# An Easy-to-use Clinical Nomogram for Predicting the Prognosis of Patients with Hepatocellular Carcinoma Concomitantly Suffer from Severe Fibrosis or Cirrhosis: A Population-based Analysis.

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**Research**

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## Abstract

Background Patients with hepatocellular carcinoma (HCC) concomitantly suffer from liver cirrhosis may have worse prognosis. Based on Surveillance, Epidemiology, and End Results (SEER) database, we evaluated the overall survival (OS) and cancer-specific survival (CSS) of these patients.

Methods A total of 2,369 patients were selected from the SEER database. They were classified into F0 (n=691) and F1 (n=1,678) groups by different Ishak fibrosis score. Propensity score matching (PSM) and Kaplan-Meier method were performed to evaluate the OS and CSS. The F1 group were randomized into training sub-set (n = 1,176, 70%) and validation sub-set (n = 502, 30%) for further construction and validation of nomogram .

Results After matched, there were statistically significant worse outcome for F1 group patients compared with F0 group (n=587, OS: P<0.001, CSS: P<0.001). Six independent predictors for both OS and CSS were identified to construct the nomograms by COX regression analyses. The nomogram performed well concerning its ability of discrimination and calibration and its net benefits compared with the conventional staging system.

Conclusions Patients with HCC concomitantly suffer from severe fibrosis or cirrhosis has a significant worse survival compared with none or moderate fibrosis patients. The validated nomograms provided useful prediction of survival.

## Introduction

Hepatocellular carcinoma(HCC), ranking as the third leading cause of cancer-specific deaths around the world, is a global health issue with its high mortality ratio.[1] Patients with cirrhosis are exposed to high risk of HCC, ranging from 1–8% per year, and HCC can emerge at any stage of cirrhosis[1–3]. For several common reasons, a great deal of patients with HCC concomitantly suffer from liver cirrhosis. [3, 4] Accordingly, in addition to the clinicopathological characteristics of tumor itself, the outcome of these patients is strongly associated with the stage of liver cirrhosis[3, 5, 6] and its severe complications.[7]

Liver biopsy is still the recognized standard for histologic evaluation of liver disease activity and degree of fibrosis, even if some limitations existed.[8] Over the past decade, the Ishak scoring system has extensively applied in clinical trials, particularly in America. Histologically, higher Ishak score reflects more scarring, thus, investigators assume that patients with a higher fibrosis stage should have an growing risk of prognosis compared to its lower counterpart. However, since clinical researches always exclude cases with underlying cirrhosis, the correlation between the degree of fibrosis and the clinical prognosis has rarely been confirmed in a prospective randomized controlled trials. Most of these studies were retrospective and cases were mostly derived from small sample size trials.[9, 10]

Surveillance, Epidemiology and End Results (SEER) database, containing the long follow-up duration and a great number of cases of patients with Ishak fibrosis score, giving us registered adequate events to discuss the differences in patients with HCC concomitantly suffer from liver cirrhosis in all-cause mortality and cancer-specific mortality.

Nomograms, a novel statistical predictive model, can accurately calculate and estimate individual survival [11, 12]. A wide variety of nomograms have been extensively established to give help to formulating personalized therapy and follow-up management strategies in various diseases. For all we know, the study to estimate prognosis of patients with HCC concomitantly suffer from cirrhosis using data derived from the SEER database has never been carried out.

In present study, we aimed to estimate the survival difference in HCC patients between no to moderate fibrosis and advanced/severe fibrosis. Then, based on clinicopathological risk factors derived from the SEER database, we aimed to construct and validate an easy-to-use and effective nomogram model to compute and estimate survival of patients with HCC concomitantly suffer from severe fibrosis or cirrhosis.

## Materials And Methods

# Patient and data collection

SEER database is one of the most representative cancer registration databases. In this study, we used the SEER 18 Regs Research Data (1975–2016) to search for cases with HCC, and a total of 108711 cases between 1975 and 2016 were fetched. These factors were eventually selected in present study: age at diagnosis, racial status, gender, marital status, international classification of diseases for oncology, third edition (ICD-O-3)[13], Edmondson–Steiner classification, American Joint Committee on Cancer (AJCC) 7th edition TNM Staging System, alpha-fetoprotein (AFP), fibrosis (or Ishak) score, treatment, months of survival, cancer-specific survival status and overall survival status,. The Ishak score[14] is a reliable and significant prognostic indicator of liver disease. The characteristics of fibrosis were classified by scores defined by the AJCC.

Ishak fibrosis scores were defined by AJCC: 1) scores from 0 to 4 means none fibrosis to moderate fibrosis, 2) scores 5 and 6 means severe fibrosis or cirrhosis. In this study, the severity of the liver fibrosis or cirrhosis were classified as F0 and F1. Patients with complete fibrosis score data in SEER database during 2010–2016 were selected. After deleting cases with an unknown data of racial status, Edmondson–Steiner classification, AFP, tumor size, AJCC 7th stage and survival time, we eventually selected 2,369 patients for this study. The flow chart (Fig. 1) shows the selection of study population in this study.

Overall survival (OS) and cancer-specific survival(CSS) were both the interest endpoints in this study. OS was regarded as the duration from the date of diagnosis to death from any cause, while CSS was defined as the duration from the date of diagnosis until death due to HCC in the absence of other causes. This study was approved by the Ethics Committee of Jinan University Ethics Committee, and written informed consent was waived.

# Propensity Score Matching

Patients were divided into F0 and F1 groups on the base of different fibrosis score. To ensure well-balanced characteristics for the two comparisons, propensity score matching (PSM) with 1:1 proportion was performed. The chi-square test was used to compare the categorical variables of both groups described as the number and percentage, and student's t-test was used to compare the continuous variables expressed as the mean and standard deviation. The short-term and long-term outcomes of patients between two groups were estimated using Kaplan-Meier survival analysis (log-rank test).

## Statistical Analysis

Those selected 1,676 patients with HCC concomitantly suffer from severe fibrosis or cirrhosis were randomized to a training set (n = 1176, 70%) and a validation set (n = 500, 30%). One was for the construction of the nomogram and another was for validating it.

Cox proportional hazards model were performed to analysis the potential confounders and identify the independent predictors in training set. [15]. Hazard ratios(HR) and their 95% confidence intervals (CI) were estimated using the univariable and multivariable Cox regression analysis. We used the backward step-down process to obtain the final factors for the development of the nomogram based on the principle of the Akaike information criterion (AIC)[16, 17].

The discrimination ability of the model was assessed by the concordance index(C-index)[18]. The accuracy of predictions was measured by plotting the calibration curves of the nomogram. The precision of the prediction for survival was estimated by using area under receiver operating characteristic (ROC) curve (AUC). In addition, the clinical efficacy and net benefit of the models was evaluated by decision curve analysis(DCA)[19, 20]. The survival differences between the different level of risk groups were compared by using Kaplan-Meier method.

The data was originated from the SEER*Stat software version 8.3.6. X-tile software was applied to calculate the optimal cut off age, tumor size and the score of nomogram based on the OS and CSS of patients. The DCA curves was plotted by R software with file "stdca.R"(available from the site www.mskcc.org) and relevant packages. Statistical analysis was performed by using R(version 3.6.1). A two-sided $P < 0.05$ was regarded as statistical significance.

## Result

## Propensity score matching

A total of 2369 patients in 2004–2016 were eventually selected from the SEER database, they were divided into two groups according to Ishak score: F0 (Ishak score was 1–4) and F1 (Ishak score was 5–6) groups. There were 1678 cases in group F0 and 691 patients in group F1. After 1:1 propensity score matching, 587 patients from each group were identified. The balance test showed that the distribution of covariates of selected cases in the two groups was adequately balanced (Fig. 2a, 2b, 2c and 2d). Table 1 shows the demographic and pathological characteristics before and after matching between the matched groups, indicating that the potential confounders in two groups were minimized.

Table 1
Characteristics of F0 and F1 group before and after propensity score matching (PSM)

| | Before matched | | | After matched | | |
|---|---|---|---|---|---|---|
| Variable | F1(n = 1678) | F0(n = 691) | p-value | F1(n = 587) | F0(n = 587) | p-value |
| Age | 61.5 ± 8.8 | 62.9 ± 11.3 | < 0.001 | 62.9 ± 9.0 | 62.7 ± 11.0 | 0.750 |
| Sex | | | 0.246 | | | 0.596 |
| male | 1314(78.3) | 526(76.1) | | 466 (79.4) | 457 (77.9) | |
| female | 364(21.7) | 165(22.9) | | 121 (20.6) | 130 (22.1) | |
| Race | | | < 0.001 | | | 0.414 |
| White | 1153(68.7) | 398(57.6) | | 339 (57.8) | 358 (61.0) | |
| Black | 230(13.7) | 80(11.6) | | 81 (13.8) | 68 (11.6) | |
| *Others | 295(17.6) | 213(30.8) | | 167 (28.4) | 161 (27.4) | |
| Marital status | | | < 0.001 | | | 0.938 |
| unmarried | 706(42.1) | 225(32.6) | | 208 (35.4) | 206 (35.1) | |
| married | 930(55.4) | 443(64.1) | | 357 (60.8) | 361 (61.5) | |
| missing | 42(2.5) | 23(3.3) | | 22 ( 3.7) | 20 ( 3.4) | |
| Edmondson–Steiner classification | | | 0.001 | | | 0.830 |
| I + II | 1394(83.1) | 533(80.0) | | 456 (79.2) | 461 (78.5) | |
| III + IV | 284(16.9) | 158(20.0) | | 122 (20.8) | 126 (21.5) | |
| Tumor size | 4.5 ± 3.8 | 7.2 ± 6.2 | < 0.001 | 5.7 ± 5.1 | 5.8 ± 5.1 | 0.192 |
| AFP | | | < 0.001 | | | 1.000 |
| Positive | 1149(68.5) | 416(70.4) | | 357 (60.8) | 357 (60.8) | |
| Negative | 529(31.5) | 275(29.6) | | 230 (39.2) | 230 (39.2) | |
| T stage | | | < 0.001 | | | 0.431 |
| Ia | 268(16.0) | 62(9) | | 75 (12.8) | 62(10.6) | |
| Ib | 624(37.2) | 313(45.3) | | 246 (41.9) | 271(46.2) | |
| II | 479(28.5) | 143(20.7) | | 131 (22.3) | 125(21.3) | |
| III | 186(11.1) | 103(15.0) | | 89 (15.2) | 77(13.1) | |
| IV | 121(7.2) | 70(10.1) | | 46 ( 7.8) | 52(8.9) | |
| N stage | | | 0.947 | | | 0.552 |
| N0 | 1611(96.0) | 663(95.9) | | 561 (95.6) | 566 (96.4) | |
| N1 | 67(4.0) | 28(4.1) | | 26 ( 4.4) | 21 ( 3.6) | |
| M stage | | | 0.183 | | | 0.799 |
| M0 | 1594(95.0) | 647(93.6) | | 553 (94.2) | 556 (94.7) | |
| M1 | 84(5.0) | 44(6.4) | | 34 ( 5.8) | 31 ( 5.3) | |
| AJCC8th TNM stage | | | < 0.001 | | | 0.518 |
| IA | 265(15.8) | 60(86.8) | | 75 (12.8) | 60 (10.2) | |
| IB | 604(36.1) | 302(43.7) | | 235 (40.0) | 264 (45.0) | |
| II | 450(26.8) | 135(19.5) | | 124 (21.1) | 118 (20.1) | |
| IIIA | 153(9.1) | 83(12.0) | | 72 (12.3) | 62 (10.6) | |
| IIIB | 83(4.9) | 51(7.4) | | 34 ( 5.8) | 41 ( 7.0) | |

Mean ± standard deviation for continuous variables and n (%) for categorical variables

*Others comprises American Indian/Alaska Native and Asian/Pacific Islander.

AFP, alpha fetoprotein

| | Before matched | | After matched | |
|---|---|---|---|---|
| | | | | |
| IVA | 39(2.3) | 16(2.3) | 13 ( 2.2) | 11 ( 1.9) |
| IVB | 84(5.0) | 44(6.4) | 34 ( 5.8) | 31 ( 5.3) |
| Mean ± standard deviation for continuous variables and n (%) for categorical variables | | | | |
| *Others comprises American Indian/Alaska Native and Asian/Pacific Islander. | | | | |
| AFP, alpha fetoprotein | | | | |

The Kaplan-Meier curve of the OS and CSS were shown in Fig. 2(e, f) after matching. The median, 1-, 3- and 5-year OS rates for group F0 (N = 587) and group F1 (N = 587) were 52 months(95%CI, 42.2 to 61.8 months), 81.5%, 60.6%, 46.7% and 33 months(95%CI, 28.3 to 37.7 months), 72.0%, 46.7%, 37.4% respectively. The median, 1-, 3- and 5-year CSS rates for two groups were 66 months(95%CI, 60.3 to 71.7 months), 83.1%, 64.8%, 52.2% and 41 months(95%CI, 30.9 to 51.1 months), 74.8%, 52.3%, 43.2% respectively. There were statistically significant better outcome for patients with undetectable to moderate fibrosis compared with those severe fibrosis or cirrhosis cases (OS: $P < 0.001$, CSS: $P < 0.001$, respectively; Fig. 2e,2f).

## Patient characteristics

A total of 1678 patients with HCC concomitantly suffer from severe fibrosis or cirrhosis were divided into a training set and a validation set by the ratio of 7:3. The demographics and clinical characteristics of patients are displayed in Table 2 with no statistically significant difference between two groups. In the training set, the ratio of male to female was 3.56:1 (918/258). The median age was 61.5 years. Most of these patients were early AJCC stage(I + II, 80.01%) and better differentiation (well + moderately differentiated, 83.58%). In this study population, over the 60% of patients underwent surgery, with 177 patients who had the radiofrequency ablation (RFA) and 263 patients who received liver transplant.

Table 2
Demographics and clinical characteristics of eligible patients with HCC.

| variable | Training set(n = 1176) | Validation set(n = 502) | p value |
|---|---|---|---|
| age | 61.55 ± 8.75 | 61.62 ± 8.94 | 0.874 |
| Sex | | | 0.708 |
| male | 918(78.1) | 396(78.9) | |
| female | 258(21.9) | 106(21.1) | |
| Marital | | | 0.870 |
| Unmarried | 498(42.3) | 208(41.4) | |
| Married | 647(55.0) | 283(56.4) | |
| Unknown | 31(2.7) | 11(2.2) | |
| Race | | | 0.748 |
| White | 811(69.0) | 342(68.2) | |
| Black | 160(13.6) | 70(13.9) | |
| *Others | 205(17.4) | 90(17.9) | |
| Edmonson-Steiner classification | | | 0.391 |
| I + II | 983(83.6) | 411(81.9) | |
| III + IV | 193(16.4) | 91(18.1) | |
| AFP | | | 0.587 |
| Negative | 366(31.1) | 163(32.5) | |
| Positive | 810(68.9) | 339(67.5) | |
| Tumor size | 44.29 ± 37.82 | 47.66 ± 39.91 | 0.101 |
| T stage | | | 0.111 |
| T1a | 189(16.1) | 79(15.7) | |
| T1b | 446(37.9) | 178(35.5) | |
| T3 | 463(39.4) | 202(40.2) | |
| T4 | 78(6.6) | 43(8.6) | |
| N stage | | | 0.271 |
| N0 | 1125(95.7) | 486(96.8) | |
| N1 | 51(4.3) | 16(3.2) | |
| M stage | | | 0.344 |
| M0 | 1121(95.3) | 473(94.2) | |
| M1 | 55(4.7) | 29(5.8) | |
| AJCC 8th TNM stage | | | 0.118 |
| I | 618(52.6) | 251(50.0) | |
| II | 323(27.5) | 127(25.3) | |
| III | 151(12.8) | 85(16.9) | |
| IV | 84(7.1) | 39(7.8) | |
| Therapy method | | | 0.748 |
| No Surgery | 466(39.6) | 202(40.2) | |

Mean ± standard deviation for continuous variables and n (%) for categorical variables;

*Others comprises American Indian/Alaska Native and Asian/Pacific Islander;

AFP, alpha fetoprotein; RFA, radiofrequency ablation

Others, comprises American Indian/Alaska Native and Asian/Pacific Islander.

| variable | Training set(n = 1176) | Validation set(n = 502) | p value |
|---|---|---|---|
| Surgery | 270(23.0) | 118(23.5) | |
| RFA | 177(15.0) | 71(14.1) | |
| Liver transplant | 263(22.4) | 111(22.1) | |
| Mean ± standard deviation for continuous variables and n (%) for categorical variables; | | | |
| *Others comprises American Indian/Alaska Native and Asian/Pacific Islander; | | | |
| AFP, alpha fetoprotein; RFA, radiofrequency ablation | | | |
| Others, comprises American Indian/Alaska Native and Asian/Pacific Islander. | | | |

## Short-term and Long-term Outcome of Patients

The median follow-up was 44.0 months (95%CI, 41.5 to 46.5 months) and 47 months(95% CI, 42.3 to 57.6 months), respectively in training set and validation set. The median OS time of training set was 40.0 months (95% CI, 34.7 to 45.3 months), and the postoperative 1-, 3- and 5-year OS rates were 72.0%, 57.3% and 47.2%, respectively. The median OS time of validation set was 32.0 months (95% CI, 26.0 to 37.9 months), and the postoperative 1-, 3- and 5-year OS rates were 72.0%, 49.9% and 41.0%, respectively. The median CSS month of training set was 55 months (95% CI, 45.8 to 64.2 months), and the postoperative 1-, 3- and 5-year CSS rates were 79.0%, 58.7% and 47.3%, respectively. The median CSS month was 43.0 months in validation set, and the postoperative 1-, 3- and 5-year CSS rates were 75.4%, 53.2% and 47.2%, respectively.

## Construction and validation of the nomograms

The univariate and multivariate Cox proportional hazards analyses showed that race, pathological grades, tumor size, T stage, AFP status and therapy method were independent predictors for both OS and CSS (Table 3). Based on multivariate analysis, the above six important prognostic factors were combined to construct the satisfactory nomograms for patients with HCC concomitantly suffer from severe fibrosis or cirrhosis (Figs. 3a,3b). The detailed scores of all variables in the nomogram were shown in Supplemental 1.

Table 3

Univariate and multivariate analysis of prognostic factors of overall survival and cancer-specific survival

| | | cancer-specific survival | | | | | | overall survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | univariable | | | multivariable | | | univariable | | | multivariable | | |
| | | HR | 95%CI | p value | HR | 95%CI | p value | HR | 95%CI | p value | HR | 95%CI | P va |
| age | < 66 | | | reference | | | reference | | | reference | | | refe |
| | ≥ 66 | 1.396 | (1.156–1.685) | < 0.001 | 1.133 | (0.895–1.434) | 0.300 | 1.363 | (1.148–1.617) | < 0.001 | 1.126 | (0.906–1.399) | 0.28 |
| Sex | male | | | reference | | | | | | reference | | | refe |
| | female | 0.920 | (0.739–1.147) | | | | | 0.962 | (0.790–1.172) | 0.702 | | | |
| Marital status | unmarried | | | reference | | | reference | | | reference | | | refe |
| | married | 0.665 | (0.555–0.797) | < 0.001 | 0.844 | (0.699–1.018) | 0.077 | 0.691 | (0.586–0.814) | < 0.001 | 0.875 | (0.738–1.037) | 0.12 |
| | unknown | 1.286 | (0.796–2.076) | 0.304 | 1.063 | (0.654–1.729) | 0.804 | 1.257 | (0.807–1.958) | 0.311 | 1.061 | (0.677–1.662) | 0.79 |
| Race | white | | | reference | | | reference | | | reference | | | refe |
| | black | 1.082 | (0.839–1.397) | 0.544 | 0.756 | (0.581–0.984) | 0.038 | 1.220 | (0.976–1.524) | 0.080 | 0.893 | (0.709–1.125) | 0.33 |
| | *others | 0.681 | (0.524–0.886) | 0.004 | 0.617 | (0.472–0.806) | < 0.001 | 0.700 | (0.552–0.888) | 0.003 | 0.641 | (0.503–0.817) | < 0. |
| E-S classification | I + II | | | reference | | | reference | | | reference | | | refe |
| | III + IV | 1.995 | (1.618–2.460) | < 0.001 | 1.598 | (1.280–1.993) | < 0.001 | 1.750 | (1.437–2.131) | < 0.001 | 1.444 | (1.175–1.775) | < 0. |
| Tumor size | 3.6 | | | reference | | | reference | | | reference | | | refe |
| | 3.6-7.0 | 2.413 | (1.967–2.960) | < 0.001 | 1.373 | (1.084–1.738) | 0.009 | 2.151 | (1.794–2.579) | < 0.001 | 1.239 | (1.005–1.528) | 0.04 |
| | 7 | 5.717 | (4.488–7.282) | < 0.001 | 2.513 | (1.836–3.441) | < 0.001 | 4.697 | (3.759–5.870) | < 0.001 | 2.074 | (1.555–2.765) | < 0. |
| T stage | T1a | | | reference | | | reference | | | reference | | | refe |
| | T1b | 3.126 | (2.095–4.663) | < 0.001 | 1.635 | (1.066–2.508) | 0.024 | 2.864 | (2.036–4.028) | < 0.001 | 1.679 | (1.165–2.419) | 0.00 |
| | T2 | 3.672 | (2.451–5.503) | < 0.001 | 2.129 | (1.398–3.242) | < 0.001 | 3.224 | (2.279–4.560) | < 0.001 | 2.065 | (1.440–2.960) | < 0. |
| | T3 | 8.564 | (5.565–13.180) | < 0.001 | 2.154 | (1.312–3.537) | 0.002 | 7.146 | (4.910–10.400) | < 0.001 | 2.220 | (1.437–3.427) | < 0. |
| | T4 | 15.215 | (9.703–23.857) | < 0.001 | 4.158 | (2.494–6.932) | < 0.001 | 11.968 | (8.038–17.819) | < 0.001 | 3.947 | (2.507–6.213) | < 0. |
| N stage | N0 | | | reference | | | reference | | | reference | | | refe |
| | N1 | 4.252 | (3.029–5.968) | < 0.001 | 1.292 | (0.866–1.928) | 0.210 | 3.909 | (2.836–5.387) | < 0.001 | 1.335 | (0.914–1.951) | 0.13 |
| M stage | M0 | | | reference | | | reference | | | reference | | | refe |
| | M1 | 4.672 | (3.417–6.387) | < 0.001 | 1.115 | (0.770–1.614) | 0.565 | 4.095 | (3.033–5.531) | < 0.001 | 1.094 | (0.764–1.565) | 0.62 |
| AFP | Negative | | | reference | | | reference | | | reference | | | refe |
| | Positive | 1.669 | (1.353–2.059) | < 0.001 | 1.358 | (1.091–1.691) | 0.006 | 1.468 | (1.222–1.765) | < 0.001 | 1.225 | (1.011–1.484) | 0.03 |
| Therapy method | no surgery | | | reference | | | reference | | | reference | | | refe |

Mean ± standard deviation for continuous random variables and n (%) for categorical variables

*Others comprises American Indian/Alaska Native and Asian/Pacific Islander.

E-S stage, Edmondson–Steiner classification; AFP, alpha fetoprotein; LT, liver transplantation

| | | cancer-specific survival | | | | | | overall survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | surgery | 0.265 | (0.207–0.339) | < 0.001 | 0.296 | (0.229–0.382) | < 0.001 | 0.302 | (0.242–0.376) | < 0.001 | 0.342 | (0.273–0.428) | < 0. |
| | RFA | 0.365 | (0.282–0.472) | < 0.001 | 0.572 | (0.434–0.754) | < 0.001 | 0.375 | (0.296–0.474) | < 0.001 | 0.548 | (0.426–0.705) | < 0. |
| | LT | 0.069 | (0.045–0.104) | < 0.001 | 0.108 | (0.071–0.166) | < 0.001 | 0.104 | (0.075–0.142) | < 0.001 | 0.155 | (0.111–0.217) | < 0. |
| Mean ± standard deviation for continuous random variables and n (%) for categorical variables | | | | | | | | | | | | | |
| *Others comprises American Indian/Alaska Native and Asian/Pacific Islander. | | | | | | | | | | | | | |
| E-S stage, Edmondson–Steiner classification; AFP, alpha fetoprotein; LT, liver transplantation | | | | | | | | | | | | | |

The nomogram constructed in our study displayed more powerful accuracy for predicting OS and CSS rates in both two datasets(Table 4). In training set, the C-index for predicting OS rate was 0.767 (95% CI, 0.747, 0.787) and the C-index for predicting CSS rate was 0.797 (95% CI, 0.777, 0.817). Meanwhile, the C-index for OS and CSS predictions were 0.791 (95% CI, 0.764, 0.818) and 0.812(95% CI, 0.785, 0.839) in validation set.

Table 4
C-indexes for the nomograms and AJCC TNM stage systems

| | Overall survival | | | Cancer-specific survival | | |
|---|---|---|---|---|---|---|
| model | Training set | Validation set | P value | Training set | Validation set | P value |
| Nomogram | 0.767(0.747–0.787) | 0.791(0.764–0.818) | Reference | 0.797(0.777–0.817) | 0.812(0.785–0.839) | Reference |
| AJCC 7th System | 0.638(0.614–0.662) | 0.648(0.613–0.683) | < 0.001 | 0.658(0.633–0.683) | 0.674(0.637–0.711) | < 0.001 |
| AJCC 8th System | 0.650(0.626–0.674) | 0.662(0.629–0.695) | < 0.001 | 0.670(0.645–0.695) | 0.682(0.645–0.719) | < 0.001 |
| C-index (95% confidence intervals) C-index, concordance index. | | | | | | |

For calibration, the 1-, 3- and − 5 year probability of OS and CSS reflected an optimal coherence between the predictive value and observed value both in training set and validation set(Figs. 4e, 4f, 4 g, 4 h).

The AUC values of novel nomogram in training set for predicting 1-, 3- and 5-year OS rates were 0.842, 0.832, 0.844, respectively, while the AUC values were 0.802, 0.807, 0.832, respectively for predicting CSS rates. As for the prediction of OS rates in validation set, the AUC values were 0,873, 0.836, 0.861,respectively, while the AUC values of CSS rates were 0.842, 0.821, 0.840, respectively. It shown that our nomogram had excellent discrimination capacity for predicting both 1-, 3- and 5-year OS and CSS in selected patients.

## Clinical Value of the Nomogram Comparison with Conventional Staging Systems

The C-index of nomogram for OS was significantly higher than those of the AJCC 7th edition staging system[0.638 (95%CI, 0.614–0.662, P < 0.001)] and the AJCC 8th edition staging system[0.650 (95%CI, 0.626–0.695, P < 0.001)] in training set. The C-indices of AJCC 7th edition system and AJCC 8th edition system were lower than that of the nomogram for CSS prediction significantly shown in Table 4 (P < 0.001). It reflected that the novel model was available tool for predicting survival of patients with HCC in severe fibrosis or cirrhosis in the training set.

DCA is a novel method for estimating clinical usefulness of a prediction model based on the threshold probability[19, 20]. It was built to assess whether the novel model improves decision-making of the 1-, 3- and 5-year OS and CSS prediction in training set. The DCA curves of the nomogram model, the AJCC 7th edition system and the AJCC 8th edition system were shown in Fig. 5(a, b, c, d, OS) and Supplemental 2(a, b, c, d, CSS). It presents the better net benefit and clinical utility of the nomograms compared with the AJCC stages in training set.

All patients were classified into four groups (For OS; For CSS, low A risk: <133, low B risk: <133, moderate risk: 133–214, and high risk: >214) on a base of optimal cut-off values originated from X-tile software. Kaplan-Meier method were plotted for evaluating the overall survival and cancer-specific survival of patients in the AJCC 7th edition system and AJCC 8th edition system as well as nomogram model, as is shown in the Fig. 5(d, e, f, training set) and the Supplemental 2(d, e, f, validation set). The all three models displayed significant differences in each of its stages(P < 0.001). However, the discrimination of nomogram risk stratification more excellent than that of AJCC stages, based on the prognostic curve of nomogram by different stages, containing low-A risk, low-B risk, moderate risk and high risk. The AJCC 7th edition system reflected acceptable risk stratification of stages II and III patients, but it was unsatisfactory in distinguishing stages III and IV patients to a some extent. Meanwhile, the AJCC$^{8th}$ edition systems performed better in risk stratification of stages I and II patients, particularly in validation set.

## Discussion

In this study, we estimated the role of liver fibrosis or cirrhosis in hepatocellular carcinoma using the national SEER database for the first time. In order to eliminate selection bias, PSM was performed in this population-based research. Processed with the combination of clinical and pathological covariates, the

propensity score matching made a comparable distribution of the clinicopathological characteristics between the F0 and F1 cohorts, thus bringing about a result that was similar to random allocation[21]. After PSM analysis, patients with severe fibrosis or cirrhosis patients in HCC showed a significantly worse prognosis, thus, more precision estimates of disease severity and proper follow-up surveillance for progression of hepatic decompensation and recurrence of hepatocellular carcinoma were needed. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and excessive drinking are major and common factors that contribute to cirrhosis and developing HCC [22, 23]. More advanced fibrosis or cirrhosis stages result in decompensation of the liver in the progression of HCC. Therefore, detection and intervention of fibrosis and its risk factors at an early stage is the most important thing for potential reversal.

Based on population-based database, we constructed a nomogram to evaluate the definite 1-, 3- and 5-year OS and CSS probabilities of patients with HCC concomitantly suffer from severe fibrosis or cirrhosis, then, the ability of the nomograms were verified concerning its discrimination and calibration. As a result, the nomograms were performing well in both the validation set and the training set. In the perspective of net benefit and clinical efficacy, the novel models showed wider range of threshold probabilities than some conventional systems.

According to our results, the type of therapy was the strongest predictor of outcome. In fact, liver transplantation(LT), derived from both cadaveric and living donation, often represents the only curative treatment which is able to simultaneously cure the HCC and the liver cirrhosis. Mazzaferro et al described that selected patients can achieve more considerable survival benefit compared with those of whom transplanted for benign cases in a published landmark paper. [24, 25] The success of LT is not subjected to the severity of liver dysfunction, it could be able to improve survival and the quality of life in selected patients with end-stage liver disease[2, 3, 24]. However, this option may be precluded to a significant number of patients because of age, comorbidities, tumor characteristics, shortage of donor organs and some other limitations[26]. Certainly, when these factors hinder the chance of LT, liver resection should be considered as a precious option. Due to severe complications (severe portal hypertension, thrombocytopenia etc.) in patients with advanced cirrhosis, Barcelona Clinic Liver Cancer (BCLC) algorithm recommend hepatectomy as the preferred therapy for patients with single tumor and well-preserved liver function (Child-Pugh A). But a recent study pointed out that hepatectomy for HCC in Child-Pugh B cirrhosis could be also feasible, after careful preoperative assessment based on patients' features, liver function and tumor pattern as well as decreasing surgical stress[27]. Unlike hepatectomy, terrible liver function does not mean a contraindication of real-time image-guided local radiofrequency ablation(RFA). Patients with tumors less than 3 cm and Child-Pugh A or B who have no indication for hepatectomy are candidates for RFA[3]. A retrospective study that contained 7,185 patients concluded that hepatectomy might contribute a lower rate of recurrence than RFA in small HCC. Another single-center study described that patients who underwent hepatectomy had a longer OS[28, 29]. Nearly 40% of the cases did not receive operation, and the reason for the non-operation therapies was that it was contraindicated or was not recommended. It indicated that severe fibrosis or cirrhosis patients with HCC were more likely to suffer from an end stage of HCC.

Tumor size is the core element of AJCC 8th edition T stage and an integral part of the AJCC 8th edition TNM stage system. T stage was always considered as a crucial predictor for HCC [30, 31]. The present study has indicated that advanced T stage meant higher risks of OS and CSS. Meanwhile, heavier weight from T stage in calculating overall survival than cancer-specific survival was observed, indicating that CSS were more largely depended on the intrinsic nature of HCC. Tumor grade, another factor showed inherent feature of tumor, is widely accepted as one of the most effective prognostic factors of outcome in patients with HCC both after hepatectomy and LT, as shown by many series study of these topics[32–38]. In accordance with the previous study, our study indicated that a poorly differentiation was associated with a worse prognosis. AFP has been highly applied not only in diagnostic biomarker but in evaluating the outcome of HCC for years. Previous studies found that high AFP level before treatment was an independent predictor concerned with tumor grade, progression and survival[39].The present study supported that the AFP level is an negative and independent predictor for both CSS and OS of severe fibrosis or cirrhosis patients with HCC.

The predictive value was not observed for N stage in this study. The proportion of patients with lymph node (LN) metastasis was fairly low. T diagnosis of LN metastasis was based on intraoperation exploration and pathological confirmation, rather than imaging examination in present study. It might result in the lower rate of LN metastasis.

Additionally, based on the risk stratification of prognostic curves, the novel nomogram-predicted models had better discrimination than that of AJCC systems both in OS and CSS, as shown in Fig. 5. For overall survival, the AJCC 7th edition system was underperformed in stratifying stages I and II patients. The AJCC 8th stage systems shown good prognostic stratification for patients, but its C-index was only 0.650(95%CI, 0.626–0.674, training set) and 0.662(95%CI,0.629–0.695, validation set) respectively. However, in both sets, four sub-groups(the low-A risk, low-B risk, moderate risk and high risk groups) in our nomograms had significant differences in OS and CSS, and showed better accuracy and discrimination in both short-term and long-term survival prediction. The most likely reason is that the AJCC system only take the tumor size, positive regional LN and metastasis into consideration. These result indicated that our nomograms were able to use as a conventional tool for predicting the short-term and long-term outcome of severe fibrosis or cirrhosis patients with HCC. However, it was ignored that racial differences, differentiation grades, and therapy methods were also independent predictors for prognosis.

As is known to us, this study established the first nomogram model for predicting the outcomes of severe fibrosis or cirrhosis patients with HCC. By calculating the score of the variables, clinicians can not only predict the prognosis immediately and accurately but also obtain valuable information to choose treatments and predict survival rates before therapy option. Meanwhile, doctors can easily distinguish different level risk of patients after treatment, careful and regular follow-up should be made in high-risk populations. Then, SEER database provided multicenter clinical data, made our results more applicable to the general population than that at a single institution.

However, some limitations were still existed. Firstly, This was an retrospective observational study exposed to potential confounding bias. Therefore, a 1:1 PSM analysis was performed to simulate a realistic scenario of two homogeneous populations. Then, liver function is also a vital factor for the prediction of both cirrhosis and HCC, but the data was not available from the SEER database in our nomograms. Therefore, external validation should be performed by using an independent external dataset for the prognostic nomograms developed in this study in the future. and further randomized evidence is required to verify the conclusions of our study.

## Conclusion

The present study shows the potential survival risk of severe fibrosis or cirrhosis in HCC by analyzing the population-based SEER database. Given the independent prognostic impact of the severe fibrosis or cirrhosis on both OS and CSS, these nomograms were constructed and validated for predicting the individualized survival probability with six easily obtained variables. These simple and visual nomograms could be a valuable tool for both the patient and the caregiver.

## Abbreviations

HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival; CSS, cancer-specific survival; PSM, Propensity score matching; ICD-O-3, international classification of diseases for oncology, third edition; AJCC, American Joint Committee on Cancer; AFP, alpha-fetoprotein; CI, confidence intervals; AIC, Akaike information criterion; HR, Hazard ratios; ROC, receiver operating characteristic; AUC, area under curve; DCA, decision curve analysis; HBV, Hepatitis B virus ; HCV, hepatitis C virus; LT, liver transplantation; Barcelona Clinic Liver Cancer; RFA, radiofrequency ablation; LN, lymph node

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

All data generated or analyzed during this study are included in the published articles

### Competing interests

The author reports no conflicts of interest in this work.


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### Author contributions

WHY and RSY acquisition of data, analysis and interpretation of data; ZYP and JL contributed to data analysis; JHS conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval; HCF critical revision, final approval.


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## Supplemental Figure

Supplemental 2: Decision curve analysis of the nomogram and AJCC TNM staging system for the 1-, 3- and 5-year cancer-specific survival prediction of patients with hepatocellular carcinoma concomitantly suffer from liver cirrhosis in the validation group. (a) 1-year survival; (b) 3-year survival, (c) 5-year survival. Kaplan–Meier survival curves for patients, according to (d) AJCC7th edition system stages, (e) AJCC8th edition system stages and (f) nomogram-based stages. The p value (< 0.001) was determined using the log-rank test. AJCC, American Joint Committee on Cancer

## Figures

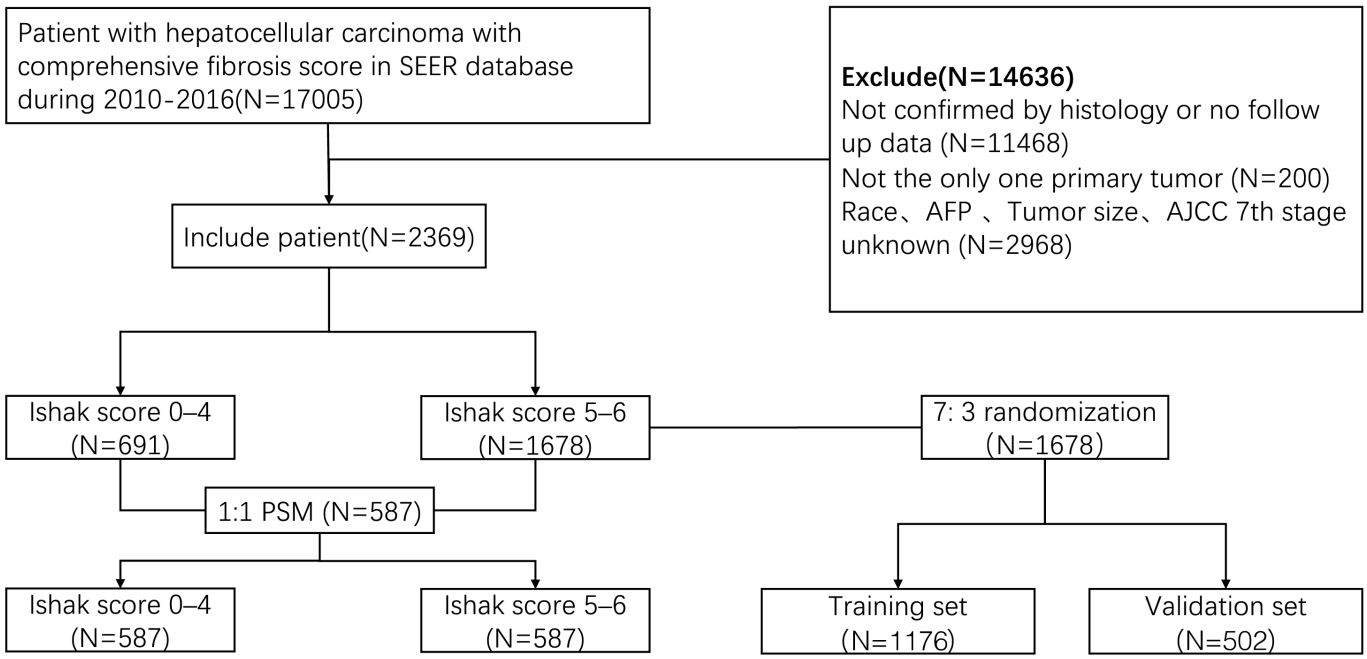


**Figure 1**

Flow diagram for selecting patients. SEER, the Surveillance; Epidemiology, and End Results database; HCC, hepatocellular carcinoma; AFP, alpha fetoprotein.

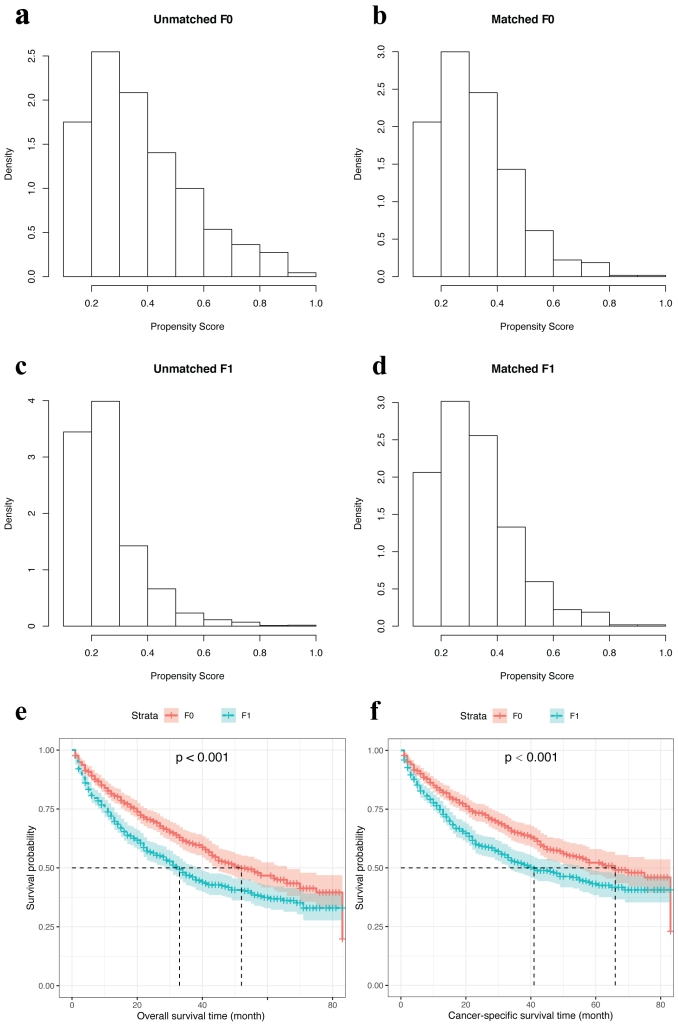


**Figure 2**

Histograms of propensity scores in planned F0(a, b) and F1(c, d) groups before (a, c) and after (b, d) matching. Kaplan-Meier curve of overall survival(e) and cancer-specific survival(f) comparing F0 group with F1 group after propensity score matching (PSM). F0 represents Ishak score 0 to 4 ; F1 represents Ishak score 5 and 6.

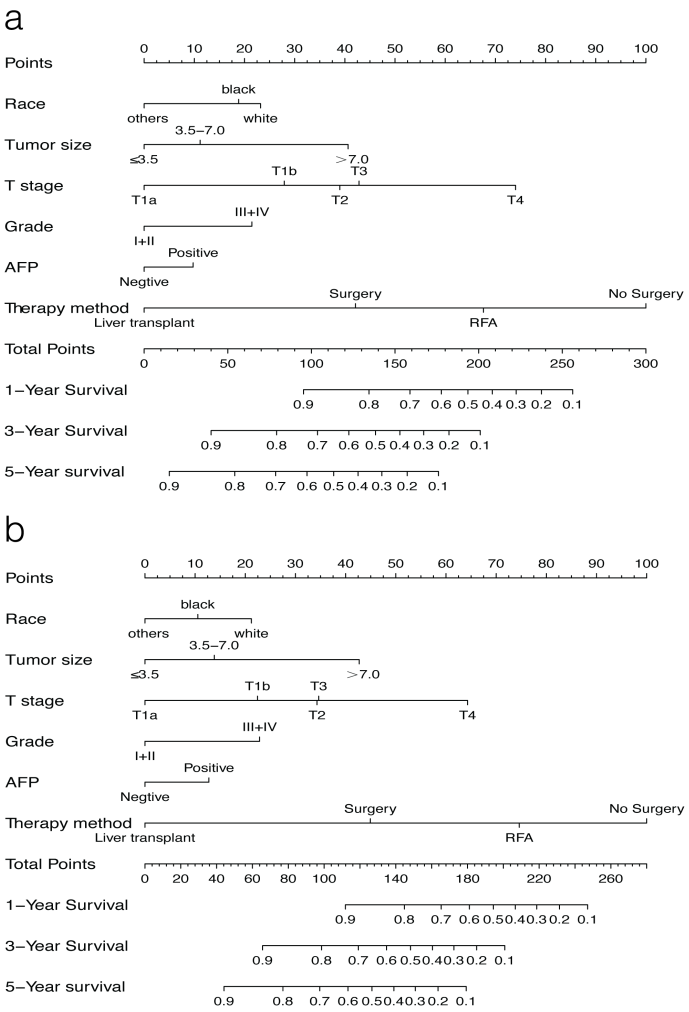


**Figure 3**

The nomogram for predicting 1-, 3- and 5-year overall survival(a) and cancer-specific survival(b) probabilities of patients with hepatocellular carcinoma concomitantly suffer from liver cirrhosis. Others comprises American Indian/Alaska Native and Asian/Pacific Islander; AFP, alpha fetoprotein; RFA, radiofrequency ablation

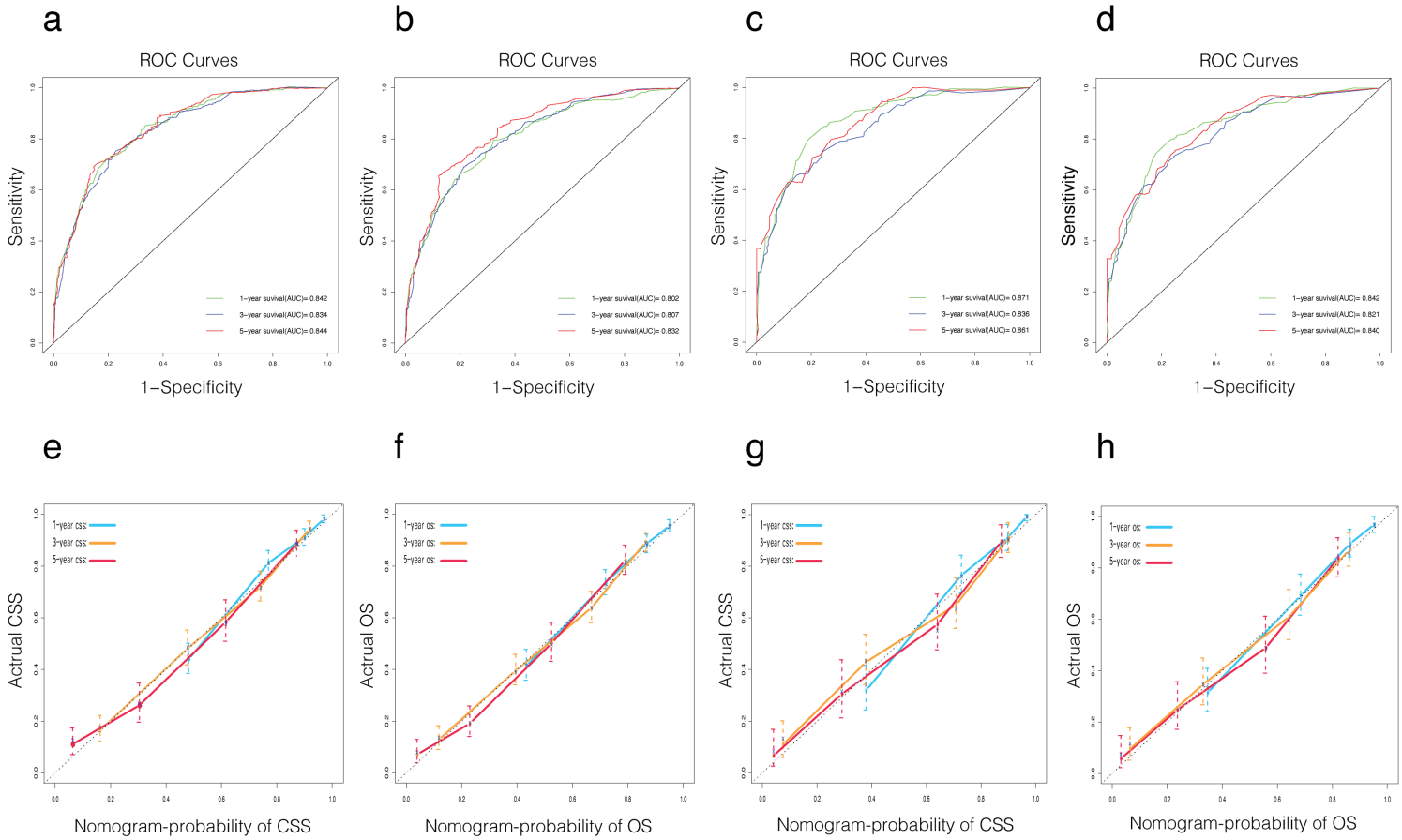


**Figure 4**

The ROC curves of the nomogram for the prognostic prediction of patients with hepatocellular carcinoma concomitantly suffer from liver cirrhosis. (a) For predicting 1-, 3- and 5-year overall survival in the training set. (b) For predicting 1-, 3- and 5-year cancer-specific survival in the validation set. (c) For predicting 1-, 3- and 5-year overall survival in the training set. (d) For predicting 1-, 3- and 5-year cancer-specific survival in the validation set. The calibration curves of the nomogram for 1-,3- and 5- year survival probabilities. (e) CSS for the training set. (f) OS for the validation set. (g) CSS for the training set. (h) OS for the validation set. AUC, area under the receiver operating characteristic curve; CSS, cancer-specific survival; OS, overall survival.

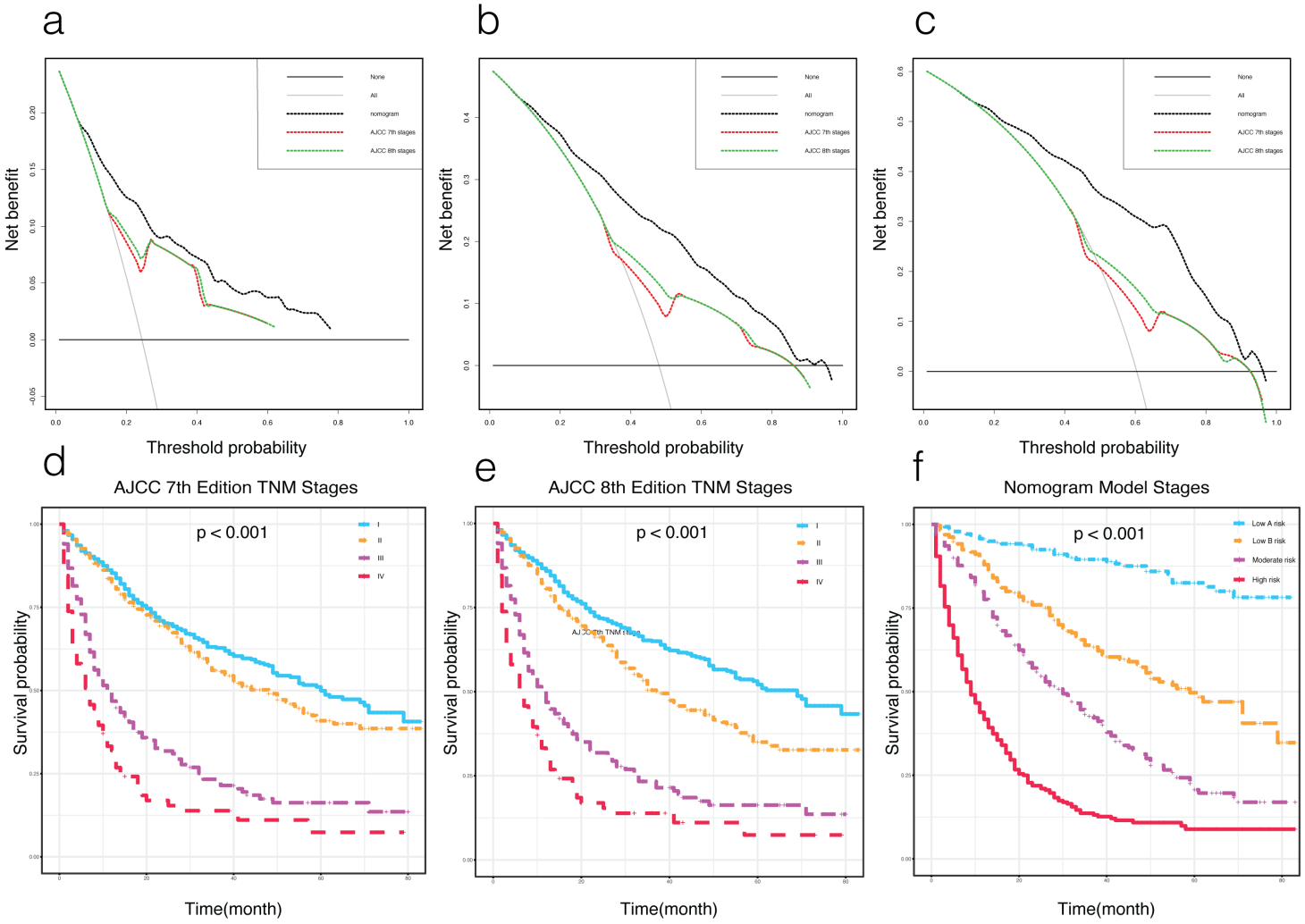


**Figure 5**

Decision curve analysis of the nomogram and AJCC TNM staging system for the 1-, 3- and 5-year overall survival prediction of patients with hepatocellular carcinoma concomitantly suffer from liver cirrhosis. (a) 1-year survival; (b) 3-year survival, (c) 5-year survival. Kaplan–Meier survival curves for patients, according to (d) AJCC7th edition system stages, (e) AJCC8th edition system stages and (f) nomogram-based stages. The p value (< 0.001) was determined using the log-rank test. AJCC, American Joint Committee on Cancer

## Supplementary Files

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