Original Article

Nomogram-based prognostic stratification for patients with large hepatocellular carcinoma: a population study of SEER database and a Chinese cohort

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Background: Large hepatocellular carcinoma (HCC) with a diameter ≥5 cm remains a significant challenge of poor survival and raises the need for prognosis evaluation. This study aimed to develop and validate a nomogram-based prognostic stratification to assess overall survival (OS) of patients with large HCC.

Methods: Data of patients with large HCC were retrospectively collected from the Surveillance, Epidemiology, and End Results (SEER) database and our hospital, and were divided into the training cohort, internal validation cohort and external validation cohort. Cox analysis was performed to identify independent prognostic factors for the construction of nomogram in training cohort. The predictive ability of the nomogram was validated compared with the tumor node metastasis (TNM) classification staging system. Furthermore, prognostic stratification system based on nomogram was developed.

Results: Independent prognostic factors including histological grade, T stage, M stage, alpha fetoprotein (AFP), fibrosis score and surgery, were incorporated to construct nomogram. C-indexes of nomogram were 0.730, 0.726 and 0.724 in the training, internal and external validation cohorts, respectively. Importantly, nomogram harbored a superior discrimination and clinical benefit than the TNM staging system. Nomogram-based prognostic stratification divided patients into three groups: 345–414 (low-risk group), 415–460 (medium-risk group) and 461–513 (high-risk group). As shown in Kaplan-Meier curves, there were significant differences in OS among low-, medium- and high-risk groups (P<0.01).

Conclusions: Nomogram showed a superior prognostic predictive ability compared with the TNM staging system. The prognostic stratification serves as a valuable tool to assist clinicians on the selection of optimal treatment method and follow-up plan, particularly for the high-risk population.

Keywords: Hepatocellular carcinoma (HCC); survival; prediction; nomogram

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Introduction

According to the global cancer statistics, hepatocellular carcinoma (HCC) accounts for more than 75% of primary liver cancer, which is the fourth leading cause of cancer-related death worldwide (1). It is reported that the prognosis of patients with HCC is associated with the tumor size (2). Approximately 32% of HCC exhibit a tumor diameter exceeding 5 cm, with an additional 10–20% of tumors greater than 10 cm at the time of diagnosis (3). Guidelines from Asia-Pacific (4), Europe (5) and America (6) regard 5 cm as the cut-off to differentiate early and intermediate stage of HCC. Large HCC, defined as a tumor ≥5 cm in diameter, is associated with a poor survival due to increased potential of invasiveness, metastasis and challenge of surgical resection, raising the need for the evaluation of prognosis for patients with large HCC (7).

Currently, there are several staging systems widely applied to assess the outcome of HCC patients, such as the American Joint Committee on Cancer (AJCC), the Barcelona Clinic Liver Cancer system, the Okuda system. However, these staging systems have limited ability to predict survival for large HCC patients (8). For instance, the AJCC staging system only takes the tumor node metastasis (TNM) classification staging into account, without consideration of additional demographic and clinicopathologic characteristics, which may introduce sampling bias into the prognosis evaluation process (9). Other factors such as physical status of patients, liver function and tumor characteristics can also significantly affect the prognosis of patients (10). Therefore, there is a need for a comprehensive prognostic model that incorporates more significant factors, to assist clinicians in making decisions regarding treatment methods and follow-up plans.

As a graphical calculating model, nomogram has gained increasing interest and application in the diagnosis and prognosis of patients in several cancers such as melanoma, liver cancer and prostate cancer, through simply generating individual survival time or incidence probability by combining all risk factors for disease development (11-13). In the context of HCC, several nomograms have been devised for prognostic purposes; however, the majority of these nomograms were derived from a single population or lack validation with an independent cohort. To our knowledge, a prognostic nomogram for survival prediction in patients with large HCC has not yet been constructed.

This population-based study aimed to establish a reliable nomogram model to predict individual 3- and 5-year overall survival (OS) rates for patients with large HCC-based on a large cohort of population from the Surveillance, Epidemiology, and End Results (SEER) database. Furthermore, the predictive ability of nomogram model was validated compared with the TNM staging system, utilizing data from an external population of patients from our hospital. In addition, we conducted a risk stratification to enable clinicians to select optimal treatment methods and formulate follow-up strategy for patients with large HCC, especially for the high-risk population. We present this article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/

Highlight box

Key findings

- The nomogram-based prognostic stratification for patients with large hepatocellular carcinoma (HCC) has been developed based on a large population and validated using a cohort of patients from our hospital.

What is known and what is new?

- Large HCC, defined as a tumor ≥5 cm in diameter, is associated with a poor survival due to increased potential of invasiveness, metastasis and challenge of surgical resection, raising the need for evaluation of prognosis for patients with large HCC.
- We identified the independent prognostic factors including histological grade, T stage, M stage, alpha fetoprotein, fibrosis score and surgery for patients with large HCC. Nomogram-based prognostic stratification divided patients into low-risk, medium-risk and high-risk groups. There were significant differences in overall survival among three risk groups.

What is the implication, and what should change now?

- Nomogram showed a superior predictive ability of survival compared with the tumor node metastasis classification staging. The prognostic stratification may serve as a valuable tool to assist clinicians on the selection of optimal treatment method and follow-up plan.

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view/10.21037/jgo-24-288/rc).

Methods

Patients

Data of patients were retrospectively collected from SEER database and the First Affiliated Hospital, Zhejiang University School of Medicine. Information on patients with HCC between 2004 and 2015 were extracted from the SEER database using SEER Stat software (version 8.4.0; NCI, Bethesda, MD, USA) (14). The International Classification of Diseases for Oncology (ICD-O-3 code: 8170, 8171, 8172, 8173, 8174 and 8175) and site codes C22.0 (liver) were used to screen out HCC patients. Inclusion criteria were as follows: (I) HCC as the primary tumor; (II) tumor diameter ≥5 cm; and (III) available demographic characteristics (age, gender, race, insurance and marital status), tumor-related factors [tumor size, histological grade, 6th TNM staging, alpha fetoprotein (AFP), fibrosis score], treatment (surgery, radiation and chemotherapy) and survival information. Exclusion criteria were as follows: (I) age ≤18 years and (II) diagnosis of HCC by death certificate or autopsy. Fibrosis score was scored as 0–4 (none or moderate fibrosis) and 5–6 (severe fibrosis or cirrhosis). There were three categories for treatment including none (no tumor-directed surgery), local tumor destruction (such as photodynamic therapy and cryosurgery) and resection (partial or total hepatectomy).

As for extracting patients from our center, we included 302 patients with large HCC from May 2019 to March 2021 as the external validation cohort. The following inclusion criteria were adopted: (I) aged more than 18 years; (II) diagnosis of HCC with tumor diameter ≥5 cm; (III) no severe chronic diseases; (IV) no other tumor history; and (V) complete data such as tumor size, AFP, treatment, and follow-up information. In cases where tumor resection was not performed, imaging modalities including contrast-enhanced ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) were utilized to assess tumor size and T stage, N stage and M stage. Moreover, the variable of AFP was divided into normal and elevated. OS was computed from the date of diagnosis to death or the last follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2016-324) and individual consent for this retrospective analysis was waived.

Construction of nomogram-based prognostic stratification

Patients from SEER database were randomly divided into the training cohort and internal validation cohort in a ratio of 7:3. In training cohort, univariate Cox regression analysis was performed to identify the association between OS and variables such as age, gender, tumor size, histological grade, TNM staging, AFP, fibrosis score, surgery and chemotherapy. Subsequently, variables with P value <0.05 in univariate analysis were included in multivariable analysis to determine the independent prognostic indicators. Based on the independent prognostic factors, a nomogram was constructed to predict 3- and 5-year survival rates for patients with large HCC.

The discrimination and calibration of nomogram were assessed by the internal and external validation cohorts compared with TNM staging system. Specifically, the concordance index (C-index) was adopted to evaluate the discriminative ability, though quantifying the discrepancies between observed and predicted outcomes, and higher C-index value meant more accurate prediction (15). Furthermore, calibration plots were applied to reflect the consistency between the actual and predicted survival probabilities. The discrimination of TNM staging system and nomogram was compared via the area under receiver operating characteristic (ROC) curve (AUC). Decision curve analysis (DCA) was used to determine the clinical benefit of nomogram. In addition, the total point of each patient was calculated according to score assignment of variables in the nomogram. Subsequently, a nomogram-based prognostic stratification system was developed to separated patients into high-, middle-, and low-risk groups. Kaplan-Meier (K-M) curves were drawn to estimated visually survival difference among the three risk groups.

Statistical analysis

All statistical analyses were performed using SPSS software (IBM Corporation, USA, version 26) and programming language R (version 3.6.2). Univariable and multivariable Cox regression analyses were conducted to identify the independent predictors associated with OS. Only the variables with P values <0.05 in univariable analysis were subsequently included in multivariable analysis. The cutoff values of the total points from nomogram were determined by X-tile program (Yale University, New Haven, CT,

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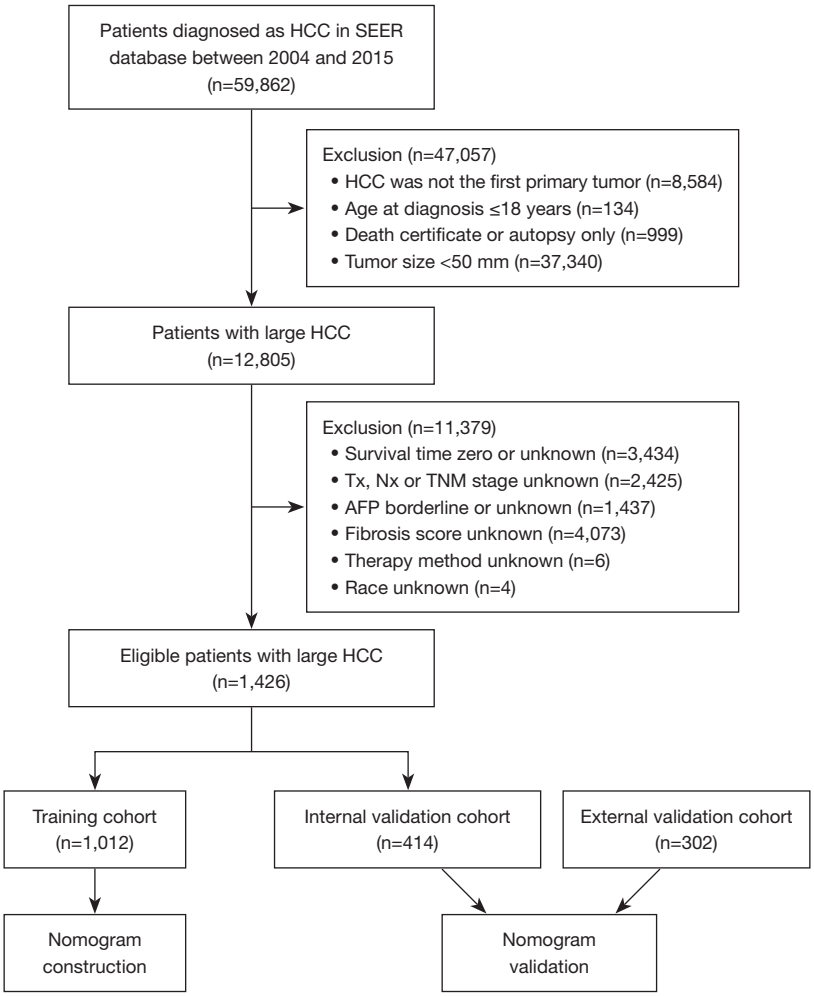

Figure 1 Flow diagram of the selection criteria of patients with large hepatocellular carcinoma. SEER, Surveillance, Epidemiology, and End Results database; HCC, hepatocellular carcinoma; TNM, tumor node metastasis staging; AFP, alpha fetoprotein.

USA). Besides, the survival differences among three groups were estimated by log-rank test. C-index, ROC curves, nomogram, calibration curves, DCA curves and K-M curves were generated in R with packages "rms", "survival", "foreign", "timeROC" and "regplot". Statistical significance was set as $P<0.05$ in a two-sided test.

Results

Patient characteristics

A total of 1,426 patients with large HCC from SEER database were eventually included and randomly divided into the training cohort (n=1,012) for nomogram construction and internal validation cohort (n=414) for internal verification. An independent cohort of 302 patients from our center formed the external validation cohort. The detailed process of patient selection is shown in *Figure 1*. Since the diagnosis of HCC mainly relies on imaging test, unknown histological grade accounted for the majority of HCC. There were more patients treated with local tumor destruction while a smaller proportion received chemotherapy in our center than SEER database. More clinicopathologic characteristics of patients in three cohorts are listed in *Table 1*.

Independent prognostic factors

Univariate Cox analyses revealed that age, race, histological grade, AJCC stage, T stage, N stage, M stage, AFP,

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Table 1 Demographic and clinical characteristics of patients with large HCC

Characteristics	Training cohort (n=1,012)	Internal validation cohort (n=414)	External validation cohort (n=302)
Age, years	62.43±11.87	62.22±11.58	55.10±10.61
Gender			
Female	217 (21.4)	92 (22.2)	45 (14.9)
Male	795 (78.6)	322 (77.8)	257 (85.1)
Race			
White	632 (62.5)	250 (60.4)	NA
Black	127 (12.5)	58 (14.0)	NA
Other[†]	253 (25.0)	106 (25.6)	302 (100.0)
Insurance status			
No	24 (2.4)	12 (2.9)	13 (4.3)
Yes	841 (83.1)	334 (80.7)	279 (92.4)
Unknown	147 (14.5)	68 (16.4)	10 (3.3)
Marital status			
Single	370 (36.6)	147 (35.5)	33 (10.9)
Married	607 (60.0)	256 (61.8)	269 (89.1)
Unknown	35 (3.5)	11 (2.7)	0
Histological grade			
Well/moderate	274 (27.1)	112 (27.1)	57 (18.9)
Poor/undifferentiated	111 (11.0)	39 (9.4)	35 (11.6)
Unknown	627 (62.0)	263 (63.5)	210 (69.5)
Tumor size, mm	92.88±67.10	94.77±61.78	85.92±39.75
TNM stage			
I	353 (34.9)	125 (30.2)	87 (28.8)
II	121 (12.0)	48 (11.6)	33 (10.9)
III	420 (41.5)	201 (48.6)	123 (40.7)
IV	118 (11.7)	40 (9.7)	59 (19.5)
T stage			
T1	382 (37.7)	137 (33.1)	93 (30.8)
T2	129 (12.7)	56 (13.5)	35 (11.6)
T3	447 (44.2)	196 (47.3)	75 (24.8)
T4	54 (5.3)	25 (6.0)	99 (32.8)
N stage			
N0	924 (91.3)	383 (92.5)	272 (90.1)
N1	88 (8.7)	31 (7.5)	30 (9.9)

Table 1 *(continued)*

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Table 1 *(continued)*

Characteristics	Training cohort (n=1,012)	Internal validation cohort (n=414)	External validation cohort (n=302)
M stage			
M0	894 (88.3)	374 (90.3)	268 (88.7)
M1	118 (11.7)	40 (9.7)	34 (11.3)
AFP			
Normal	313 (30.9)	123 (29.7)	153 (50.7)
Elevated	699 (69.1)	291 (70.3)	149 (49.3)
Fibrosis score			
0–4	416 (41.1)	177 (42.8)	113 (37.4)
5–6	596 (58.9)	237 (57.2)	189 (62.6)
Surgery			
None	497 (49.1)	201 (48.6)	59 (19.5)
Local destruction[‡]	63 (6.2)	26 (6.3)	139 (46.0)
Resection[§]	452 (44.7)	187 (45.2)	104 (34.5)
Radiation			
No	987 (97.5)	404 (97.6)	289 (95.7)
Yes	25 (2.5)	10 (2.4)	13 (4.3)
Chemotherapy			
No/unknown	567 (56.0)	224 (54.1)	266 (88.1)
Yes	445 (44.0)	190 (45.9)	36 (11.9)

Data are presented as mean ± standard deviation or number (percentage). [†], other: American Indian/Alaska Native and Asian/Pacific Islander. [‡], local destruction: photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, percutaneous ethanol injection, thermal ablation, ultrasound and acetic acid. [§], resection: partial and total hepatectomy. TNM, tumor node metastasis staging; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; NA, not applicable.

fibrosis score, surgery and chemotherapy were significantly associated with OS in the training set. It is worth mentioning that AJCC stage was not involved in subsequent multivariate analysis due to its dependence from T, N and M stages. Multivariate Cox analysis demonstrated that histological grade, T stage, M stage, AFP, fibrosis score, surgery and chemotherapy were independent prognostic factors of OS (*Table 2*). As for chemotherapy, there are many different types of chemotherapy with varied therapeutic effects, and it is unclear which chemotherapy drug was used in SEER database. Therefore, chemotherapy is excluded as independent prognostic factor in the following analysis.

Development and validation of nomogram

A nomogram model integrating the independent prognostic factors was established for prediction of 3- and 5-year survival rates for patients with large HCC in the training set (*Figure 2*). As nomogram showed, surgery made the largest contribution, followed by histological grade, M stage, AFP, fibrosis score and T stage. Each level of the variables is assigned a score on the Points scale in the light of its prognostic value, and the total point can be simply acquired by summing the score of each factor. The sizes of the blue boxes in the middle and the yellow block on the total points axis represented the proportion of patients. The score assignment for variables included in nomogram is shown in *Table 3*. For instance, as shown in *Figure 2*, if a patient presented with a fibrosis score of 0–4 (69 points), an elevated AFP level (84 points), histological grade poor/undifferentiated (100 points), T2 stage (80 points) and M1 stage (95 points), and

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Table 2 Univariate and multivariate Cox regression analyses of overall survival for patients with large HCC

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.009	1.003–1.015	0.005			
Gender						
Female	Reference					
Male	1.177	0.981–1.411	0.07			
Race						
White	Reference					
Black	0.920	0.734–1.153	0.46			
Other[†]	0.766	0.641–0.914	0.003			
Insurance status						
No	Reference					
Yes	0.732	0.464–1.157	0.18			
Unknown	0.797	0.492–1.293	0.35			
Marital status						
Single	Reference					
Married	0.870	0.747–1.012	0.07			
Unknown	0.931	0.618–1.402	0.73			
Histological grade						
Well/moderate	Reference			Reference		
Poor/undifferentiated	1.394	1.145–1.698	0.001	1.754	1.410–2.164	<0.001
Unknown	0.921	0.773–1.098	0.36	1.266	1.054–1.521	0.01
Tumor size	1.001	1.000–1.002	0.051			
TNM stage						
I	Reference					
II	1.034	0.786–1.359	0.81			
III	1.872	1.575–2.225	<0.001			
IV	3.590	2.836–4.544	<0.001			
T stage						
T1	Reference			Reference		
T2	1.037	0.801–1.343	0.78	1.254	0.959–1.640	0.09
T3	1.896	1.608–2.237	<0.001	1.394	1.174–1.654	<0.001
T4	2.378	1.746–3.238	<0.001	1.375	0.991–1.907	0.057
N stage						
N0	Reference					
N1	2.407	1.897–3.055	<0.001			
M stage						
M0	Reference			Reference		
M1	2.632	2.139–3.240	<0.001	1.615	1.297–2.011	<0.001

Table 2 *(continued)*

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Table 2 *(continued)*

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
AFP						
Normal	Reference			Reference		
Elevated	1.657	1.405–1.956	<0.001	1.378	1.161–1.635	<0.001
Fibrosis score						
0–4	Reference			Reference		
5–6	1.593	1.368–1.854	<0.001	1.245	1.062–1.459	0.007
Surgery						
None	Reference			Reference		
Local destruction‡	0.429	0.318–0.577	<0.001	0.427	0.314–0.579	<0.001
Resection§	0.270	0.229–0.318	<0.001	0.235	0.192–0.287	<0.001
Radiation						
No	Reference					
Yes	0.856	0.521–1.406	0.53			
Chemotherapy						
No/unknown	Reference			Reference		
Yes	1.241	1.072–1.437	0.004	0.636	0.541–0.747	<0.001

†, other: American Indian/Alaska Native and Asian/Pacific Islander. ‡, local destruction: photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, percutaneous ethanol injection, thermal ablation, ultrasound and acetic acid. §, resection: partial and total hepatectomy. HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; TNM, tumor node metastasis staging.

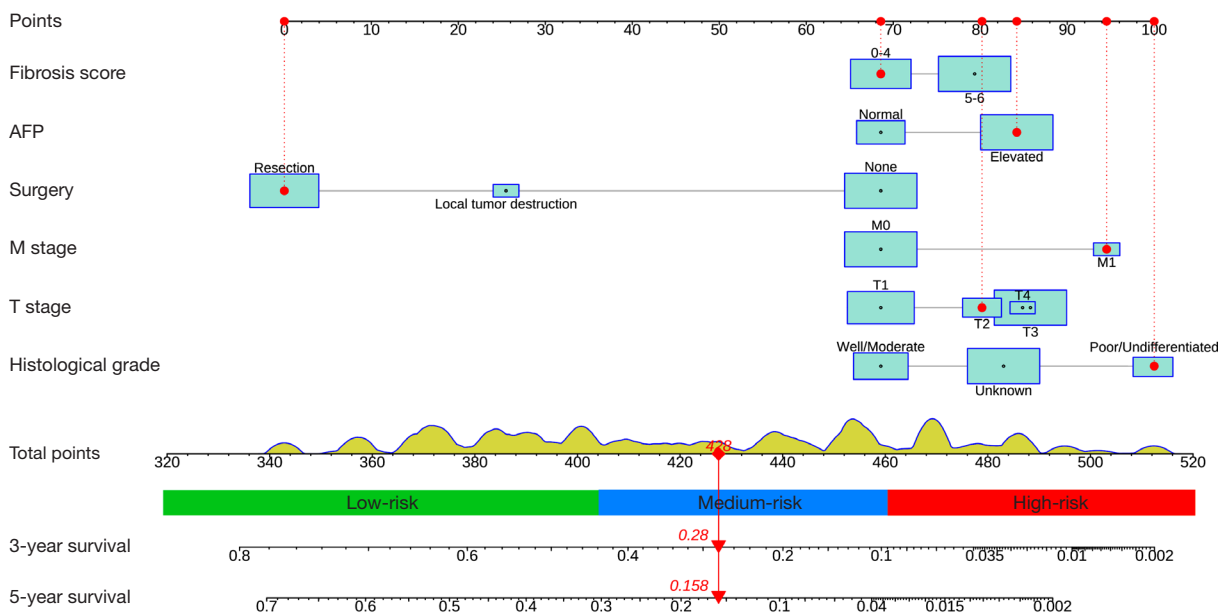

Figure 2 Nomogram for predicting prognosis of patients with large hepatocellular carcinoma. Each category of the prognostic variables is assigned a score on the points scale. The sum of these scores is located on the total points scale and a line is drawn downward to determine the specific probability of 3- and 5-year overall survival. AFP, alpha fetoprotein.

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subsequently undergone surgical resection (0 points), his/her total point amounted to 428. This point corresponded to an estimated 3- and 5-year survival rates of 28.0% and 15.8%, respectively. Total points and survival rate in the nomogram were shown in *Table 4*. Furthermore, an online version of nomogram was provided at https://jikun.shinyapps.io/large_hcc (*Figure 3*), so as to enable calculation easy and avoid the manual calculation errors.

Table 3 Score assignment for variables included in the nomogram

Characteristics	Points
AFP	
Normal	69
Elevated	84
Fibrosis score	
0–4	69
5–6	79
T stage	
T1	69
T2	80
T3	86
T4	85
M stage	
M0	69
M1	95
Histological grade	
Well/moderate	69
Unknown	83
Poor/undifferentiated	100
Surgery	
None	69
Local destruction‡	25
Resection§	0

‡, local destruction: photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, percutaneous ethanol injection, thermal ablation, ultrasound and acetic acid. §, resection: partial and total hepatectomy. AFP, alpha fetoprotein.

C-indexes of nomogram were 0.730 (95% CI, 0.712–0.748) in the training cohort, 0.726 (95% CI, 0.695–0.757) in the internal validation cohort, and 0.724 (95% CI, 0.677–0.771) in the external validation cohort, manifesting accurate capability in prognosis prediction. The calibration curves for probability of survival at 3 and 5 years exhibited excellent agreement between the actual and predicted observation in three cohorts (*Figure 4*). Meanwhile, AUCs of nomogram in ROC curves revealed superior discrimination in comparison to that of AJCC TNM staging [training cohort: 3-year survival (0.799 *vs.* 0.675) and 5-year survival (0.811 *vs.* 0.676); internal validation cohort: 3-year survival (0.834 *vs.* 0.683) and 5-year survival (0.873 *vs.* 0.712); external validation cohort: 3-year survival (0.843 *vs.* 0.720) and 5-year survival (0.790 *vs.* 0.685)] (all P<0.01) (*Figure 5*). Importantly, DCA curves showed that nomogram gained more clinical benefits than TNM staging for predicting OS at 3 and 5 years in three cohorts (*Figure 6*).

Construction of prognostic stratification

The median survival time was 19, 17 and 25 months in the training, internal validation and external validation cohorts, respectively. Based on the total points calculated from nomogram, patients were divided into three groups: 345–414 (low-risk group), 415–460 (medium-risk group) and 461–513 (high-risk group). The median OS of patients in low-risk, medium-risk and high-risk group were 45, 14 and 5 months in the training set; 45, 12 and 4 months in the internal validation set; >45, 19 and 8.6 months in the external validation set, respectively. K-M curves of three risk groups were clearly separated in three cohorts (P<0.01), which implied a stronger correlation between lower risk and longer OS (*Figure 7*).

Table 4 Total points and survival rate in the nomogram

Time	Survival rate, %							
	10	20	30	40	50	60	70	80
3 years	459	440	424	410	395	378	360	335
5 years	439	420	405	390	375	359	340	–

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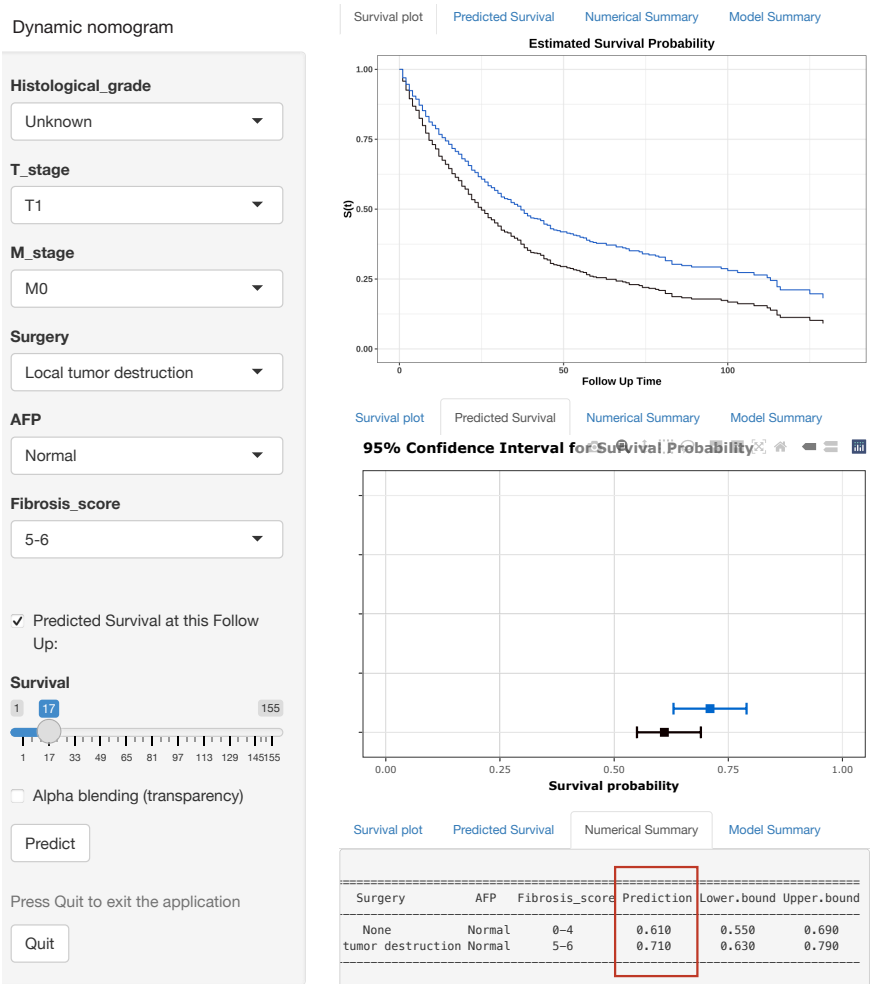

Figure 3 Layout of an online version of the developed nomogram (https://jikun.shinyapps.io/large_hcc). The black line stands for the estimated survival probability of the patients with a fibrosis score of 0–4, normal AFP level, unknown histological grade, T1 and M0 stage, and no surgery. The blue line stands for those with a fibrosis score of 5–6, normal AFP level, well/moderate histological grade, T1 and M0 stage, and undergoing local tumor destruction. AFP, alpha fetoprotein.

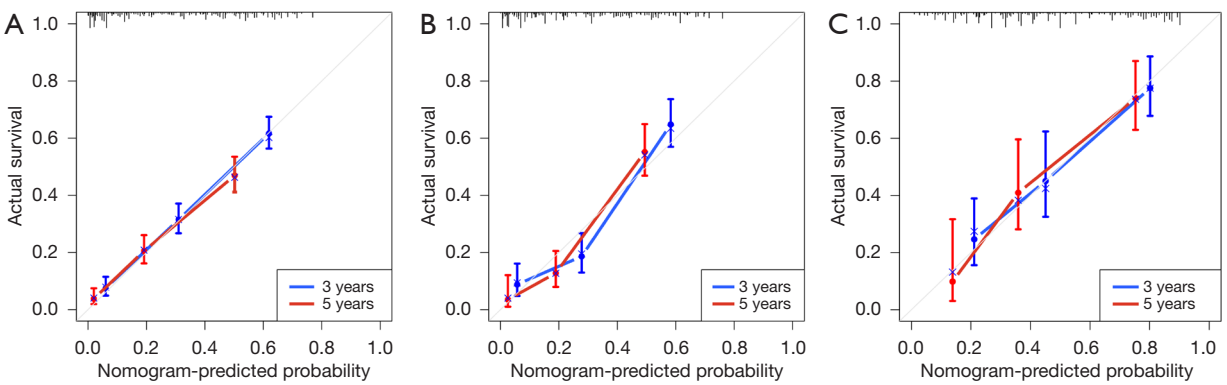

Figure 4 Calibration curves of nomogram for predicting overall survival at 3- and 5-year in the training cohort (A), internal validation cohort (B) and external validation cohort (C), respectively.

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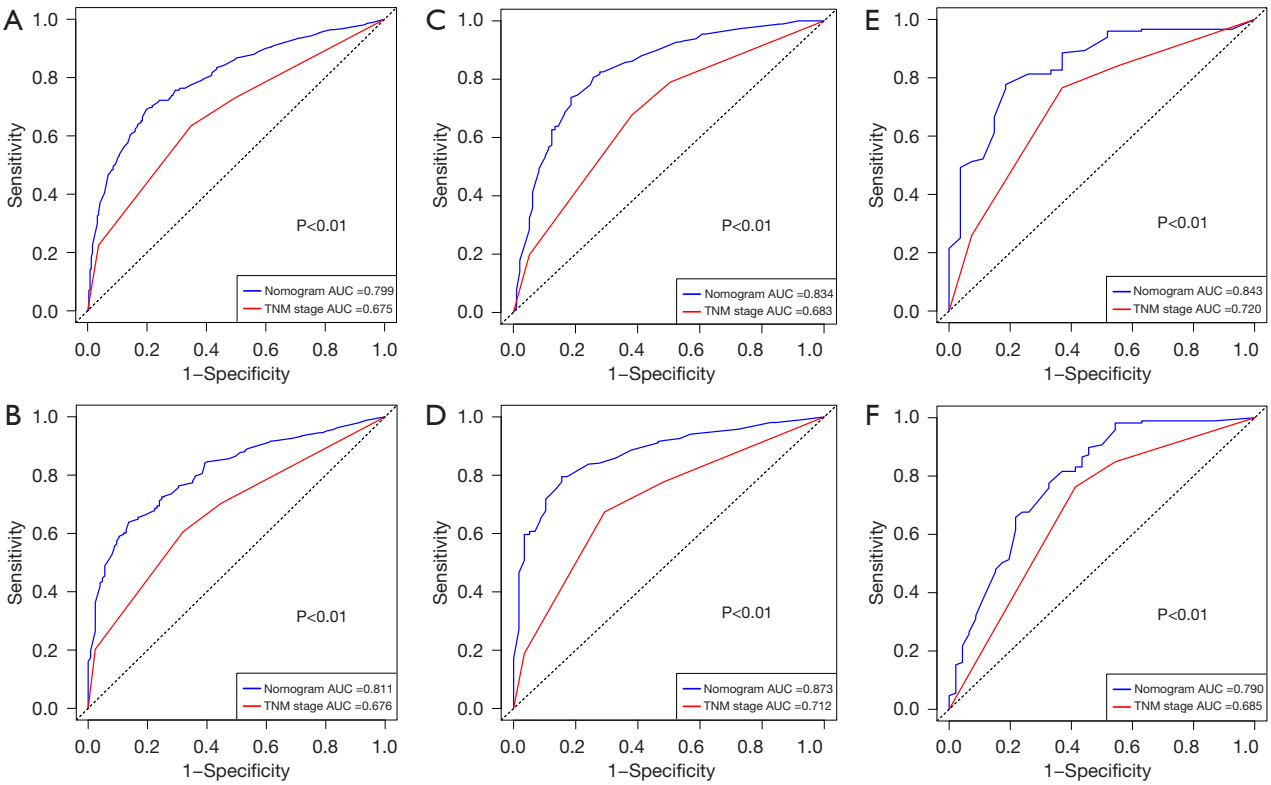

Figure 5 ROC curves of nomogram and TNM staging for predicting overall survival at 3- and 5-year in the training cohort (A,B), internal validation cohort (C,D) and external validation cohort (E,F), respectively. ROC, receiver operating characteristic curve; AUC, areas under the curve; TNM, tumor node metastasis staging.

Discussion

Advances in imaging modalities and health monitoring strategy in high-risk population have facilitated the early detection of HCC, leading to improved outcomes in terms of OS (16). However, large HCC with a diameter ≥5 cm is frequently diagnosed at an advanced stage, presenting a challenge to clinicians because of high likelihood of microvascular invasion, satellite nodules, recurrence and metastasis (17,18). Previous studies have revealed that some factors such as cirrhosis, vascular invasion and treatment are associated with OS in patients with large HCC (9,19). Nevertheless, until now, there is limited study having developed nomogram to predict outcomes for large HCC. In the present study, we developed and validated a nomogram model based on a large population from SEER database and an independent cohort of patients from our center to accurately estimate individual 3- and 5-year survival probabilities for patients with large HCC. The nomogram showed excellent discrimination and calibration of valuable consistencies between the prediction and observation especially in the external validation cohort, indicating a superior external utility of nomogram.

Although the AJCC TNM staging has been widely applied to determine treatment method and expected survival for HCC patients (6), there is still controversy regarding its ability in predicting prognosis (8,12). This nomogram exhibited a superiority over the TNM staging system in predictive ability of prognosis, with a higher AUCs in internal and external validation cohorts. In DCA curves, improved clinical value of nomogram was observed compared with the TNM staging system. These results clearly illustrated considerable difference between the TNM staging based on T, N, and M stages solely and nomogram model integrating various significant clinicopathological factors for prognoses prediction of patients with large HCC.

Liver fibrosis, as a result of chronic liver injury, makes a considerable contribution to the formation of cirrhosis and HCC (20). Accordingly, the current study illustrated a correlation between the worsening prognosis and increasing

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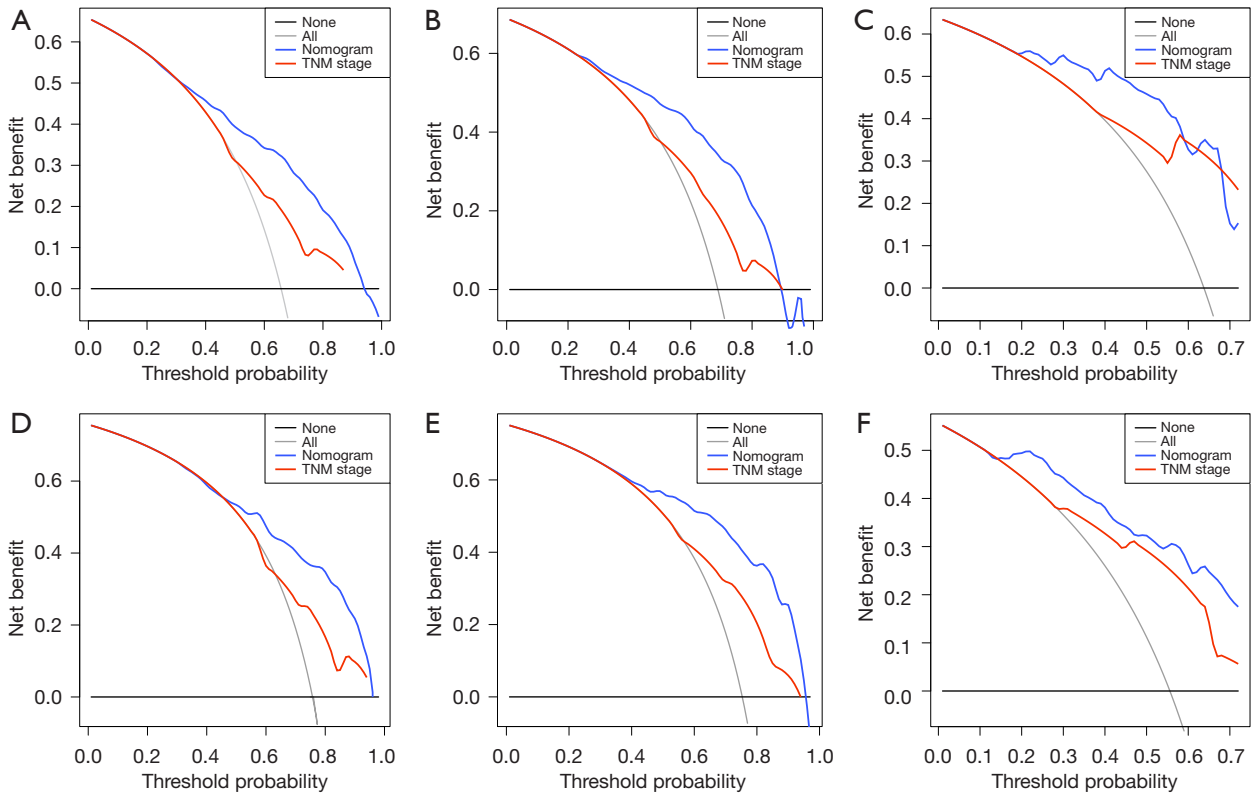

Figure 6 Decision curves of nomogram and TNM staging for clinical utility of overall survival at 3- and 5-year in the training cohort (A,B), internal validation cohort (C,D) and external validation cohort (E,F), respectively. TNM, tumor node metastasis staging.

fibrosis degree, potentially attributed to the advancement of fibrosis leading to liver failure, hepatic encephalopathy, and portal hypertension (21,22). Moreover, the tumor resection rate of patients with none or moderate fibrosis was over twice that of those with severe fibrosis or cirrhosis in this study (64.7% *vs.* 30.6%, P<0.01), indicating that the severity of fibrosis may impact patient survival by influencing the selection of treatment.

In accordance with findings of Liu *et al.* (23), the level of AFP turned out to be an independent prognostic factor for large HCC. Two staging system, Cancer of the Liver Italian Program (CLIP) (24) and Chinese University Prognostic Index (CUPI), have emphasized and incorporated the preoperative AFP levels into prognostic assessment. The underlying rationale for the correlation between increased levels of AFP and poorer prognosis remains unclear (25). Studies found that a high level of AFP was related to the dysfunctional antigen-presenting cells and the impaired dendritic cells in patients with HCC (26,27), and this interaction between AFP and the immune system may account for poor outcomes.

It was observed that histological grade, a indicator of biological aggressiveness of HCC, had a stronger correlation with tumor recurrence and survival (12,28). In this study, the median survival of patients with histological grade of well/moderate and poor/undifferentiated were 22 and 9 months, respectively (P<0.01), illustrating that degree of differentiation of tumor posed significant influence on prognosis. Furthermore, our study found that the tumor metastasis rate of poor differentiation was significantly higher than that of well differentiation (19% *vs.* 9.1%, P<0.01), indicting an increased invasiveness and metastatic nature of poor differentiation. Surgery plays a most important role in impacting prognosis in our study. Although surgical resection remains the mainstay of curative treatment for HCC, only 41% of patients are candidates for hepatectomy because of decompensated liver function, vascular invasion and metastasis (29-31), in accordance with fewer than half of the cases had undergone hepatectomy in this study. When it comes to unresectable HCC, the optional therapy includes radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) (32).

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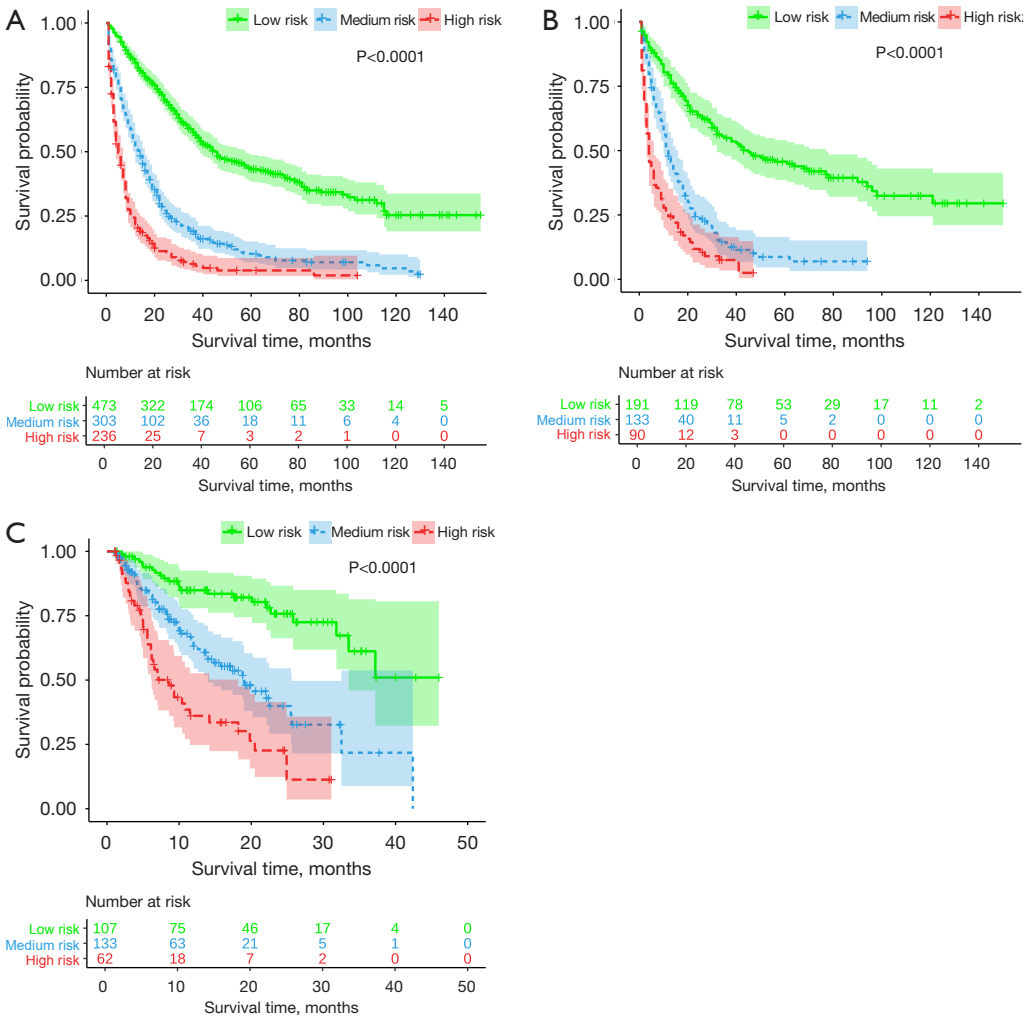

Figure 7 Kaplan-Meier curves for comparing different risk groups of patients with large hepatocellular carcinoma in the training cohort (A), internal validation cohort (B) and external validation cohort (C).

In addition, prognostic stratification system including high-, middle-, and low-risk groups was constructed based on the total scores from nomogram. As shown in the K-M curves, the population at high risk was significantly associated with poor prognosis. The prognostic stratification system may be helpful to formulate individual therapy method and follow-up plan according to the different risk groups. The patients at low risk could have more treatment options based on liver function and tumor status; for patients at medium risk, a combination of targeted therapy or immunotherapy may be recommended to improve survival; patients at high risk may need palliative treatment. For patients deemed to be at high risk, it is recommended that the follow-up interval should be shortened and adjusted according to tumor status. Conversely, for patients classified as low risk group, the follow-up interval may be prolonged appropriately.

There are some limitations in the present study. First, the retrospective design of the study may lead to unavoidable selection bias. Second, nomogram did not include prognostic predictors such as liver function, since information of liver function was unavailable in SEER database. Besides, another limitation was a lack of validation using data of patients from other countries, though we have confirmed the reliable predictive power of nomogram-based prognostic stratification in Chinese patients. Therefore, further multicenter studies should be warranted in order to verify the prognostic stratification worldwide.

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Conclusions

In summary, this study proposed a nomogram model on basis of a large population to predict 3- and 5-year survival rates for patients with large HCC, which showed preferable prediction ability in comparison with the TNM staging. Furthermore, nomogram-based prognostic stratification was developed as a valuable tool to assist clinicians on the selection of optimal treatment method and follow-up plan, particularly for high-risk population.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-288/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-288/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-288/coif). The authors have no conflicts of interest to declare.

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). The study was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2016-324) and individual consent for this retrospective analysis was waived.

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