)	139 (14.72%)	59 (14.68%)	
Unknown[a]	149 (11.07%)	98 (10.38%)	51 (12.69%)	
Fibrosis score				0.692
0–4	1,008 (74.89%)	713 (75.53%)	295 (73.38%)	
5–6	75 (5.57%)	52 (5.51%)	23 (5.72%)	
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%)	
51–100	601 (44.65%)	431 (45.66%)	170 (42.29%)	
≥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.

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			
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 metastasis			
No	1 (reference)		
Yes	3.4	7.18–1.61	0.0013

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis		
	HR	95% CI	P value
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			
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

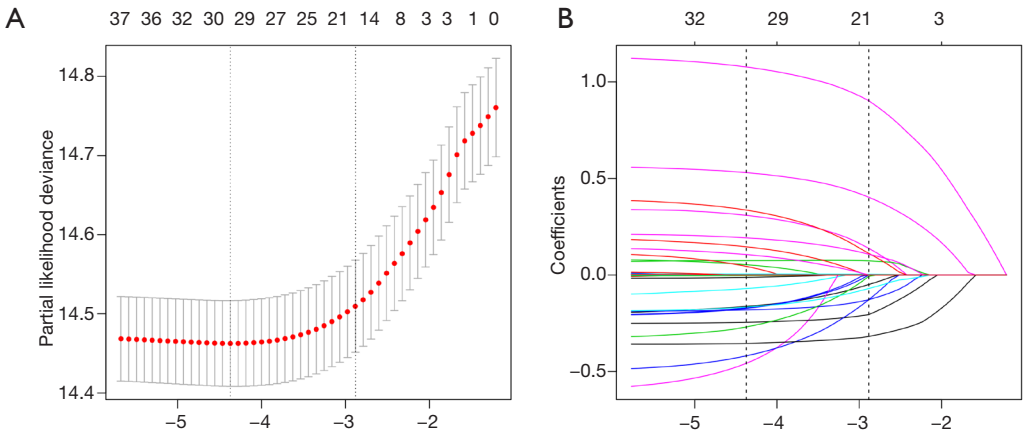

Figure 2 Lasso regression to determine the variables included in the model. (A) Lasso regression search for the optimal coefficient when lambda was –4.37. (B) A 10× cross-validation approach used to determine lambda at the least partial likelihood deviance.

radiation recode, Insurance recode, AFP, tumor size group, fibrosis score, and M stage were associated with OS.

We used the Lasso regression method to reduce the risk of over-fitting of our model, which compresses partial factorial regression coefficients to zero (22). The glmnet package was used in R software. A 10× cross-validation was applied to search for the least partial likelihood deviance, which represented the complexity of the model. A simplified model avoids over-fitting as much as possible. The variables that we chose when the partial likelihood deviance was lowest (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, and M stage. Combined with the results of the univariate Cox analysis, we removed the variables of age group and intrahepatic metastasis, and 14 variables were included in multivariate analysis (*Figure 2*).

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

Construction and validation of the nomogram

A nomogram was created based on the significant variables determined by multivariate Cox regression analysis, as shown in *Figure 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 AUC values for 1 and 2 years were 0.76 and 0.80, respectively. Harrell's C index for OS prediction in the validation group was 0.73 (95% CI, 0.70 to 0.76), and the AUC values for 1 and 2 years were 0.79 and 0.75, respectively. However, the C-index values of the AJCC staging system were only 0.58 (95% CI, 0.56 to 0.60) and 0.59 (95% CI, 0.56 to 0.62) in the training and validation groups, respectively. The nomogram model showed good discrimination.

We further assessed the accuracy of our model predictions using a calibration plot. The calibration curves were drawn according to the training and validation groups. The calibration plots for the probability of survival at 1 and 2 years showed good agreement between the prediction by nomogram and actual observations (*Figure 4*).

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 (*Figure 5*).

Discussion

According to previous reports, the incidence of LN metastasis during the treatment of liver cancer varied from 1.6% to 5.9%, and was 25.5% on autopsy, which indicates that incidence of LN metastasis may be overlooked during clinical assessment (11). In our study, 6.6% of all HCC patients presented LN metastasis, which is consistent with previous studies. The emergence of novel treatments,

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)		
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

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Multivariate analysis		
	HR	95% CI	P value
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

including radiation, ablation, interventional therapy, and sorafenib, has improved the prognosis of these patients (18,23-25). Our study also showed that HCC patients with LN metastasis benefited from radiation and chemotherapy; we also found that patients with LN metastasis did not benefit from lymphadenectomy, and previous studies showed similar results (26-28). However, a benefit for surgery at the primary site (i.e., the liver) was detected in our study. We considered three possible reasons for these findings. First, over 38% of the patients included in our study were diagnosed without histology or cytology evaluation. The diagnosis of primary liver cancer is made via clinical diagnosis, imaging, and laboratory examinations (29-31). Therefore, we included patients whose diagnoses were established according to clinical diagnostic criteria. The diagnosis of LN metastasis in many patients was based on clinical and radiographic findings, and many patients may not have had cancerous LN metastasis. HCC patients often have chronic inflammation of the liver, such as hepatitis B, hepatitis C, and non-alcoholic fatty liver disease. Inflammation of the liver may also enlarge LNs, and one study showed that the proportion of enlarged LNs in hepatitis B virus-infected patients reached 9.4% (32). Hence, HCC patients with LN metastasis may be classified with cancerous metastasis and benign perihepatic LN enlargement (PLNE) in the absence of pathological diagnosis of the LN. One study showed that PLNE was an independent positive prognostic factor that may improve the prognosis of HCC patients (33). Some patients may benefit from surgery to the primary site in these cases. Second, only a few patients underwent liver surgery, which may have affected our statistical analysis. Third, patients undergoing surgery may have better basic indicators, such as performance status and liver function, than non-surgical patients. These facts may affect patient outcome. In summary, cytological or histological confirmation is recommended to determine whether LN metastasis is truly present, especially in patients with hepatitis, and thus we should choose treatment more carefully for HCC patients without pathological diagnosis of LN metastasis.

The Edmondson-Steiner classification scores pathological grade, whereby a higher grade indicates a lower degree of

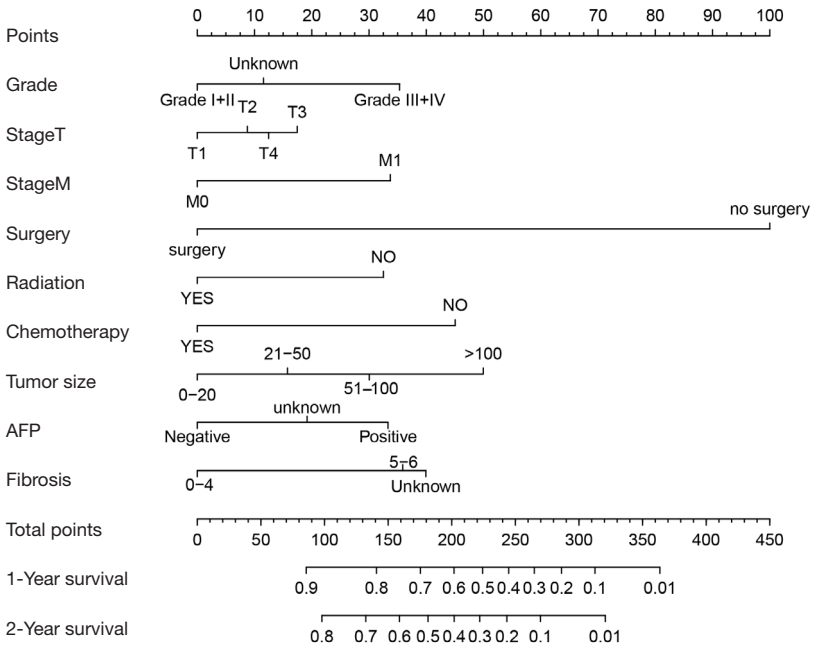

Figure 3 Nomogram predictions of 1- and 2-year overall survival probability.

differentiation and a higher degree of malignancy. Some reports have reported a relationship between the Edmondson-Steiner classification and HCC patient prognosis. A higher grade indicates that the prognosis is likely to be worse (34,35). Zhang *et al.* reviewed whether the degree of cirrhosis affected the prognosis of patients. They found that the histological severity of cirrhosis was a vital adverse factor that affected the long-term outcomes of HCC patients undergoing liver surgery (36). Similar results have been found in three reports (37-39). The effects of AFP levels on patient prognosis are controversial. Some studies found that elevated AFP levels indicated a worse HCC patient prognosis (40-42). Other scholars found that AFP exerted no significant effect on patient survival (43), perhaps because the studies were performed in different populations. Our findings indicated that elevated AFP levels were an adverse prognostic factor.

With respect to pathological stage and tumor characteristics, T stage, M stage, and tumor size were associated with the prognosis of HCC patients with LN metastasis. Wu *et al.* determined that tumor size may be used as an independent risk predictor associated with survival in HCC (44). In combination with the T stage, we grouped patients according to different tumor sizes and obtained similar conclusions. The effects of the M stage on patient prognosis is not in doubt. Previous studies have shown that the prognosis of HCC patients with different metastatic sites was different (45,46). We included the following prognostic indicators: bone metastasis, brain metastasis, intrahepatic metastasis, pulmonary metastasis, and M stage, and our findings showed that only the M stage was an independent risk factor, which suggests that differences in the metastatic site may not be as significant in these patients compared to HCC without LN metastasis. The T stage was also an independent risk factor for worse prognosis. In general, the prognosis of patients worsened with an increase in the T stage. However, T3 stage patients exhibited greater reduced survival than T4 stage patients in our analysis. The AJCC stage was used by SEER in the original data. According to the seventh edition of AJCC staging (47), the T stage includes information about the size of the tumor, visceral vessel invasion and the number of hepatic tumors. T3a indicates multiple tumors, at least one of which is >5 cm. T3b indicates that cancer has invaded the main trunk of the portal vein or/and hepatic vein, which would lead to worse prognosis (48,49), and has been included in stage T4 of the eighth AJCC cancer staging manual. In the seventh edition AJCC staging manual, T4 was defined as the tumor invading adjacent organs, except the gallbladder, or penetrating the serous membrane. Therefore, for patients with liver cancer with LN metastasis, the prognostic significance of the number of liver tumors and vascular invasion may be greater than the invasion of adjacent organs.

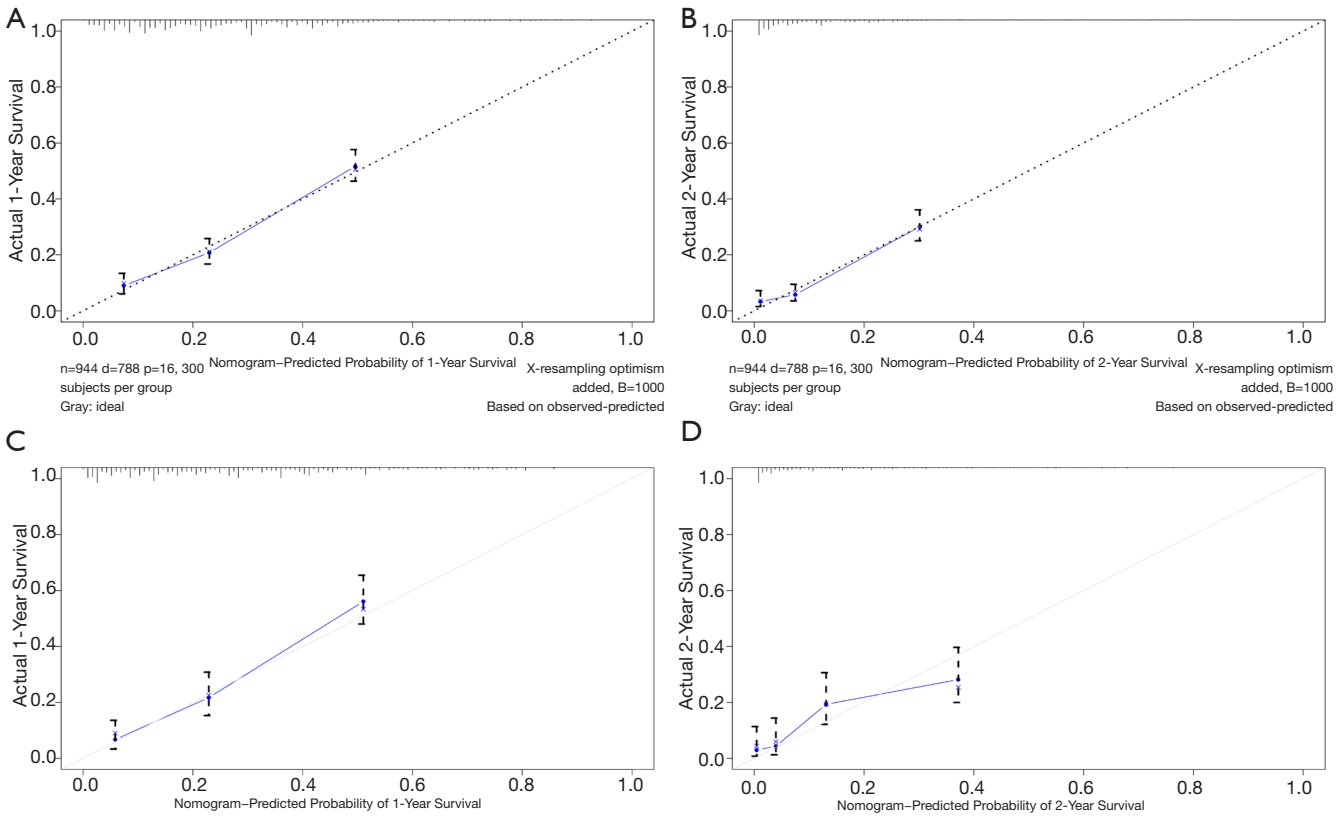

Figure 4 Calibration curves for 1- and 2-year survival in the training group (A,B) and in the validation group (C,D).

As previously mentioned, the prognosis of HCC patients with LN metastasis is improving, and some studies have shown that stage IV HCC patients had a different prognosis (16-18). Thus, it is essential to distinguish differences in the prognosis of these patients.

In this study, we identified risk factors and constructed and validated a nomogram model that distinguished differences in the prognoses of HCC patients with LN metastasis, and thus provides a basis for the choice of treatment for these patients. Only by reasonable stratification of patients with different prognoses can a reasonable treatment plan be proposed. The establishment of the model may help to distinguish the differential prognoses of HCC patients with LN metastasis and may provide a basis for follow-up treatment. To the best of our knowledge, no similar studies have been performed. Compared to other models that require some technology to generate scores, our model used several clinically accessible indicators. We evaluated predictors that were clinically relevant so that the model could easily be applied in clinical practice.

However, our study has some limitations. First, a bias is inevitable in this type of retrospective study. For example, we removed many patients with LN metastasis for whom important clinical data were not available. This omission would cause a selection bias in our study because the enrolled patients may not be representative of this patient subset. Details relative to many 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, history of hepatitis B or hepatitis C infections, details of chemotherapy, radiation therapy, and surgery. Second, internal validation was used for the model, which may in general affect the accuracy of models HCC patients with LN metastasis. We will validate this model in the future using our clinical data. Prospective, randomized, controlled studies should also be performed.

Conclusions

In summary, our study showed that grade, surgery to the liver, T stage, chemotherapy, radiation recode, AFP, fibrosis score, tumor size group, and M stage were independent risk factors for the prognosis of HCC patients with LN

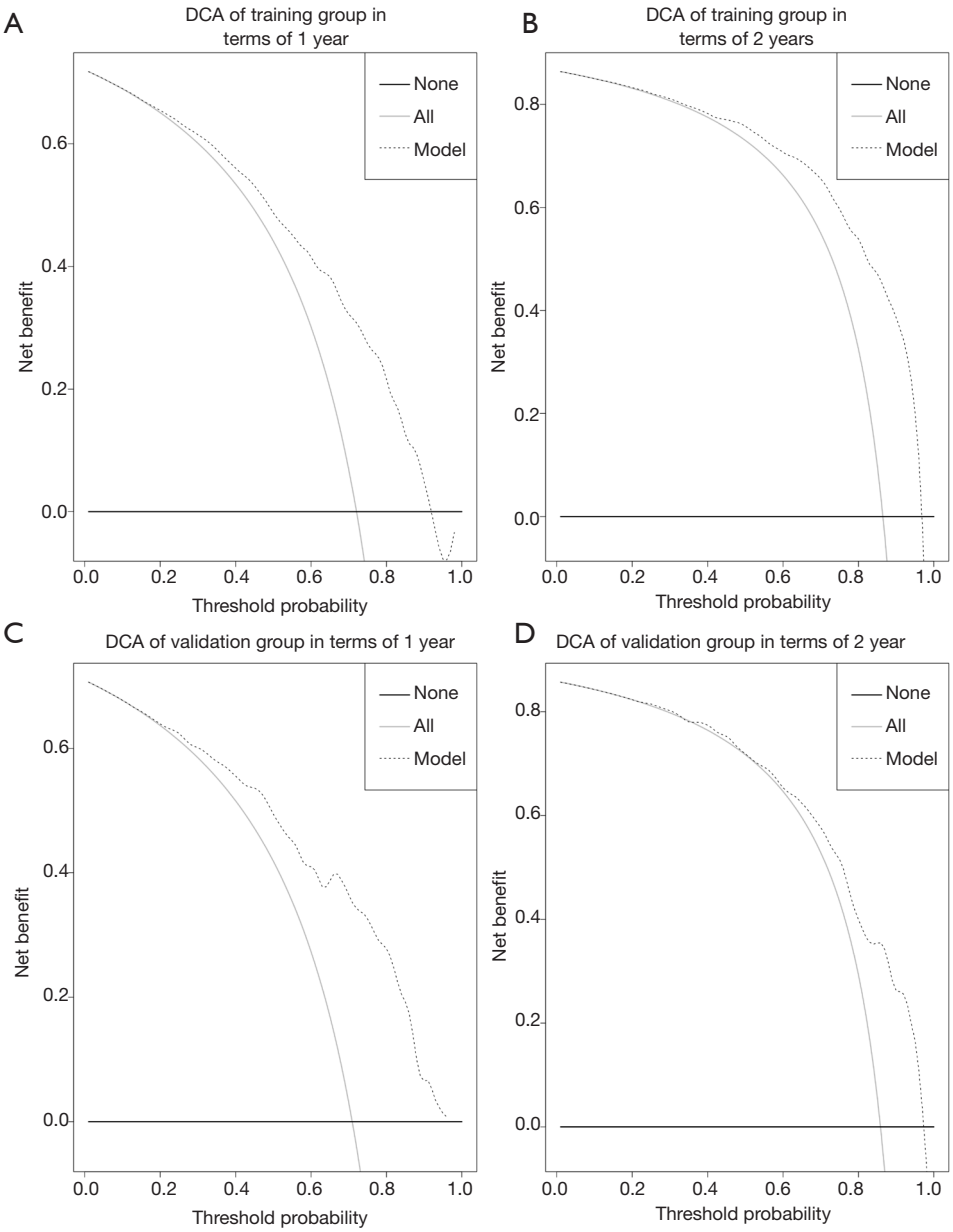

Figure 5 Clinical decision curve analysis (DCA) of the training group (A,B) and validation group (C,D) for 1- and 2-year clinical benefits.

metastases. Furthermore, we established a nomogram that may assist clinicians in predicting the prognosis of HCC patients with LN metastasis in order to provide a practical rationale for patient treatment.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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