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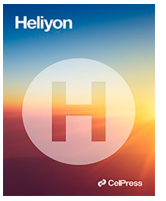

Research article

# Development and validation of nomograms for predicting prognosis in patients with solitary HCC: A TRIPOD-Compliant study☆

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ABSTRACT

*Objective:* To develop and validate nomograms for predicting the OS and CSS of patients with Solitary Hepatocellular Carcinoma (HCC).

*Methods:* Using the TRIPOD guidelines, this study identified 5206 patients in the Surveillance, Epidemiology, and End Results (SEER) 17 registry database. All patients were randomly divided in a ratio of 7:3 into a training cohort (n = 3646) and a validation cohort (n = 1560), and the Chinese independent cohort (n = 307) constituted the external validation group. The prognosis-related risk factors were selected using univariate Cox regression analysis, and the independent prognostic factors of OS and CSS were identified using the Lasso-Cox regression model. The nomograms for predicting the OS and CSS of the patients were constructed based on the identified prognostic factors. Their prediction ability was evaluated using the concordance index (C-index), receiver operating characteristic (ROC) curve, and calibration curve in both the training and validation cohorts.

*Results:* We identified factors that predict OS and CSS and constructed two nomograms based on the data. The ROC analysis, C-index analysis, and calibration analysis indicated that the two nomograms performed well over the 1, 3, and 5-year OS and CSS periods in both the training and validation cohorts. Additionally, these results were confirmed in the external validation group. Decision curve analysis (DCA) demonstrated that the two nomograms were clinically valuable and superior to the TNM stage system.

*Conclusion:* We established and validated nomograms to predict 1,3, and 5-year OS and CSS in solitary HCC patients, and our results may also be helpful for clinical decision-making.

## 1. Introduction

Liver cancer represents one of the most frequent malignant diseases globally, and hepatocellular carcinoma (HCC) is the most common type [1,2]. Hepatitis B and C virus infections were the most common cause of HCC. We believe that the high Incidence of Hepatocellular Carcinoma caused by virus-infected might be controlled in the coming few years because the HBV vaccine is recommended for all newborns and hepatitis B and C with antiviral agents in infected populations in most countries and regions [3].

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**Abbreviations**

| | |
|---|---|
| HCC | hepatocellular carcinoma |
| TRIPOD | Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis |
| OS | overall survival |
| CSS | cancer-specific survival |
| C-index | the concordance index |
| ROC curve | receiver operating characteristic curve |
| AUC | areas under the receiver operating characteristic curve |
| DCA | decision curve analysis |
| SEER | Surveillance, Epidemiology, and End Results |
| AJCC | American Joint Committee on Cancer |
| AFP | alpha-fetoprotein |

However, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) is increasing worldwide. It may soon exceed Hepatitis B and C virus infections as the world's primary cause of Hepatocellular Carcinoma [4]. Though in recent years, the therapeutic approaches for Hepatocellular Carcinoma have been continuously developed and improved, the prognosis of HCC patients is still far from optimal, and the rate of tumor recurrence five years after resection is more than 70% [5]. So, HCC is a significant and challenging global health problem based on situation [6].

Tumor number has an impact on the survival of individuals with different types of tumors. According to the number, tumors was classified as single or multiple ($\geq$2), of which the single also known as solitary tumors. In American Joint Committee on Cancer (AJCC) TNM staging system (7th edition), a primary solitary HCC without vascular invasion is categorized as T1. In contrast, a solitary HCC with vascular invasion is classified as T2. Nomograms were constructed according to independent predictors and had been frequently used for cancer prognosis prediction via a simple visualization modality [7]. Although there are many research and prognostic models in HCC, regrettably, the nomogram to predict the overall prognosis of patients with solitary HCC is still lacking. Several studies have established survival prediction models for patients with postoperative solitary HCC, despite the C-index of one model being 0.87. However, it should be noted that these models were developed for the patients who underwent hepatic resections only [8,9]. Because

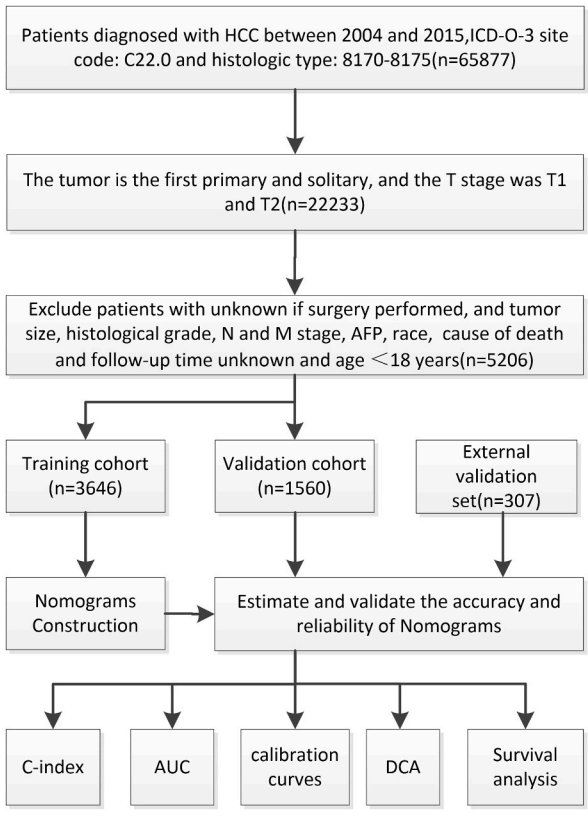


**Fig. 1.** Flow diagram for selecting solitary hepatocellular carcinoma patients.

only 5%–15% of patients are eligible for surgical removal, most patients with HCC are unsuitable for surgery [10], limiting the models' wide application described above.

The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) is a guiding report for building prediction models [11], and this study complies with TRIPOD guidance on multivariable prediction models (see Supplementary **doc s1**, a table with the TRIPOD checklist). We aimed to use the Surveillance, Epidemiology, and End Results (SEER) database to develop and validate prognostic nomograms to predict the overall prognosis of solitary HCC patients. We hope that our results will help clinicians and surgeons in clinical decision-making.

## 2. Material and methods

### 2.1. Participants

This was a retrospective study, and data were obtained from the SEER database using the SEER 17 Registries Database (https://seer.cancer.gov/). The dataset was released in April 2022 and was based on a November 2021 submission. The SEER database, managed by the National Cancer Institute, is the world's largest cancer database, and our authorized account was 12,666-Nov2021. The details included demographic information, Clinicopathological information, treatment, and follow-up information of patients with HCC between 2004 and 2015, which were extracted from the SEER database using SEER*Stat software (v8.4.0.1).

Only patients with complete data were included in this study, and the inclusion/exclusion criteria were as follows: (1) primary site code C20.0 and histologic type code 8170–8175; (2) T stage was categorized as T1 and T2 according to the AJCC 7th and primary tumor number single; (3) Hepatocellular carcinoma as the only tumor or first primary tumor, and complete information of each variable for all patients; age$\geq$18 years. The therapy information was an essential indicator for observation, and treatment modality was categorized as no-surgery, Local treatment, hepatectomy, and transplantation. Eventually, 5206 patients were included in the study and were randomly divided into the training (n = 3646) and the validation (n = 1560) cohorts at the ratio of 7:3 (Fig. 1). The external verification (n = 307)set was composed of 204 patients from the Chinese Liver Cancer Clinical Survey (CLCS) and 103 patients with solitary HCC in our hospital. They all underwent surgical resection and had no relationship to the SEER database.

### 2.2. Outcome

The survival outcomes of this study were cancer-specific survival (CSS) and overall survival (OS). SEER defines OS as the time from diagnosis until death reported in vital status, and CSS was calculated from the time of diagnosis to the time of cancer-specific death. It was written in SEER as 'SEER cause-specific survival.' All data was extracted directly from the SEER database, and we did not make any changes to the original records. Follow-up of external validation sets was performed by clinic visits, medical record review, and telephone contact. All the people who recorded the information were not involved in the performance of statistical analyses.

### 2.3. Predictors

The predictors were defined according to the records of the SEER database. Patient's demographic information, such as age, gender, and ethnicity; Clinical and Pathological information, such as tumor differentiation, histologic type, AJCC stage, TNM stage, and A-fetoprotein (AFP); Information of treatment, such as whether to treat and the specific therapeutic modality and prognosis were collected. Retrospective clinical data and treatment histories could obtain the original collection data and be more objective and accurate. This study did not include several indicators, such as chemotherapy, radiotherapy, fibrosis score, etc. Known limitations of SEER data include a lack of detailed information about chemotherapy and radiotherapy. The liver fibrosis score was also excluded because this variable has too many missing values (>80%).

### 2.4. Missing data

Only patients with complete data were analyzed in this study to improve the model's prediction accuracy. Missing data was recorded as "unknown," "999", or other unclear formations in the SEER dataset, and patients with missing information would be removed from this study. Variables like fibrosis scores with greater than 80% missing values were excluded from predictive modeling analyses according to the absent data imputation strategy described in a previous study.

### 2.5. Ethics

The study was conducted by the Helsinki declaration and its subsequent amendments from 1964, and our Institutional Ethics Committee approved it.

### 2.6. Statistical analysis

#### 2.6.1. Predictors processing

These continuous variables, including age and tumor size, were translated into categorical variables based on the optimal cut-off value generated by X-tile software version 3.6.1 (Yale University School of Medicine, US) (Figure s1). The histologic subtype was

categorized as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated, and subpopulations like undifferentiated with small sample sizes had been merged into poorly differentiated. In the treatment modalities, radiofrequency ablation (RFA), cryotherapy, and ethanol injection were grouped into local treatment, and all surgical resections were classified as hepatectomy. Race, Sex, T stage, N stage, M stage, and AFP, documented in SEER, were included as categorical variables.

#### 2.6.2. Cox regression modeling

The Chi-square test was used to compare the training and validation cohorts' differences. Factors associated with OS or CSS were evaluated using the univariate cox regressions. Those variables with univariate $p < 0.1$ were included to select the independent predictors by lasso-cox regression analysis. Statistical analyses were completed using SPSS software (version 26) and R software (version 4.1.2). P-value $<0.05$ was considered statistically significant.

#### 2.6.3. Nomograms construction

The nomograms for predicting OS and CSS in patients with solitary HCC were constructed using R software based on the results of the lasso-cox regression analysis.

#### 2.6.4. Validation

The C-index, ROC curve, calibration curve, and DCA were used to evaluate the nomogram's abilities in the training and internal validation sets, respectively. While in the external validation set, which was completely independent of the SEER dataset, only the ROC curve and calibration curve was used to evaluate the predictive performance of the nomograms because of insufficient sample size. It was considered satisfactory when the AUC (areas under the ROC curve) or C-index was greater than 0.7.

### 2.7. Risk groups

In the training set and internal validation set, patients were divided into high-risk and low-risk groups based on the median score of the patients in the training set. Kaplan–Meier curves performed survival analyses, and the log-rank test compared the groups.

**Table 1**
Baseline demographic and clinical characteristics of solitary HCC patients in the training cohort and validation cohort.

| Characteristics | All cohort | Training cohort | Validation cohort | P |
|---|---|---|---|---|
| | (n = 5206) | (n = 3646) | (n = 1560) | |
| Age (years) | | | | 0.271 |
| ≤63 | 2862 (55.0%) | 1986 (54.5%) | 876 (56.2%) | |
| 63-75 | 1503 (28.9%) | 1052 (28.9%) | 451 (28.9%) | |
| ≥75 | 841 (16.2%) | 608 (16.7%) | 233 (14.9%) | |
| Sex | | | | 0.805 |
| Female | 1343 (25.8%) | 937 (25.7%) | 406 (26.0%) | |
| Male | 3863 (74.2%) | 2709 (74.3%) | 1154 (74.0%) | |
| Race | | | | 0.288 |
| White | 3390 (65.1%) | 2393 (65.6%) | 997 (63.9%) | |
| Black | 573 (11.0%) | 386 (10.6%) | 187 (12.0%) | |
| Other | 1243 (23.9%) | 867 (23.8%) | 376 (24.1%) | |
| Grade | | | | 0.417 |
| I | 1773 (34.1%) | 1253 (34.4%) | 520 (33.3%) | |
| II | 2421 (46.5%) | 1674 (45.9%) | 747 (47.9%) | |
| III + IV | 1012 (19.4%) | 719 (19.7%) | 293 (18.8%) | |
| T stage | | | | 0.941 |
| T1 | 4468 (85.8%) | 3130 (85.8%) | 1338 (85.8%) | |
| T2 | 738 (14.2%) | 516 (14.2%) | 222 (14.2%) | |
| N stage | | | | 0.56 |
| N0 | 5063 (97.3%) | 3549 (97.3%) | 1514 (97.1%) | |
| N1 | 143 (2.7%) | 97 (2.7%) | 46 (2.9%) | |
| M stage | | | | 0.997 |
| M0 | 4979 (95.6%) | 3487 (95.6%) | 1492 (95.6%) | |
| M1 | 227 (4.4%) | 159 (4.4%) | 68 (4.4%) | |
| Treatment | | | | 0.412 |
| No surgery | 1880 (36.1%) | 1317 (36.1%) | 563 (36.1%) | |
| Local-treatment | 806 (15.5%) | 576 (15.8%) | 230 (14.7%) | |
| Hepatectomy | 1834 (35.2%) | 1262 (34.6%) | 572 (36.7%) | |
| Liver transplantation | 686 (13.2%) | 491 (13.5%) | 195 (12.5%) | |
| Size (cm) | | | | 0.903 |
| ≤3.7 | 2327 (44.7%) | 1636 (44.9%) | 691 (44.3%) | |
| 3.7–5.6 | 1107 (21.3%) | 770 (21.1%) | 337 (21.6%) | |
| ≥5.6 | 1772 (34.0%) | 1240 (34.0%) | 532 (34.1%) | |
| AFP | | | | 0.175 |
| Negative | 1983 (38.1%) | 1367 (37.5%) | 616 (39.5%) | |
| Positive | 3223 (61.9%) | 2279 (62.5%) | 944 (60.5%) | |

## 3. Results

### 3.1. Participants

The study comprised a total of 5513 patients, and among them, there were 5206 patients from the SEER database and 307 patients from China. Patients were divided into the training cohort (n = 3646), the validation cohort (n = 1560), and the external validation set (n = 307). In the SEER dataset, 3464 (66.5%) patients died with the median OS was 41 months, and the 1-, 3-, and 5-year overall survival rates were 75.1%, 52.6%, and 42.0%, respectively; 2760 (53.0%) patients died of cancer with the median CSS was 58 months, and the 1-, 3-, and 5-year cancer-specific survival rate were 78.6%, 58.9%, and 49.5%, respectively. In the external validation set, 195 (63.5%) patients died with the median OS was 56 months, and the 1-, 3-, and 5-year overall survival rates were 89.9%, 72.2%, and 43.8%, respectively; 164 (53.4%) patients died of cancer with the median CSS was 60 months, and the 1-, 3-, and 5-year cancer-specific survival rate were 90.5%, 75.3%, and 48.9%, respectively.

The demographics and the main baseline characteristics of the all cohort, training cohort, and internal validation cohort are described in Table 1. As we can see from the table, white, male, and no-surgery patients accounted for the majority. Only a minority of the patients were stage N1 and stage M1, which might indicate that the incidence of extra-hepatic metastasis in patients with solitary HCC was low. There was no statistical difference in baseline characteristics between the training and validation cohorts. The baseline characteristics of the external validation cohort are indicated in Supplementary Table S1.

### 3.2. Model development

#### 3.2.1. Screen predictors

Univariate Cox regression analysis indicated that Age, Sex, Race, Grade, N-stage, M-stage, Treatments, Size, and AFP were correlated with OS($p < 0.1$); Age, Race, Grade, T-stage, N-stage, M-stage, Treatments, Size, and AFP were associated with CSS($p < 0.1$) (Table 2). Those factors with $P < 0.1$ in univariate cox regression analyses were further screened by Lasso-Cox regression analysis to filter independently significant predictors. The results show that the independent predictors of OS included Age, Race, Grade, M-stage,

**Table 2**
Univariate analysis of prognostic factors for OS and CSS.

| Characteristics | Univariable Analysis for OS | | Univariable Analysis for CSS | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| Age (years) | | | | |
| ≤63 | | reference | | reference |
| 63-75 | 0.431 (0.388–0.478) | <0.001 | 0.434 (0.386–0.487) | <0.001 |
| ≥75 | 0.611 (0.546–0.683) | <0.001 | 0.623 (0.550–0.706) | <0.001 |
| Sex | | | | |
| Female | | reference | | reference |
| Male | 1.091 (0.995–1.197) | 0.065 | 1.073 (0.967–1.190) | 0.182 |
| Race | | | | |
| White | | reference | | reference |
| Black | 1.395 (1.263–1.541) | <0.001 | 1.341 (1.201–1.498) | <0.001 |
| Other | 1.505 (1.300–1.743) | <0.001 | 1.410 (1.195–1.663) | <0.001 |
| Grade | | | | |
| I | | reference | | reference |
| II | 0.738 (0.663–0.822) | <0.001 | 0.666 (0.592–0.750) | <0.001 |
| III + IV | 0.653 (0.588–0.724) | <0.001 | 0.606 (0.541–0.679) | <0.001 |
| T stage | | | | |
| T1 | | reference | | reference |
| T2 | 1.042 (0.932–1.166) | 0.467 | 1.125 (0.995–1.271) | 0.060 |
| N stage | | | | |
| N0 | | reference | | reference |
| N1 | 2.698 (2.187–3.329) | <0.001 | 3.025 (2.423–3.777) | <0.001 |
| M stage | | | | |
| M0 | | reference | | reference |
| M1 | 4.136 (3.508–4.875) | <0.001 | 4.757 (4.005–5.649) | <0.001 |
| Treatment | | | | |
| No surgery | | reference | | reference |
| Local-treatment | 7.324 (6.212–8.634) | <0.001 | 12.591 (10.005–15.846) | <0.001 |
| Hepatectomy | 3.133 (2.613–3.756) | <0.001 | 4.975 (3.889–6.365) | <0.001 |
| Liver-transplantation | 2.121 (1.791–2.513) | <0.001 | 3.438 (2.718–4.349) | <0.001 |
| Size (cm) | | | | |
| ≤3.7 | | reference | | reference |
| 3.7–5.6 | 0.415 (0.379–0.455) | <0.001 | 0.335 (0.302–0.371) | <0.001 |
| ≥5.6 | 0.678 (0.611–0.752) | <0.001 | 0.603 (0.537–0.676) | <0.001 |
| AFP | | | | |
| Negative | | reference | | reference |
| Positive | 1.305 (1.201–1.418) | <0.001 | 1.400 (1.274–1.538) | <0.001 |

Treatments, Size, and AFP, and the independent predictors of CSS included Age, Grade, M-stage, Treatments, Size, and AFP. The procedures for selecting predictors are shown in Supplementary Figure s2.

A p-value <0.05 was set as the threshold for significance, and the Hazard Ratios (HR) and coefficient of the multivariable regression model(β) indicated the effect of independent variables on death. The predictor had been identified as a risk factor for death if the corresponding $\beta > 0$ or the HR value > 1 significantly. In multivariate Cox regression analysis, Age, Grade, M-stage, Treatments, Size, and AFP were independent prognostic factors for OS and CSS. The race was also an independent prognostic factor for OS. Among these, advanced age ($\beta = 0.491$, HR = 1.634), poor differentiation ($\beta = 0.399$, HR = 1.490), distant metastases ($\beta = 0.681$, HR = 1.976), and larger tumor size ($\beta = 0.582$, HR = 1.789) were significant risk factors associated with poor oncologic outcomes. Distant metastases had the most significant effect on survival. The risk of death and cancer-specific death in patients with distant metastasis were 1.976 and 2.091 times that of patients without distant metastasis. Conversely, Treatment was a significant protective factor for prognosis, and the lowest risk of death was observed in patients receiving Liver transplantation ($b = -1.571$, HR = 0.208) compared to no treatment. More results are detailed in Table 3. This study has been carried out on patients with complete data sets. As various practical reasons, such as patients with incomplete data sets or unknown factors, might have extraordinary clinical implications, we know that the prediction models may not be available for all HCC patients.

#### 3.2.2. Nomogram construction

Based on the results of LASSO-COX regression analysis, two nomograms were developed to predict and visualize the 1-,3-, and 5-year OS and CSS rates in patients with solitary HCC (Fig. 2A/2B). For example, if the participant with solitary HCC chose hepatectomy, we first need to get the several parameters and the position of each parameter on the corresponding axes; the score for each parameter was calculated by drawing a perpendicular line to the 0- to 100-point scale axis. Secondly, each parameter's scores were added and given a total score. Thirdly, find the location of the full scores on the "Total Points" axis and draw a perpendicular line to the 1-, 3-, and 5-year survival probabilities axis. The corresponding positions on the survival probabilities axis were 1-, 3-, and 5-year OS/CSS of the participant.

### 3.3. Model validation

In the training and internal validation cohorts, the C-indexes of the nomogram for predicting OS were respectively 0.732 (95%CI, 0.722–0.742) and 0.726 (95%CI, 0.710–0.742); and for predicting CSS was 0.758 (95%CI, 0.748–0.768) and 0.743 (95%CI, 0.725–0.761), respectively. The ROC curves found that area under the curve (AUC) of OS nomogram at 1-, 3-, and 5-year were 0.801, 0.793, and 0.802 in the training cohort (Fig. 3A); 0.779, 0.800, and 0.792 in internal validation cohort (Fig. 3B); 0.726, 0.710, and 0.725 in external validation cohort (Fig. 3C). The AUC of CSS nomogram at 1-, 3-, and 5-year were 0.833, 0.814, and 0.816 in the training cohort (Fig. 3D); 0.803, 0.812, and 0.801 in internal validation cohort (Fig. 3E); 0.720, 0.686, and 0.720 in external validation

**Table 3**
Multivariate analysis of prognostic factors for OS and CSS.

| Characteristics | Multivariable regression for OS | | | Multivariable regression for CSS | | |
|---|---|---|---|---|---|---|
| | β | HR (95% CI) | P | β | HR (95% CI) | P |
| Race | | | | | | |
| White | 0 | Ref | <0.001 | | | |
| Black | 0.105 | 1.111 (0.976–1.264) | 0.110 | | | |
| Other | −0.279 | 0.756 (0.683–0.837) | <0.001 | | | |
| Age (years) | | | | | | |
| ≤63 | 0 | Ref | <0.001 | 0 | Ref | <0.001 |
| 63-75 | 0.217 | 1.242 (1.131–1.365) | <0.001 | 0.185 | 1.203 (1.084–1.336) | 0.001 |
| ≥75 | 0.491 | 1.634 (1.467–1.820) | <0.001 | 0.383 | 1.467 (1.302–1.652) | <0.001 |
| Grade | | | | | | |
| I | 0 | Ref | <0.001 | 0 | Ref | <0.001 |
| II | 0.095 | 1.099 (1.002–1.206) | 0.046 | 0.126 | 1.134 (1.021–1.260) | 0.019 |
| III + IV | 0.399 | 1.490 (1.330–1.668) | <0.001 | 0.461 | 1.586 (1.399–1.797) | <0.001 |
| M stage | | | | | | |
| M0 | 0 | Ref | | | Ref | |
| M1 | 0.681 | 1.976 (1.667–2.343) | <0.001 | 0.738 | 2.091 (1.750–2.498) | <0.001 |
| Treatment | | | | | | |
| No surgery | 0 | Ref | <0.001 | 0 | Ref | <0.001 |
| Local-treatment | −0.55 | 0.577 (0.511–0.650) | <0.001 | −0.583 | 0.558 (0.488–0.639) | <0.001 |
| Hepatectomy | −1.168 | 0.311 (0.281–0.344) | <0.001 | −1.283 | 0.277 (0.248–0.310) | <0.001 |
| Liver-transplantation | −1.571 | 0.208 (0.175–0.247) | <0.001 | −2.042 | 0.130 (0.102–0.165) | <0.001 |
| Size (cm) | | | | | | |
| ≤3.7 | 0 | Ref | <0.001 | 0 | Ref | <0.001 |
| 3.7–5.6 | 0.292 | 1.339 (1.200–1.493) | <0.001 | 0.383 | 1.467 (1.295–1.663) | <0.001 |
| ≥5.6 | 0.582 | 1.789 (1.618–1.979) | <0.001 | 0.767 | 2.154 (1.922–2.413) | <0.001 |
| AFP | | | | | | |
| Negative | 0 | Ref | | 0 | Ref | |
| Positive | 0.224 | 1.251 (1.148–1.363) | <0.001 | 0.286 | 1.331 (1.207–1.467) | <0.001 |

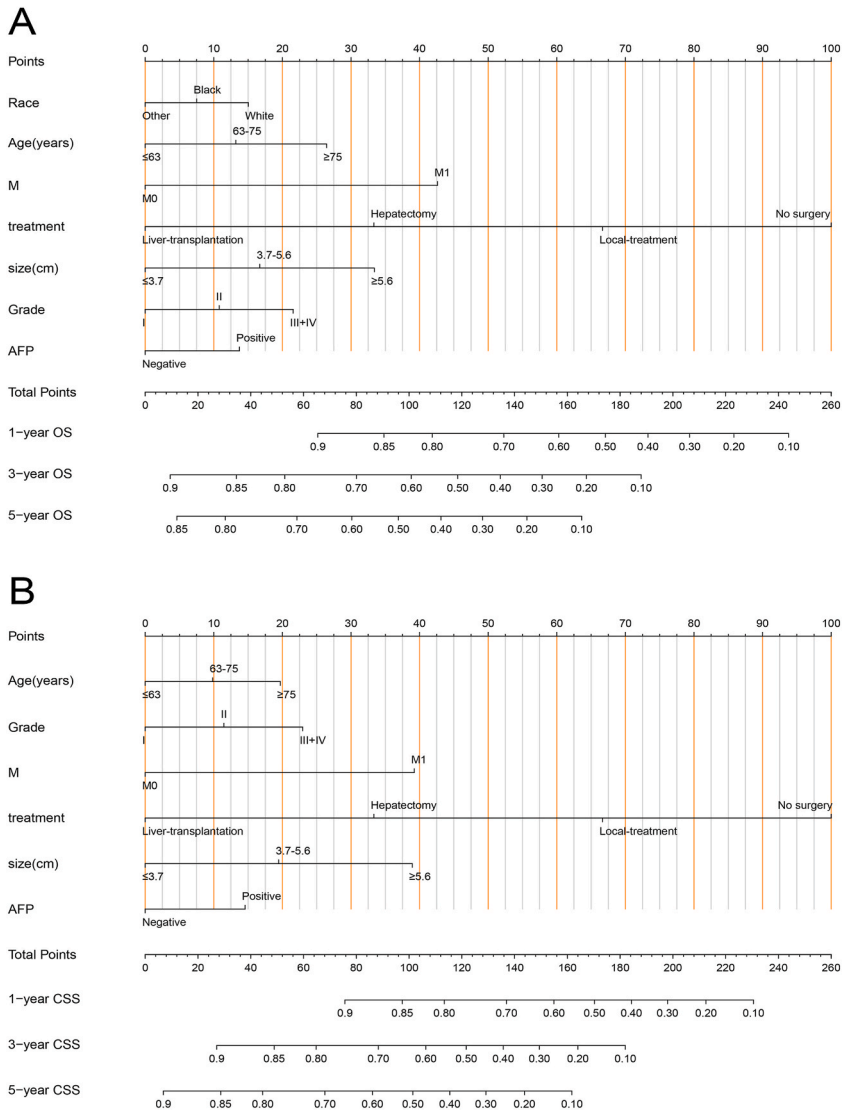


**Fig. 2.** Nomograms for predicting 1-, 3-, and 5-year OS(A) and CSS(B) of patients with solitary HCC. OS, overall survival; CSS, cancer-specific survival.

cohort (Fig. 3F).

The Calibration plots for the nomogram-predicted probabilities of 1-, 3-, and 5- year OS and CSS showed high consistency with the actual survival in the three cohorts (Fig. 4A–F). Decision curve analysis (DCA) demonstrated that the two nomograms were clinically valuable and superior to the 7th edition of the TNM staging system (Supplementary Figure s3/s4). We calculated the risk score for every patient according to the nomograms, and patients were divided into high-risk and low-risk groups based on the median score of the patients in the training set. According to the Kaplan-Meier (KM) survival analysis, patients in the low-risk group had better prognoses than those in the high-risk group ($P < 0.05$; Fig. 5).

## 4. Discussion

The study developed and validated prognostic nomogram models for OS and CSS patients with solitary HCC based on the SEER database and validated externally using a separate Chinese cohort. The nomogram for OS included seven prognostic factors (Age, Race, Grade, M-stage, Treatments, Size, and AFP), and that for CSS included six prognostic factors (Age, Grade, M-stage, Treatments, Size, and AFP). All information could be easily obtained in clinical knowledge and follow-up data. C-indexes, ROC curves, and calibration curves assessed the performance of the nomograms, and the results were satisfactory. The DCA showed that nomograms were more useful for clinical applications than the TNM staging system (7-th edition). Validation with independent data showed that the predictabilities of models were also satisfactory (mean AUC >0.7). Kaplan-Meier analysis indicated that high- and low-risk groups could

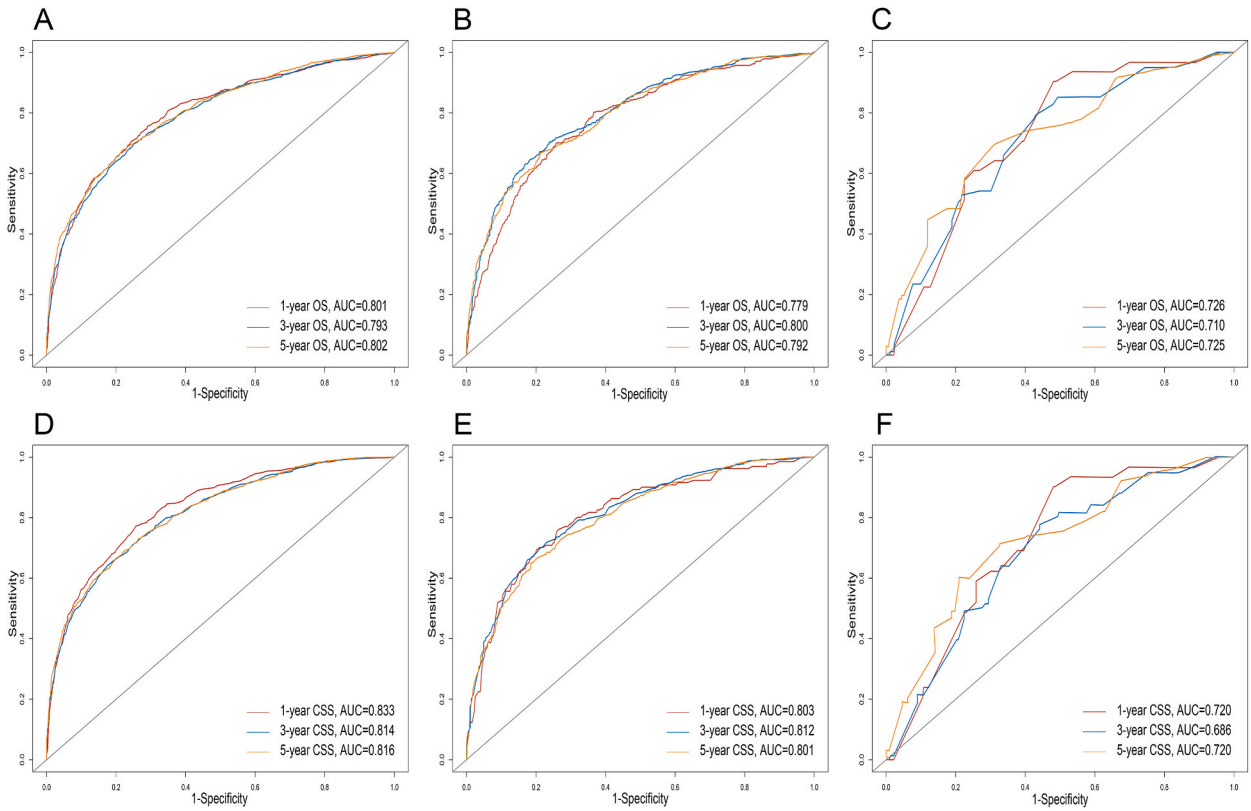


**Fig. 3.** ROC of the nomograms for 1-, 3-, and 5-year OS and CSS in the training cohort (A/D), internal validation cohort (B/E), and external validation cohort (C/F). A/B/C, nomogram for OS; D/E/F, nomogram for CSS.

be identified based on the nomograms.

Multivariate regression analysis revealed that Age, Race, Grade, M-stage, Treatments, Size, and AFP were significantly associated with the prognosis of patients with solitary HCC. Of these, treatment was the most significant protective factor on prognosis, and Liver transplantation was currently the best treatment for identical conditions. However, due to a shortage of donors, surgical resection remains the preferred method for treating HCC [12]. It is a pity that the resection rate of HCC patients was not as high, even though only about 5%–15% of those with early-stage HCC were suitable for surgical resection [10]. The median OS of the study cohort was 41 months, and the corresponding OS at five years was 42%. Despite the surgical treatment being performed, the 5-year survival rate is only 48.9% (external validation set), similar to that reported in previous studies (46.5%) [9]. Tumor size was a significant risk factor for the prognosis of patients with solitary HCC; the larger the tumor at a diagnosis, the worse the prognosis [13]. The reason might be that the large (diameter of 3 cm) tumors may promote malignant biological behavior such as tumor occurrence, proliferation, and invasion [14,15], as well as unfavorable prognoses such as microvascular invasion (MVI) and satellite lesions [16,17]. Meanwhile, tumor size might also influence the choice of treatment regimens. According to the Milan criteria, liver transplantation (LT) is the treatment of choice for patients with solitary tumors smaller than 5 cm; however, because of these difficulties, including lack of liver donors, long waiting times, and high costs, most patients received surgical resection or other minimally invasive therapy. In recent years, minimally invasive, local ablation therapies have been increasingly used as an effective treatment for HCC [18], but the therapeutic efficacy remained controversial. When the HCC nodule was smaller than 3 cm, the survival rates of RFA and surgical resection were not significantly different [12]. Still, another randomized controlled trial revealed that RFA for early HCC was not superior to surgical resection in terms of overall and disease-free survival [19]. Many studies have confirmed that the prognosis of liver tumors positive for AFP was poor, and AFP has been widely used for diagnosis, prognosis, and surveillance of HCC [20]. Other studies showed that the change in AFP concentration before and after treatment was more significantly associated with prognosis and reflected a better response to the therapy [21,22]. In this study, AFP was shown to be an independent risk factor of solitary HCC($\beta = 0.224$, HR $= 1.251$); these patients with positive AFP should be treated with liver transplantation [23]. The differentiation of HCC was associated with prognosis. The lower the degree of tumor differentiation pathologically, the higher the protein expression of invasion and metastasis, which were related to poor prognosis [24]. Another study proved that a poorly differentiated tumor hurt the recurrence and long-term survival of solitary HCC [25]. There was a correlation between age and many diseases, and liver cancer was no exception [26]. In addition to the functional decline of organs and more basic diseases, the low surgical resection rate seemed to be responsible for the poor prognosis of elderly patients. There are reports in the literature that the surgical resection rate in elderly HCC patients was 0%–14% while 12%–28% in younger [27].

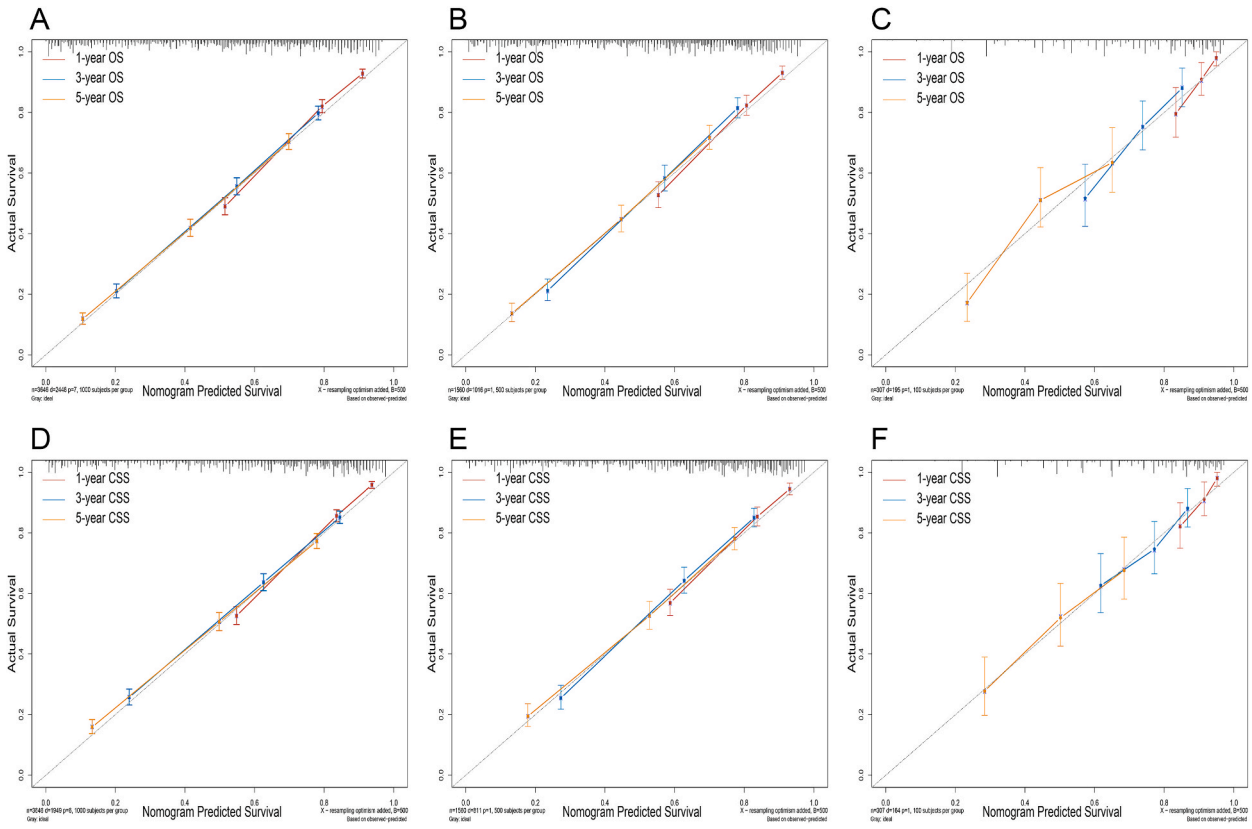


**Fig. 4.** Calibration plots of the nomograms for 1-, 3-, and 5-year OS and CSS in the training cohort (A/D), internal validation cohort (B/E), and external validation cohort (C/F). A/B/C, nomogram for OS; D/E/F, nomogram for CSS.

To our knowledge, this study was the first to develop and validate nomograms for predicting survival outcomes in patients with solitary HCC under the guidance of the TRIPOD statement. Although several previous studies had focused on prognostic models of patients with solitary HCC [8,9], they were not performed according to the TRIPOD statement. Furthermore, only surgical resection patients were included; they might not be applied to all patients with solitary HCC. In this study, we focused on all patients with solitary HCC and had a large number of populations from the SEER database to construct prediction models. Comparison with previous studies, selection criteria in this study were far more stringent. Patients were included according to the T stage in previous studies, however, in the AJCC 7th and 8th edition, the T2 stage included multiple tumors. In this study, the patients were further screened according to the 'CS Extension' to ensure that they were solitary tumors. And the clinical utility and predictive ability of the prognostic models we established were satisfactory and acceptable. Despite this, our research still had some limitations that couldn't be ignored. First, the related information provided in the SEER database was incomplete, such as whether the patients were infected with the hepatitis virus and the type of virus infection, personal history such as smoking and drinking, the number of tumors, disease recurrence, and so on. Secondly, this was a retrospective study and might have some inevitable selection bias. Finally, we failed large-sample, prospective, and multi-center studies to validate our results. These limitations may have an impact on results, so they should be taken into account when designing future studies.

## 5. Conclusion

In conclusion, under the guidance of the TRIPOD statement, we established and validated two nomograms for predicting 1-, 3-, and 5-year OS and CSS rates in patients with Solitary Hepatocellular Carcinoma. After validation, their clinical utility and predictive ability were satisfactory, acceptable, and superior to the traditional TNM stage system. Our results should be helpful for clinicians and surgeons in clinical decision-making.

## Funding information

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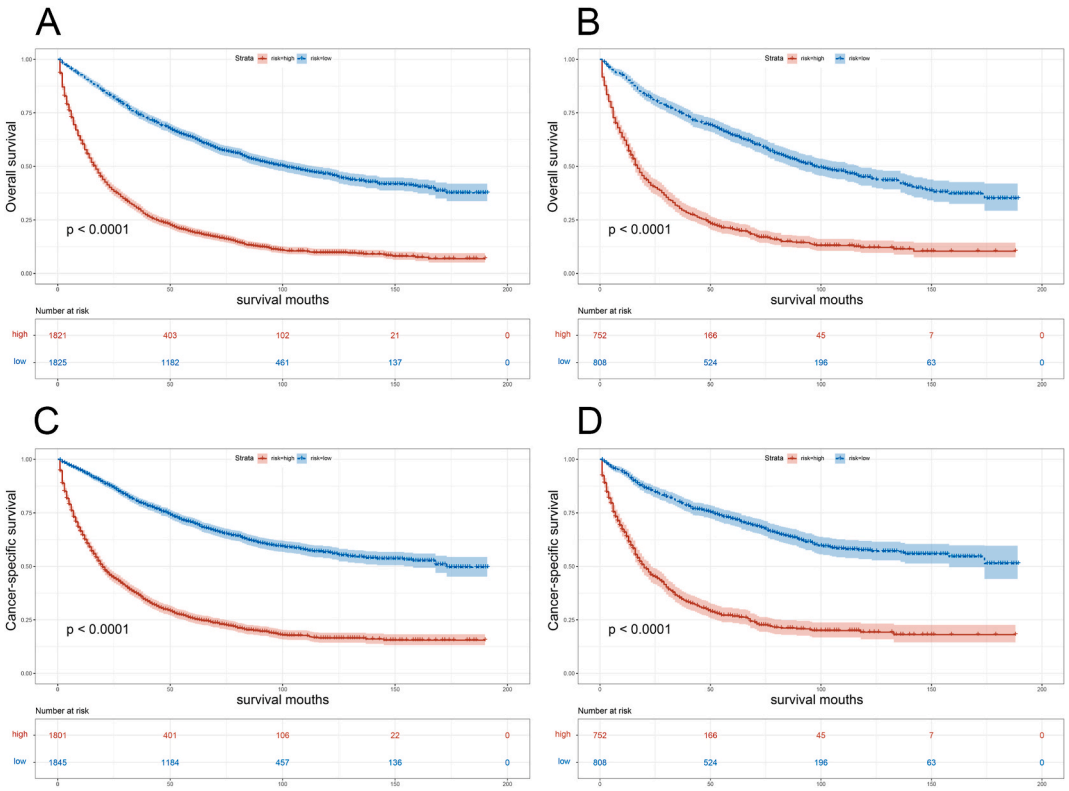


**Fig. 5.** Kaplan-Meier survival curves for OS and CSS for high-risk and low-risk groups. (A) The risk subgroup of the nomogram for OS in the training cohort; (B) the risk subgroup of the nomogram for OS in the internal validation cohort; (C) the risk subgroup of the nomogram for CSS in the training cohort; (D) the risk subgroup of the nomogram for CSS in the internal validation cohort.

## Disclosure of ethical statements

Approval of the research protocol: This study was approved by Ethics Committee of the First Affiliated Hospital of Army Medical University, PLA. The approval number is (B)KY2023041.

## Informed consent

This retrospective study was reviewed and approved by the ethics committee of our hospital, and informed consent was waived in this study.

Registry and the Registration No. of the study/trial: N/A.

## Animal studies

N/A.

## Research involving recombinant DNA

N/A.

## CRediT authorship contribution statement

**Chuanhong Li:** Conceptualization, Data curation, Methodology, Writing – original draft. **Yong Deng:** Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. **Rui Liao:** Investigation, Resources, Validation. **Leida Zhang:** Funding acquisition, Supervision, Writing – review & editing. **Yongpeng Gu:** Data curation, Investigation, Visualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28877.

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