BMJ Open

Prognostic risk factor analysis and nomogram construction for primary liver cancer in elderly patients based on SEER database

Fangyuan Li,[1] Ting Zheng,[1] Xuewei Gu [2]

To cite: Li F, Zheng T, Gu X. Prognostic risk factor analysis and nomogram construction for primary liver cancer in elderly patients based on SEER database. *BMJ Open* 2022;**12**:e051946. doi:10.1136/bmjopen-2021-051946

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051946).

Received 01 April 2021
Accepted 28 September 2022

[1]Department of Medical Oncology, The First People's Hospital of Linping District, Hangzhou, Zhejiang, China
[2]Department of Gastroenterology, Zhuji People's Hospital, Zhuji, Zhejiang, China

Correspondence to
Dr Xuewei Gu;
gxwgxw1234567@163.com

ABSTRACT

Objective To evaluate the risk factors and construct a nomogram model for the prognosis of primary liver cancer in the elderly based on the data from the US SEER database.

Methods The latest data of patients with primary liver cancer were extracted from the SEER database using SEER*STAT software, and the required variables were included. The data were screened and then divided into a training cohort and a validation cohort. A nomogram model was constructed by screening the variables through univariate and multivariate Cox analysis. The C-Index, ROC and calibration curves were used for model evaluation.

Results A total of 10 824 eligible cases from 2004 to 2017 were extracted, among which, 7757 cases were included in the training cohort and 3247 in the validation cohort. The C-Index of the model was 0.747 (in the training cohort) and 0.773 (in the validation cohort). The 3-year area under the curve (AUCs) of the training and the validation cohorts were 0.760 and 0.750, and the 5-year AUCs of the two cohorts were 0.761 and 0.748. The calibration curves showed an ideal calibration of the constructed model.

Conclusions The nomogram model constructed followed by Cox regression analysis showed moderate calibration and discrimination property, and can provide reference to a certain extent for furture clinical application of primary liver cancer in the elderly.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A large and sufficient number of elderly cases with liver cancer were collected from the SEER database.
⇒ A novel and ideal prognostic model was constructed for the elderly patients with liver cancer.
⇒ Selection bias might exist, because all the cases were retrived from the same database.
⇒ Some of the classifications carried out in the SEER database were not specific enough.
⇒ Information such as ancillary tests was absent from the SEER database.

INTRODUCTION

Primary liver cancer is currently the sixth most common cancer worldwide, and is the fourth-leading cause of cancer-related deaths globally according to epidemiological surveys, posing a major threat to the health of the entire human population.[1 2] Furthermore, many studies have pointed out that although middle-aged (30–59 years) or young (<30 years old) patients with primary liver cancer are not uncommon worldwide, the average age of diagnosis of the disease is 60. In addition, in contrast to the yearly decrease of the age-standardised incidence rate (ASR) among young patients, the incidence in elderly patients has continuously increased in more than half of the countries and regions during the last 30 years.[3–5] Global population expansion, increasing ageing, as well as obesity, diabetes, overmedication and lagging effects of HBV (Hepatitis B Virus) infection in the elderly may be responsible for the high or even increased ASR in elderly patients with primary liver cancer, imposing a heavy burden on the health sectors of all countries.[6–8] Surgery remains the first choice for the treatment of primary liver cancer. Therefore, based on the epidemiological characteristics and treatment modalities of primary liver cancer, it is necessary to accurately assess the prognosis of the disease in elderly patients for the guide of clinical practice. However, different pathological types and heterogeneity of the disease still make its prognostic assessment difficult.

Recently, the nomogram model has gained widespread popularity due to its superior predictive performance over the traditional TNM (Tumor Node Metastasis.) staging in the aspects of its convenient modelling method and ability to incorporate multiple variables.[9 10] This study intended to construct a nomogram model to analyse the risk factors of primary liver cancer in elderly patients base on the SEER (Surveillance, Epidemiology, and End Results) database and to predict the prognosis of the disease. The evaluation effect

Table 1 Baseline data of the extracted cases

Variates	Total cohort 10824 (100%)	Training cohort 7577 (100%)	Validation cohort 3247 (100%)
Age			
65–69	3600 (33.3)	2540 (33.5)	1060 (32.6)
70–74	2829 (26.1)	1994 (26.3)	835 (25.7)
75–79	2228 (20.6)	1544 (20.4)	684 (21.1)
80–84	1451 (13.4)	1001 (13.2)	450 (13.9)
>84	716 (6.61)	498 (6.57)	218 (6.71)
Sex			
Male	7309 (67.5)	5122 (67.6)	2187 (67.4)
Female	3515 (32.5)	2455 (32.4)	1060 (32.6)
Race			
White	7722 (71.3)	5390 (71.1)	2332 (71.8)
Black	956 (8.83)	672 (8.87)	284 (8.75)
Asian or others	2146 (19.8)	1515 (20.0)	631 (19.4)
Primary site			
Liver	9508 (87.8)	6674 (88.1)	2834 (87.3)
IBD	1316 (12.2)	903 (11.9)	413 (12.7)
Histological type			
HCC	9171 (84.7)	6419 (84.7)	2752 (84.8)
ICC	1570 (14.5)	1095 (14.5)	475 (14.6)
CHC	83 (0.77)	63 (0.83)	20 (0.62)
Grade			
I	3108 (28.7)	2163 (28.5)	945 (29.1)
II	5040 (46.6)	3510 (46.3)	1530 (47.1)
III	2504 (23.1)	1785 (23.6)	719 (22.1)
IV	172 (1.59)	119 (1.57)	53 (1.63)
T			
T1	5028 (46.5)	3523 (46.5)	1505 (46.4)
T2	2547 (23.5)	1786 (23.6)	761 (23.4)
T3	2765 (25.5)	1932 (25.5)	833 (25.7)
T4	484 (4.47)	336 (4.43)	148 (4.56)
N			
N0	9910 (91.6)	6931 (91.5)	2979 (91.7)
N1	914 (8.44)	646 (8.53)	268 (8.25)
M			
M0	9605 (88.7)	6716 (88.6)	2889 (89.0)
M1	1219 (11.3)	861 (11.4)	358 (11.0)
Surgery			
Resection	1901 (17.5)	1315 (17.4)	586 (18.0)
Lobectomy	1116 (10.3)	807 (10.7)	309 (9.52)
Transplantation	328 (3.03)	238 (3.14)	90 (2.77)
Destruction	1087 (10.0)	769 (10.1)	318 (9.79)
Extended resection	277 (2.56)	195 (2.56)	82 (2.53)
None	6115 (56.5)	4253 (56.1)	1862 (57.3)
Tumour size (mm)			
<46	4168 (38.5)	2925 (38.6)	1243 (38.3)
46–81	3532 (32.6)	2491 (32.9)	1041 (32.1)
>81	3124 (28.9)	2161 (28.5)	963 (29.7)

CHC, combined hepatic carcinoma; HCC, hepatocellular carcinoma; IBD, intrahepatic bile duct; ICC, intrahepatic cholangiocarcinoma.

of the model was analysed by the test of discrimination and calibration, through which an optimal assessment system was established for the clinical practice such as the treatment of elderly patients with primary liver cancer.

METHODS AND DATA

Patient and public involvement

No patient involved.

Case selection

Case data of primary liver cancer with complete follow-up records were selected from the 2004–2017 SEER database (SEER research data, 18 Registries, November 2019 Sub (2000–2017)) using SEER*Stat V.8.3.6.

Inclusion criteria:

1. Ethnic groups are Asians, Pacific Islanders, American Indians and Alaskans.
2. The main site of primary liver cancer is liver or intrahepatic bile duct (IBD).
3. The histological types of primary liver cancer are intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC) and associated liver cancer (combined hepatic carcinoma, CHC).

Exclusion criteria:

1. For patients under 65 years.
2. For incomplete follow-up records.
3. Non-tumor-related death.

Race, year of diagnosis, age, sex, primary site, histological type, grade, TNM stage, tumour size, surgery on the primary site (including photodynamic therapy, percutaneous ethanol injection and radiofrequency ablation, etc), survival time, cause of death and survival status were all extracted variables. Among them, patients over 65 years were selected; Asians and Pacific Islanders, American Indians and Alaskan natives were included as the race variable of Asians and others; liver or IBD was selected as the primary site; ICC, HCC and CHC were selected as the histological type.

Statistical processing

The survival endpoint and survival time were defined as 3 years and 5 years, separately. The statistical test is carried out by grouping different values as cut-off values through the 'enumeration method' using X-Tile software, and the result with the smallest p value can be considered as the best cut-off value. It was concluded that the variables of high, medium and low risks are divided into <46 mm,

Table 2 Univariate Cox analysis

Variates	P value	HR	95% CI lower	95% CI upper
Age	<0.001			
65–69	Reference			
70–74	<0.001	1.168	1.085	1.257
75–79	<0.001	1.420	1.314	1.534
80–84	<0.001	1.639	1.502	1.788
>84	<0.001	2.072	1.855	2.314
Sex	0.003			
Male	Reference			
Female	0.003	0.914	0.862	0.969
Race	<0.001			
White	Reference			
Black	0.224	1.062	0.964	1.170
Asian or others	<0.001	0.737	0.685	0.792
Primary site	0.232 (excluded)			
Liver	Reference			
IBD	0.232	1.055	0.967	1.151
Histological type	0.032			
HCC	Reference			
ICC	0.383	0.881	0.663	1.171
CHC	0.861	0.974	0.727	1.305
Grade	<0.001			
I	Reference			
II	0.043	0.934	0.875	0.998
III	<0.001	1.464	1.360	1.577
IV	0.001	1.437	1.162	1.776
T	<0.001			
T1	Reference			
T2	<0.001	1.213	1.129	1.304
T3	<0.001	2.446	2.290	2.614
T4	<0.001	2.493	2.200	2.825
N	<0.001			
N0	Reference			
N1	<0.001	2.265	2.072	2.476
M	<0.001			
M0	Reference			
M1	<0.001	3.025	2.798	3.271
Surgery	<0.001			
Resection	Reference			
Lobectomy	<0.001	0.234	0.213	0.256
Transplantation	<0.001	0.268	0.241	0.299
Destruction	<0.001	0.079	0.060	0.104
Extended resection	<0.001	0.366	0.332	0.403
None	<0.001	0.372	0.308	0.449
Tumour size (mm)	<0.001			
<46	Reference			
46–81	<0.001	1.744	1.630	1.867
>81	<0.001	2.577	2.405	2.761

Continued

Table 2 Continued

Variates	P value	HR	95% CI lower	95% CI upper

CHC, combined hepatic carcinoma; HCC, hepatocellular carcinoma; IBD, intrahepatic bile duct; ICC, intrahepatic cholangiocarcinoma.

46–81 mm and >81 mm, respectively. After that, all the cases were randomly assigned to a training or a validation cohort at a ratio of 7:3 using SPSS V.18.0 by random number 20200222, followed by the collection of baseline information. Univariate and multivariate (Forward: LR) Cox analyses were performed using the R software or SPSS to screen statistically significant variables for nomogram construction, based on which, C-Index, ROC curves and the area under the curve (AUC) were figured out. Calibration curves of the model for 3 and 5 years were plotted with the R software after Bootstrap sampling for 1000 times. A p<0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the cases

A total of 10824 elderly cases with primary liver cancer were extracted in accordance with the screening conditions, including 7757 in the training cohort and 3247 in the validation one. Among them, the majority of patients were male (67.5%), white (71.3%), with primary site in the liver (87.8%), HCC (84.7%), grade II (46.6%), T1 (46.5%), N0 (91.6%), M0 (88.7%) and unoperated (56.5%) (table 1).

Screening for prognostic risk factors.

Univariate Cox regression analysis was performed on the training cohort, and the variates of age, sex, race, histological type, grade, TNM stage, surgery and tumour size were proved to be statistically significant (p<0.05) and included in the follow-up multivariate Cox analysis. However, the primary site was excluded according to the analysis (p=0.232) (table 2). Subsequently, the variable of sex was further excluded from the experiment by Forward: LR multivariate Cox (table 3). In the end, age, race, histological type, grade, TNM stage, surgery and tumour size were all independent risk factors affecting the prognosis of elderly patients with primary liver cancer, and could be used for constructing nomogram prediction model.

Nomogram model construction and verification

The 3-year and 5-year nomogram prediction model for primary liver cancer in the early were constructed based on the independent risk factors affecting the prognosis of the disease derived from the above analysis. The total score was calculated by aggregating the scores of each variable to predict the 3-year and 5- year survival rate of patients (figure 1). It can be seen that the most important factor affecting the score in this model was surgery on the primary site, followed by tumour size, TNM stage and age. The C-Index of the model was 0.747 (in the

Table 3 Multivariates Cox analysis

Variates	P value	HR	95% CI lower	95% CI upper
Age				
65–69	Reference			
70–74	0.029	1.086	1.009	1.170
75–79	<0.001	1.219	1.127	1.318
80–84	<0.001	1.307	1.196	1.428
>84	<0.001	1.484	1.326	1.660
Sex	(Excluded)			
Male				
Female				
Race				
White	Reference			
Black	0.325	1.051	0.952	1.159
Asian or others	<0.001	0.813	0.756	0.875
Histological type				
HCC	Reference			
ICC	0.159	0.940	0.863	1.024
CHC	0.005	1.508	1.132	2.010
Grade				
I	Reference			
II	0.001	1.121	1.047	1.199
III	<0.001	1.567	1.449	1.695
IV	<0.001	1.683	1.358	2.086
T				
T1	Reference			
T2	<0.001	1.282	1.190	1.381
T3	<0.001	1.542	1.435	1.657
T4	<0.001	1.689	1.484	1.923
N				
N0	Reference			
N1	<0.001	1.253	1.136	1.382
M				
M0	Reference			
M1	<0.001	1.556	1.429	1.694
Surgery				
Resection	Reference			
Lobectomy	0.833	1.014	0.889	1.157
Transplantation	<0.001	0.417	0.313	0.557
Destruction	<0.001	1.851	1.632	2.100
Extended resection	0.007	1.325	1.080	1.626
None	<0.001	3.552	3.229	3.906
Tumour size (mm)				
<46	Reference			
46–81	<0.001	1.291	1.199	1.391
>81	<0.001	1.597	1.474	1.730

CHC, combined hepatic carcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

training cohort) and 0.773 (in the validation cohort). The AUC was calculated after plotting the ROC curves of the training and the validation cohorts. Specifically, the AUC is 0.760 (3 years) and 0.761 (5 years) in the training cohort, and 0.750 (3 years) and 0.748 (5 years) in the validation cohort (figure 2). Furthermore, the model showed an ideal calibration for 3-year and 5-year survival prediction in both groups after creating the calibration curves for the training and the validation cohorts (figure 3). By comapring the predictive value of the nomogram model with the TNM model, it was revealed that their 3-year AUC were 0.758 and 0.698 ($p<0.05$) separately, and their 5-year AUC were 0.750 and 0.609 ($p<0.01$), respectively (figure 4.).

DISCUSSION

Analysis of cases revealed that male patients accounted for more than 60% of all the elderly patients with primary liver cancer. Some statistics have presented that the mean annual change rate of men suffering from the disease is higher than that of women (3.7% vs 2.7%) in the USA.[11] In China, a population-based study of hepatic carcinoma in Zhejiang Province demonstrated that the ASR for hepatic carcinoma was 33.24 in men compared with 1.21 in women.[12] Not only differences in lifestyle—including alcohol consumption and smoking—have led to higher cancer rates in men, but different physiological conditions such as hormone secretion and even genetic differences may be responsible for these epidemiological differences.[13] Therefore, it has been proposed that gender is a critical biological variable that should be considered in all studies aimed at improving carcinoma.[14] Analysis of baseline data also suggested that the population of elderly patients with primary liver cancer was predominantly white and mostly with the primary site in the liver, HCC histological type, grade II (moderately differentiated), T1 and without lymph node metastasis or distant metastasis. Moreover, in this population, more than half of the cases were not treated surgically. The possible reason for this phenomenon is that most of the patients were over 60 years at the time of diagnosis, missing the best time to receive radical surgery. In addition, in consideration of the decline in their physical function as well as

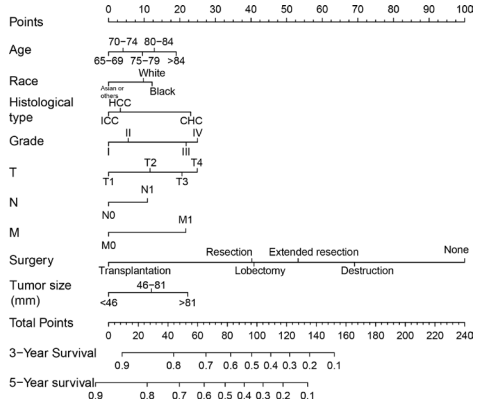

Figure 1 Constructed nomogram. CHC, combined hepatic carcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

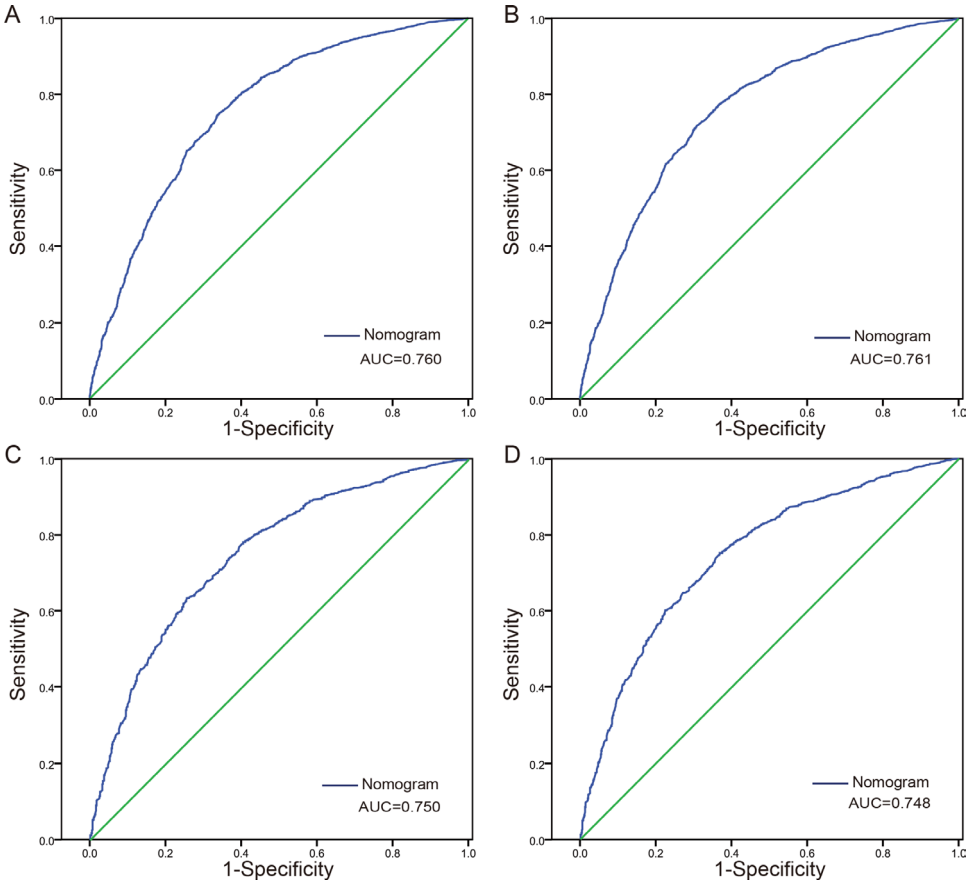

Figure 2 Three-year and 5-year survival ROC (Receiver Operating Characteristic) curves for the training and the validation cohorts. (A) 3-year survival ROC curve for the training cohort. (B) 5-year survival ROC curve for the training cohort. (C) 3-year survival ROC curve for the validation cohort. (D) 5-year survival ROC curve for the validation cohort. AUC, area under the curve; ROC, Receiver Operating Characteristic.

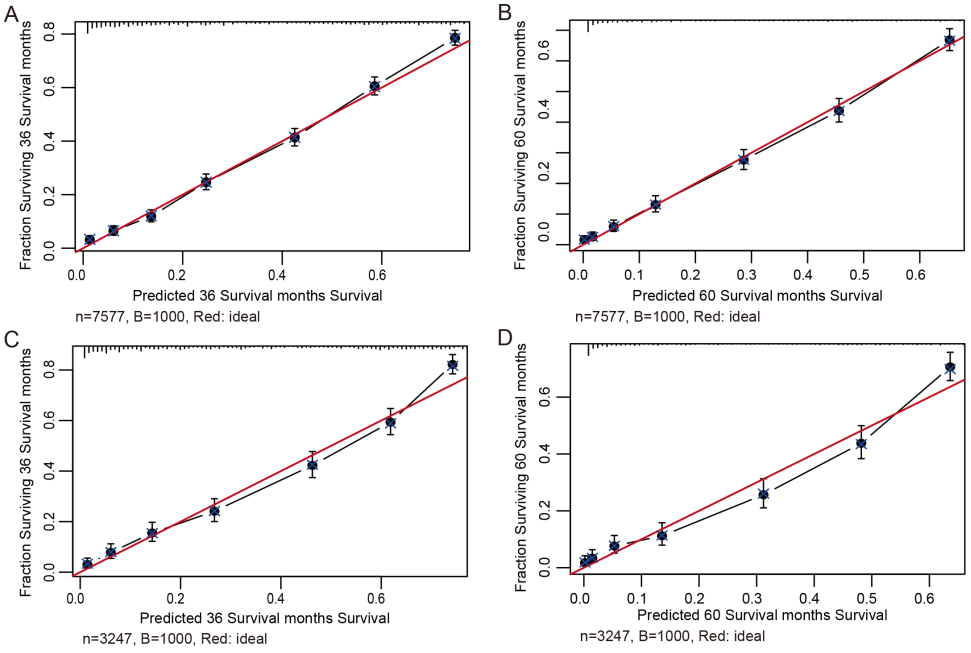

Figure 3 Three-year and 5-year survival calibration curves for the training and the validation cohorts. (A) 3-year survival calibration curve for the training cohort. (B) 5-year survival calibration curve for the training cohort. (C) 3-year survival calibration curve for the validation cohort. (D) 5-year survival calibration curve for the validation cohort.

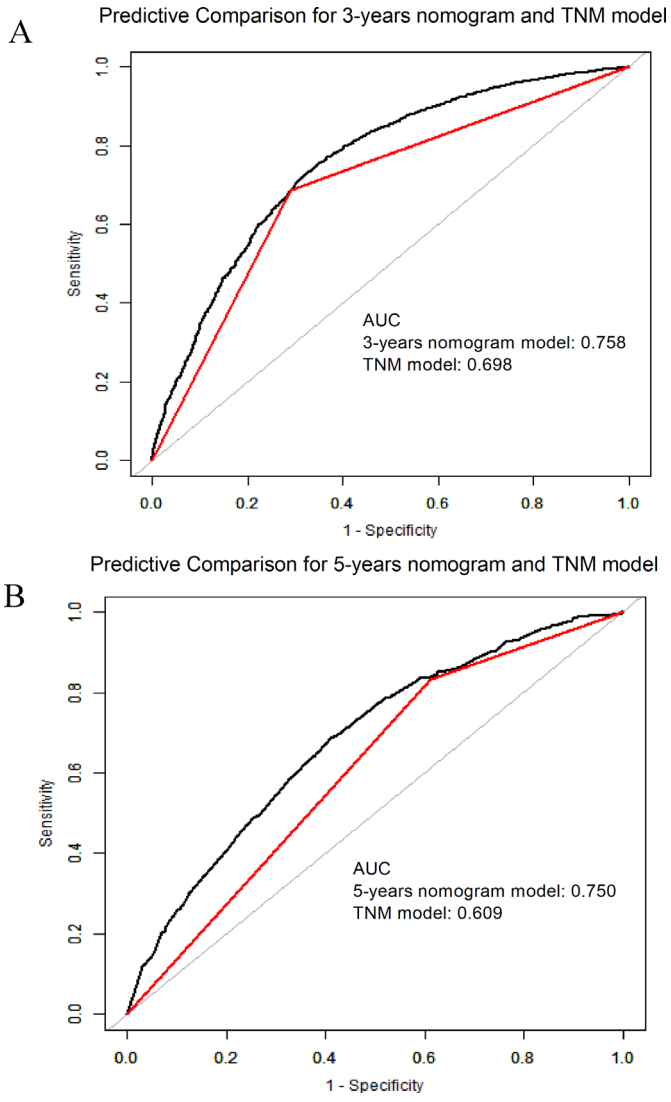

Figure 4 The comparison of ROC (Receiver Operating Characteristic) between the nomogram model and the TNM (Tumor Node Metastasis) model. (A) 3-year nomogram model, (B) 5-year nomogram model). AUC, area under the curve.

intolerance to surgery, a palliative treatment was chosen for most of these patients.

Based on further univariate and multivariate Cox analyses, several independent risk factors affecting the prognosis of the disease were obtained, including age, race, histological type, grade, TNM stage, surgery and tumour size. Sex, though not negligible as previously mentioned, was not a main factor affecting prognosis in this population after comprehensive analysis, which is consistent with several current retrospective studies on hepatic carcinoma.[15–17] Some clinical information affecting the operation, such as metastatic cancer, can be reflected in the TNM staging. In terms of histological types, the prognosis of CHC is obviously worse than that of the common HCC, with a lower incidence but a higher degree of malignancy.[18 19] Analysis of the age factor revealed that the higher the age group of the patient, the worse the prognosis, suggesting a linear negative correlation trend. The nomogram model also indicated that surgery was the most crucial factor influencing the prognosis of the disease. Although just a small number of patients received liver transplantation, they showed a relatively good prognosis, followed by patients with resection or lobectomy and local destruction. In contrast, patients without surgery showed a relatively poor prognosis. This factor alone reduced the 3-year and 5-year predicted survival rates to less than 50%, suggesting that the invention of new methods or enhanced surgery is still urgent for improving the prognosis of elderly patients with primary liver cancer. The influence of other factors on the prognosis of the disease is basically in line with the current consensus that the worse the grade, the higher the T-stage, the occurrence of lymph node metastasis, the occurrence of distant metastasis and the larger the tumour and the worse the prognosis of the patients.

After that, the performance of the established model was evaluated by C-Index, ROC curves and calibration curves. A nomogram model is considered to have good discrimination if its C-Index and AUC exceed 0.7.[20 21] As the two indicators of the model constructesd in this study were all above 0.7 in both the training and the validation cohorts and the calibration plots scattered in accordance with the reference line, it could be concluded that the model has good discrimination and calibration and hence the capacity to predict the prognosis of the disease.

However, this study also has shortcomings. First, the cases in this study were all from the US SEER (Surveillance, Epidemiology, and End Results) database, which is not representative for regions outside the USA and is subject to selection bias. In addition, the case data included in this database lacked some important ancillary tests related to the diagnosis and treatment of liver cancer, such as CEA, AST and vascular invasion. More importantly, the radiotherapy and chemotherapy information contained in this database can only be obtained by signing some agreements, which can not be obtained for the time being, so we are unable to study the relationship between radiotherapy, chemotherapy, targeted therapy and the prognosis of liver cancer.[22]

There are also deficiencies in our statistical conclusions. Limited by time and skills, our model did not reach an ideal state, and its AUC is only 0.75, indicating that there is still room for improvement. This affects the prediction accuracy to a certain extent and reduces the prediction credibility. In the future, we will continue to refine our nomogram model to make it achieve a more accurate degree.

In conclusion, a nomogram model with moderate prediction was developed by using the case data in the SEER database after performing univariate and multivariate Cox screening, which could provide reference for future diagnosis and treatment of elderly patients with primary liver cancer.

Contributors FL wrote and revised the manuscript; TZ conducted most of the analysis of data; XG reviewed the manuscript. XG had full access to all of the data

in the study, took responsibility for the conduct of the study, the integrity of the data and the accuracy of the data analysis, and controlled the decision to publish. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Informed consent was not required from patients to obtain data from the US SEER database since cancer is publicly reportable in every state in the USA.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID iD

Xuewei Gu http://orcid.org/0000-0002-6762-6337

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2 Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
3 Liu Z, Suo C, Mao X, *et al*. Global incidence trends in primary liver cancer by age at diagnosis, sex, region, and etiology, 1990-2017. *Cancer* 2020;126:2267–78.
4 Kanwal F, Kramer JR, Mapakshi S, *et al*. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 2018;155:1828–37.
5 Zhang S, Zheng R, Zeng H, *et al*. [The incidence differences among sex, geographical areas and mean age of diagnosis for liver cancer in China, 1989-2008]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2014;48:355–60.
6 Baumeister SE, Schlesinger S, Aleksandrova K, *et al*. Association between physical activity and risk of hepatobiliary cancers: a multinational cohort study. *J Hepatol* 2019;70:885–92.
7 Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nat Rev Clin Oncol* 2017;14:85–99.
8 Smittenaar CR, Petersen KA, Stewart K, *et al*. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer* 2016;115:1147–55.
9 Chen S, Liu Y, Yang J, *et al*. Development and validation of a nomogram for predicting survival in male patients with breast cancer. *Front Oncol* 2019;9:361.
10 Zhang Y, Hong Y-K, Zhuang D-W, *et al*. Bladder cancer survival nomogram: development and validation of a prediction tool, using the seer and TCGA databases. *Medicine* 2019;98:e17725.
11 Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control* 20 17;24:1073274817729245:107327481772924.
12 Fei F-R, Hu R-Y, Gong W-W, *et al*. Analysis of mortality and survival rate of liver cancer in Zhejiang Province in China: a general population-based study. *Can J Gastroenterol Hepatol* 2019;2019:1074286:1–6.
13 Kim SY, Song HK, Lee SK, *et al*. Sex-Biased molecular signature for overall survival of liver cancer patients. *Biomol Ther* 2020;28:491–502.
14 Gabriele L, Buoncervello M, Ascione B, *et al*. The gender perspective in cancer research and therapy: novel insights and on-going hypotheses. *Ann Ist Super Sanita* 2016;52:213–22.
15 Liu K, Huang G, Chang P, *et al*. Construction and validation of a nomogram for predicting cancer-specific survival in hepatocellular carcinoma patients. *Sci Rep* 2020;10:21376.
16 Zhang F, Lu S, Tian M, *et al*. Albumin-to-Alkaline phosphatase ratio is an independent prognostic indicator in combined hepatocellular and cholangiocarcinoma. *J Cancer* 2020;11:5177–86.
17 Ramai D, Ofosu A, Lai JK, *et al*. Combined hepatocellular cholangiocarcinoma: a population-based retrospective study. *Am J Gastroenterol* 2019;114:1496–501.
18 Stavraka C, Rush H, Ross P. Combined hepatocellular cholangiocarcinoma (cHCC-CC): an update of genetics, molecular biology, and therapeutic interventions. *J Hepatocell Carcinoma* 2019;6:11–21.
19 Leoni S, Sansone V, De Lorenzo S, *et al*. Treatment of combined hepatocellular and cholangiocarcinoma. *Cancers*;12:794.
20 EW S*et al*. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. *J. Urol*:107.
21 Iasonos A, Schrag D, Raj GV, *et al*. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 2008;26:1364–70.
22 Yang J, Li Y, Liu Q, *et al*. Brief introduction of medical database and data mining technology in big data era. *J Evid Based Med* 2020;13:57–69.