# Risk Factors and Predictive Nomograms for Early Death of Patients with Advanced Hepatocellular Carcinoma: A Large Retrospective Study Based on the SEER Database

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## Abstract

# Background

Hepatocellular carcinoma (HCC) is a kind of tumor with insidious early symptoms and high invasiveness, and it is often in the advanced stage when clinically discovered. Patients with advanced HCC have a higher risk of early death (survival time ≤ 3 months). This study aims to identify the risk factors of early death in patients with advanced HCC and establish predictive nomograms.

# Methods

Patients diagnosed with stage IV HCC between 2010 and 2015 were collected from the Surveillance, Epidemiology, and End Results (SEER) database for model establishment and verification. The univariate and multivariate logistic regression analyses were used to identify the risk factors, which were used to construct nomograms. The concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve (AUC) were used to evaluate the accuracy of the models. The calibration curves and the decision curves analysis (DCA) were used to verify the true consistency and clinical application value of the models. Internal validation was performed using bootstrapping (1000 re-samplings) and cross-validation (k = 10).

# Results

A total of 6799 patients were selected from the SEER database. After strict screening conditions, 1392 patients with stage IVA HCC and 5,211 patients with stage IVB HCC were finally identified. 621 (44.6%) patients in stage IVA and 3271 (62.8%) patients in stage IVB experienced early death. 9 risk factors related to early death of patients with stage IVA and 10 risk factors related to early death of patients with stage IVB were finally identified. Reliable nomograms were constructed using the above risk factors. Internal verification showed that the nomograms had good accuracy for predicting early death. The DCA showed that the nomograms had good clinical applicability.

# Conclusion

The nomograms are helpful for clinicians and oncologists to identify the risk factors for early death of patients with advanced HCC and predict the probability of early death, so as to accurately select individualized treatment plans.

## 1 Background

Liver cancer is the fifth most frequent cancer in the world, ranking fourth in the incidence of cancer-related mortality[1, 2]. Hepatocellular carcinoma (HCC) represents about more than 80% of primary liver

cancer and ranks second in cancer migration[3]. Due to its insidious symptoms and high metastatic potential, more than 30% of hepatocellular carcinoma patients already have extrahepatic metastases at the time of initial diagnosis[4], which leads to the five-year survival rate of advanced HCC is only 8.1%[5].

The prognosis of HCC has always been poor. Surgical treatment is the only opportunity for cure[6]. However, only 5%~15% of patients with early HCC have the opportunity to perform surgical resections[7], most commonly including liver transplantation, surgical resection, and radiofrequency ablation[8]. For patients who have lost the opportunity for surgery, studies have shown that compared with conservative treatment, Transcatheter Arterial Chemoembolization (TACE) can increase the 2-year survival rate of patients with intermediate liver cancer by 23%[7]. At present, for patients with advanced HCC, sorafenib, an oral multi-kinase inhibitor, is the most accepted option worldwide, but even with serious side effects and drug resistance, the median survival time is only 12.3 months[9, 10]. According to the data, which was collected from the SEER database, the 1-year survival rate of patients with stage IV HCC was merely 15.6%, and approximately 57% of patients died within 3 months, which was defined as early death. Because the early symptoms of liver cancer are hidden and the progress is rapid, liver cancer patients are prone to early death. Early identification of risk factors for early death of advanced HCC patients and assessment of the incidence of early death will not only help clinicians discern high-risk patients in time but also be conducive to reducing the pain and economic burden of patients. So far, there has been no research on the nomograms of early death for patients with advanced HCC. Thus, developing nomograms to guide clinicians in identifying risk factors for early death of patients and implementing individualized treatment is immensely essential.

The Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/data/), supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS), is one of the most representative broad-scale tumor registration databases[11] that records 34.6% of the US cancer registry population[12]. SEER database provides a large amount of evidence-based medical information, including patients' general information (such as gender, age, race, and marital status.), as well as tumor size, stage, grade, survival time, vital status, which contribute to clinical medical research and evidence-based medical practice. Therefore, a group of patients with stage IV HCC, selected from the SEER database, were collected to identify the risk factors of early death and construct predictive nomograms.

# 2 Methods

# 2.1 Patients

In this study, SEER∗Stat (version 8.3.9.2) was used to collect all data including patients' clinical information. The inclusion criteria were as follows: (1) stage IV HCC registered between 2010 and 2015, (2) site code: C22.0, (3) histological codes:8170/3-8175/3[in the light of the International Classification of Tumor Diseases Third Edition (ICD-O-3)]. The exclusion criteria were (1) with T0 stage, (2) with missing ethnic information, (3) with missing surgery-related information, (4) with missing survival time, (5) with

the cause of death unknown. Figure 1 shows the patient selection flowchart. Considering the malignant degree and early metastasis performance of HCC as well as previous studies, early death was defined as death that occurred within 3 months after initial diagnosis[13, 14].

## 2.2 Data Collection

The information of patients with advanced HCC was extracted from the SEER database. (1) Baseline information including age, gender, race, and marital status. (2) Clinical characteristics including tumor size, histological grade, AFP, fibrosis scores, T stage, N stage, bone metastasis, brain metastasis, lung metastasis, surgery information, radiotherapy information, chemotherapy information, survival time, vital status, cause of death. (3) Main results: patients with stage IV HCC often live for less than 3 months.

## 2.3 Statistical analysis

Basic characteristics of the categorical variables in the patients were described by numbers and percentages (n, %). R software (Version 4.1.2; https://www.R-project.org) was used for all statistical analyses. In the SEER data set, the univariate and multivariate logistic regression analyses were used to identify variables that were significantly associated with early death of patients with advanced HCC. The variables selected from the multivariate logistic regression analysis were considered to have odds ratio (OR) with 95% confidence interval (CI) and have p-values. Two-sided P-values < 0.05 were considered statistically significant. Finally, the statistically significant risk factors in the multivariate regression analysis were used to construct the predictive nomograms. The concordance index (C-index) was calculated and the area under the receiver operating characteristic (ROC) curve (AUC) was plotted to facilitate the evaluation of the discriminative performance of the nomograms[15, 16]. Plot calibration curves to verify the accuracy and reliability of the nomograms[17]. Decision curves analysis (DCA) can show the net benefit rate of the nomograms, so as to evaluate the applicability of the nomograms in clinical practice[18, 19]. Bootstrapping (1,000 re-samplings) and cross-validation (k = 10) were performed for internal validation, comparing the C-index after bootstrapping and cross-validation between the verification model and the original data to measure the accuracy of the nomograms.

# 3 Results

## 3.1 Characteristics of patients

A total of 6799 patients with stage IV HCC in the SEER database were included in this research. After a rigorous screening process, 6603 patients were finally screened out, of which 1392 were in stage IVA and 5,211 were in stage IVB. 621 (44.6%) patients in stage IVA and 3271 (62.8%) patients in stage IVB occurred early death. In general, about 98% of patients with advanced HCC were older than 40 years old and most of them were male (about 80%). About 70% of patients with advanced HCC were white and 16% were black. Patients with tumors larger than 50mm were more than twice as likely as those with tumors

smaller than 50mm. More than 65% of patients with advanced HCC are AFP positive. The liver fibrosis score of 5 ~ 6 in patients with advanced HCC is about 5 times higher than that of 0 ~ 4. In stage IVB patients, some of them had bone metastasis (29.3%) and lung metastasis (40.3%), but fewer patients had brain metastasis (2.2%). Few patients received surgery (in stage IVA about 7.3% and in stage IVB about 3.4%) and radiotherapy (in stage IVA about 9.3% and in stage IVB about 16.0%), but relatively many patients (more than 35%) received chemotherapy, and patients receiving chemotherapy were less likely to suffer early death (about 21%). The characteristics of all patients were shown in Table 1.

Table 1
Characteristics with advanced HCC patients.

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| | Overall | Non early death | Early death | Overall | Non early death | Early death |
| | (N = 1392) | (N = 771) | (N = 621) | (N = 5211) | (N = 1940) | (N = 3271) |
| **Age (%)** | | | | | | |
| < 40 | 27 (1.9) | 23 (3.0) | 4 (0.6) | 104 (2.0) | 58 (3.0) | 46 (1.4) |
| >=40 | 1365(98.1) | 748 (97.0) | 617 (99.4) | 5107 (98.0) | 1882 (97.0) | 3225 (98.6) |
| **Gender (%)** | | | | | | |
| Female | 258 (18.5) | 149 (19.3) | 109 (17.6) | 972 (18.7) | 353 (18.2) | 619 (18.9) |
| Male | 1134(81.5) | 622 (80.7) | 512 (82.4) | 4239 (81.3) | 1587 (81.8) | 2652 (81.1) |
| **Race (%)** | | | | | | |
| White | 992 (71.3) | 543 (70.4) | 449 (72.3) | 3573 (68.6) | 1363 (70.3) | 2210 (67.6) |
| Black | 225 (16.2) | 125 (16.2) | 100 (16.1) | 830 (15.9) | 292 (15.1) | 538 (16.4) |
| Others* | 175 (12.6) | 103 (13.4) | 72 (11.6) | 808 (15.5) | 285 (14.7) | 523 (16.0) |
| **Marital status (%)** | | | | | | |
| Unmarried | 340 (24.4) | 182 (23.6) | 158 (25.4) | 1344 (25.8) | 474 (24.4) | 870 (26.6) |
| Married | 670 (48.1) | 387 (50.2) | 283 (45.6) | 2372 (45.5) | 934 (48.1) | 1438 (44.0) |
| Divorced or separated | 208 (14.9) | 106 (13.7) | 102 (16.4) | 754 (14.5) | 274 (14.1) | 480 (14.7) |
| Widowed | 104 (7.5) | 55 (7.1) | 49 (7.9) | 478 (9.2) | 164 (8.5) | 314 (9.6) |
| Unknown | 70 (5.0) | 41 (5.3) | 29 (4.7) | 263 (5.0) | 94 (4.8) | 169 (5.2) |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| **Tumor size (%)** | | | | | | |
| <=20mm | 49 (3.5) | 39 (5.1) | 10 (1.6) | 184 (3.5) | 76 (3.9) | 108 (3.3) |
| 21 ~ 50mm | 323 (23.2) | 232 (30.1) | 91 (14.7) | 813 (15.6) | 375 (19.3) | 438 (13.4) |
| 51 ~ 100mm | 518 (37.2) | 293 (38.0) | 225 (36.2) | 1534 (29.4) | 621 (32.0) | 913 (27.9) |
| > 100mm | 275 (19.8) | 121 (15.7) | 154 (24.8) | 1149 (22.0) | 413 (21.3) | 736 (22.5) |
| Unknown | 227 (16.3) | 86 (11.2) | 141 (22.7) | 1531 (29.4) | 455 (23.5) | 1076 (32.9) |
| **Histological grade (%)** | | | | | | |
| Well/moderately | 284 (20.4) | 169 (21.9) | 115 (18.5) | 889 (17.1) | 438 (22.6) | 451 (13.8) |
| Poorly/undifferentiated | 160 (11.5) | 76 (9.9) | 84 (13.5) | 665 (12.8) | 202 (10.4) | 463 (14.2) |
| Unknown | 948 (68.1) | 526 (68.2) | 422 (68.0) | 3657 (70.2) | 1300 (67.0) | 2357 (72.1) |
| **AFP (%)** | | | | | | |
| Negative | 188 (13.5) | 132 (17.1) | 56 (9.0) | 624 (12.0) | 290 (14.9) | 334 (10.2) |
| Positive | 989 (71.0) | 526 (68.2) | 463 (74.6) | 3383 (64.9) | 1212 (62.5) | 2171 (66.4) |
| Unknown | 215 (15.4) | 113 (14.7) | 102 (16.4) | 1204 (23.1) | 438 (22.6) | 766 (23.4) |
| **Fibrosis scores (%)** | | | | | | |
| Ishak 0 ~ 4 | 57 (4.1) | 42 (5.4) | 15 (2.4) | 193 (3.7) | 102 (5.3) | 91 (2.8) |
| Ishak 5 ~ 6 | 267 (19.2) | 149 (19.3) | 118 (19.0) | 782 (15.0) | 317 (16.3) | 465 (14.2) |
| Unknown | 1068(76.7) | 580 (75.2) | 488 (78.6) | 4236 (81.3) | 1521 (78.4) | 2715 (83.0) |
| **T stage (%)** | | | | | | |
| T1 ~ 2 | 497 (35.7) | 346 (44.9) | 151 (24.3) | 1604 (30.8) | 686 (35.4) | 918 (28.1) |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| T3 ~ 4 | 779 (56.0) | 378 (49.0) | 401 (64.6) | 2462 (47.2) | 888 (45.8) | 1574 (48.1) |
| TX | 116 (8.3) | 47 (6.1) | 69 (11.1) | 1145 (22.0) | 366 (18.9) | 779 (23.8) |
| **N stage (%)** | | | | | | |
| N0 | NA | NA | NA | 3071 (58.9) | 1208 (62.3) | 1863 (57.0) |
| N1 | 1392(100) | N = 771(100) | N = 621(100) | 1224 (23.5) | 433 (22.3) | 791 (24.2) |
| NX | NA | NA | NA | 916 (17.6) | 299 (15.4) | 617 (18.9) |
| **Bone metastasis (%)** | | | | | | |
| No | NA | NA | NA | 3441 (66.0) | 1207 (62.2) | 2234 (68.3) |
| Yes | NA | NA | NA | 1527 (29.3) | 650 (33.5) | 877 (26.8) |
| Unknown | NA | NA | NA | 243 (4.7) | 83 (4.3) | 160 (4.9) |
| **Brain metastasis (%)** | | | | | | |
| No | NA | NA | NA | 4801 (92.1) | 1797 (92.6) | 3004 (91.8) |
| Yes | NA | NA | NA | 114 (2.2) | 43 (2.2) | 71 (2.2) |
| Unknown | NA | NA | NA | 296 (5.7) | 100 (5.2) | 196 (6.0) |
| **Lung metastasis (%)** | | | | | | |
| No | NA | NA | NA | 2856 (54.8) | 1289 (66.4) | 1567 (47.9) |
| Yes | NA | NA | NA | 2098 (40.3) | 555 (28.6) | 1543 (47.2) |
| Unknown | NA | NA | NA | 257 (4.9) | 96 (4.9) | 161 (4.9) |
| **Surgery (%)** | | | | | | |
| No | 1291(92.7) | 677 (87.8) | 614 (98.9) | 5036 (96.6) | 1798 (92.7) | 3238 (99.0) |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| Local tumor destruction | 45 (3.2) | 41 (5.3) | 4 (0.6) | 76 (1.5) | 65 (3.4) | 11 (0.3) |
| Wedge resection | 23 (1.7) | 21 (2.7) | 2 (0.3) | 34 (0.7) | 24 (1.2) | 10 (0.3) |
| Lobectomy | 33 (2.4) | 32 (4.2) | 1 (0.2) | 54 (1.0) | 46 (2.4) | 8 (0.2) |
| Surgery but the specific operation unknown | NA | NA | NA | 11 (0.2) | 7 (0.4) | 4 (0.1) |
| **Radiotherapy (%)** | | | | | | |
| No/Unknown | 1262(90.7) | 654 (84.8) | 608 (97.9) | 4377 (84.0) | 1416 (73.0) | 2961 (90.5) |
| Yes | 130 (9.3) | 117 (15.2) | 13 (2.1) | 834 (16.0) | 524 (27.0) | 310 (9.5) |
| **Chemotherapy (%)** | | | | | | |
| No/Unknown | 757 (54.4) | 283 (36.7) | 474 (76.3) | 3339 (64.1) | 754 (38.9) | 2585 (79.0) |
| Yes | 635 (45.6) | 488 (63.3) | 147 (23.7) | 1872 (35.9) | 1186 (61.1) | 686 (21.0) |

Others*: American Indian/AK Native, Asian/Pacific Islander.

AJCC: American Joint Commission on Cancer

HCC: hepatocellular carcinoma

# 3.2 Risk Factors Analysis For Early Death

It has been reported that the division of young liver cancer was bounded by < 40 years old, which is why we chose 40 years old as the age cut-off point[20]. Univariate and multivariate logistic regression analyses were used to determine risk factors for early death in advanced HCC. In patients with stage IVA, the univariate logistic analysis showed that age, tumor size, histological grade, AFP, fibrosis scores, T stage, surgery, radiotherapy, and chemotherapy were risk factors for early death. In stage IVB patients, the univariate logistic analysis showed that age, marital status, histological grade, AFP, fibrosis scores, T stage, N stage, bone metastasis, lung metastasis, surgery, radiotherapy, and chemotherapy were significantly related to early death. Incorporating the above statistically significant univariate logistic analysis results into the multivariate logistic regression analysis, the results revealed that, in stage IVA patients, the risk factors that were statistically significant in univariate logistic analysis still had statistical significance among the multivariate logistic analysis; in stage IVB patients, the marital status

and fibrosis score were not statistically significant. Tables 2 and 3 described the results of univariate and multivariate logistic regression analysis.

Table 2
The univariable logistic regression analysis for analyzing the risk factors for early death of advanced HCC.

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| **Age (%)** | | | | | | |
| < 40 | Ref | | | Ref | | |
| >=40 | 4.743 | 1.813–16.240 | 0.004 | 2.161 | 1.464–3.208 | < 0.001 |
| **Gender (%)** | | | | | | |
| Female | Ref | | | Ref | | |
| Male | 1.125 | 0.857–1.481 | 0.398 | 0.953 | 0.824–1.101 | 0.514 |
| **Race (%)** | | | | | | |
| White | Ref | | | Ref | | |
| Black | 0.967 | 0.722–1.294 | 0.824 | 1.136 | 0.971–1.331 | 0.112 |
| Others* | 0.845 | 0.609–1.169 | 0.313 | 1.132 | 0.966–1.328 | 0.128 |
| **Marital status (%)** | | | | | | |
| Unmarried | Ref | | | Ref | | |
| Married | 0.842 | 0.648–1.096 | 0.200 | 0.839 | 0.730–0.964 | 0.013 |
| Divorced or Separated | 1.108 | 0.785–1.566 | 0.559 | 0.954 | 0.793–1.150 | 0.623 |
| Widowed | 1.026 | 0.660–1.593 | 0.908 | 1.043 | 0.839–1.301 | 0.706 |
| Unknown | 0.815 | 0.480–1.367 | 0.441 | 0.980 | 0.745–1.294 | 0.883 |
| **Tumor size (%)** | | | | | | |
| <=20mm | Ref | | | Ref | | |
| 21 ~ 50mm | 1.530 | 0.759–3.357 | 0.257 | 0.822 | 0.593–1.135 | 0.236 |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| 51 ~ 100mm | 2.995 | 1.520–6.462 | 0.003 | 1.035 | 0.756–1.409 | 0.830 |
| > 100mm | 4.964 | 2.469–10.883 | < 0.001 | 1.254 | 0.911–1.719 | 0.162 |
| Unknown | 6.394 | 3.146–14.148 | < 0.001 | 1.664 | 1.213–2.273 | 0.001 |
| **Histological grade (%)** | | | | | | |
| Well/moderately | Ref | | | Ref | | |
| Poorly/undifferentiated | 1.624 | 1.100-2.404 | 0.015 | 2.226 | 1.804–2.753 | < 0.001 |
| Unknown | 1.179 | 0.902–1.546 | 0.231 | 1.761 | 1.519–2.042 | < 0.001 |
| **AFP (%)** | | | | | | |
| Negative | Ref | | | Ref | | |
| Positive | 2.075 | 1.489–2.923 | < 0.001 | 1.555 | 1.309–1.847 | < 0.001 |
| Unknown | 2.128 | 1.414–3.224 | < 0.001 | 1.518 | 1.248–1.848 | < 0.001 |
| **Fibrosis scores (%)** | | | | | | |
| Ishak 0 ~ 4 | Ref | | | Ref | | |
| Ishak 5 ~ 6 | 2.217 | 1.196–4.311 | 0.014 | 1.644 | 1.198–2.259 | 0.002 |
| Unknown | 2.356 | 1.320–4.435 | 0.005 | 2.001 | 1.498–2.676 | < 0.001 |
| **T stage (%)** | | | | | | |
| T1 ~ 2 | Ref | | | Ref | | |
| T3 ~ 4 | 2.431 | 1.920–3.087 | < 0.001 | 1.325 | 1.165–1.506 | < 0.001 |
| TX | 3.364 | 2.224–5.129 | < 0.001 | 1.591 | 1.358–1.865 | < 0.001 |
| **N stage (%)** | | | | | | |
| N0 | NA | NA | NA | Ref | | |
| N1 | NA | NA | NA | 1.185 | 1.033–1.360 | 0.016 |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| NX | NA | NA | NA | 1.338 | 1.146–1.565 | < 0.001 |
| **Bone metastasis (%)** | | | | | | |
| No | NA | NA | NA | Ref | | |
| Yes | NA | NA | NA | 0.729 | 0.644–0.825 | < 0.001 |
| Unknown | NA | NA | NA | 1.042 | 0.794–1.375 | 0.771 |
| **Brain metastasis (%)** | | | | | | |
| No | NA | NA | NA | Ref | | |
| Yes | NA | NA | NA | 0.988 | 0.676–1.459 | 0.950 |
| Unknown | NA | NA | NA | 1.172 | 0.918–1.507 | 0.208 |
| **Lung metastasis (%)** | | | | | | |
| No | NA | NA | NA | Ref | | |
| Yes | NA | NA | NA | 2.287 | 2.025–2.584 | < 0.001 |
| Unknown | NA | NA | NA | 1.380 | 1.063-1.800 | 0.017 |
| **Surgery (%)** | | | | | | |
| No | Ref | | | Ref | | |
| Local tumor destruction | 0.108 | 0.032–0.268 | < 0.001 | 0.094 | 0.047–0.171 | < 0.001 |
| Wedge resection | 0.105 | 0.017–0.360 | 0.002 | 0.231 | 0.105–0.471 | < 0.001 |
| Lobectomy | 0.034 | 0.002–0.161 | < 0.001 | 0.097 | 0.042–0.194 | < 0.001 |
| Surgery but the specific operation unknown | NA | NA | NA | 0.317 | 0.083–1.052 | 0.067 |
| **Radiotherapy (%)** | | | | | | |
| No/Unknown | Ref | | | Ref | | |
| Yes | 0.120 | 0.064–0.206 | < 0.001 | 0.283 | 0.242–0.330 | < 0.001 |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| **Chemotherapy (%)** | | | | | | |
| No/Unknown | Ref | | | Ref | | |
| Yes | 0.180 | 0.142–0.227 | < 0.001 | 0.169 | 0.149–0.191 | < 0.001 |
| Others*: American Indian/AK Native, Asian/Pacific Islander. | | | | | | |
| AJCC: American Joint Commission on Cancer | | | | | | |
| HCC: hepatocellular carcinoma | | | | | | |
| CI: confidence interval | | | | | | |

Table 3
The multivariate logistic regression analysis for analyzing the risk factors for early death of advanced HCC.

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| **Age (%)** | | | | | | |
| < 40 | Ref | | | Ref | | |
| >=40 | 3.868 | 1.075–16.309 | 0.047 | 1.950 | 1.225–3.116 | 0.005 |
| **Marital status (%)** | | | | | | |
| Unmarried | NA | NA | NA | Ref | | |
| Married | NA | NA | NA | 1.057 | 0.897–1.245 | 0.506 |
| Divorced or Separated | NA | NA | NA | 1.033 | 0.832–1.284 | 0.769 |
| Widowed | NA | NA | NA | 0.989 | 0.769–1.276 | 0.934 |
| Unknown | NA | NA | NA | 0.996 | 0.727–1.373 | 0.982 |
| **Tumor size (%)** | | | | | | |
| <=20mm | Ref | | | NA | NA | NA |
| 21 ~ 50mm | 1.670 | 0.759–3.947 | 0.219 | NA | NA | NA |
| 51 ~ 100mm | 2.548 | 1.163-6.000 | 0.024 | NA | NA | NA |
| > 100mm | 5.393 | 2.387–13.056 | < 0.001 | NA | NA | NA |
| Unknown | 4.322 | 1.873–10.661 | 0.001 | NA | NA | NA |
| **Histological grade (%)** | | | | | | |
| Well/moderately | Ref | | | Ref | | |
| Poorly/undifferentiated | 1.754 | 1.078–2.870 | 0.024 | 2.180 | 1.706–2.794 | < 0.001 |
| Unknown | 0.830 | 0.593–1.160 | 0.276 | 1.399 | 1.176–1.665 | < 0.001 |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| **AFP (%)** | | | | | | |
| Negative | Ref | | | Ref | | |
| Positive | 1.806 | 1.198–2.743 | 0.005 | 1.467 | 1.198–1.796 | < 0.001 |
| Unknown | 1.394 | 0.849–2.299 | 0.191 | 1.236 | 0.981–1.558 | 0.072 |
| **Fibrosis scores (%)** | | | | | | |
| Ishak 0 ~ 4 | Ref | | | Ref | | |
| Ishak 5 ~ 6 | 2.587 | 1.200-5.795 | 0.018 | 1.078 | 0.738–1.572 | 0.698 |
| Unknown | 2.068 | 1.004–4.438 | 0.054 | 1.247 | 0.880–1.766 | 0.214 |
| **T stage (%)** | | | | | | |
| T1 ~ 2 | Ref | | | Ref | | |
| T3 ~ 4 | 2.087 | 1.522–2.871 | < 0.001 | 1.364 | 1.171–1.588 | < 0.001 |
| TX | 1.733 | 0.989–3.052 | 0.056 | 1.254 | 1.034–1.521 | 0.022 |
| **N stage (%)** | | | | | | |
| N0 | NA | NA | NA | Ref | | |
| N1 | NA | NA | NA | 1.220 | 1.037–1.436 | 0.017 |
| NX | NA | NA | NA | 1.000 | 0.826–1.212 | 0.997 |
| **Bone metastasis (%)** | | | | | | |
| No | NA | NA | NA | Ref | | |
| Yes | NA | NA | NA | 1.236 | 1.048–1.460 | 0.012 |
| Unknown | NA | NA | NA | 0.707 | 0.482–1.046 | 0.079 |
| **Lung metastasis (%)** | | | | | | |
| No | NA | NA | NA | Ref | | |

| Characteristics | | AJCC stage IVA | | | AJCC stage IVB | |
|---|---|---|---|---|---|---|
| Yes | NA | NA | NA | 2.199 | 1.905–2.542 | < 0.001 |
| Unknown | NA | NA | NA | 1.223 | 0.846–1.776 | 0.286 |
| **Surgery (%)** | | | | | | |
| No | Ref | | | Ref | | |
| Local tumor destruction | 0.186 | 0.053–0.498 | 0.003 | 0.140 | 0.067–0.266 | < 0.001 |
| Wedge resection | 0.081 | 0.012–0.327 | 0.002 | 0.206 | 0.090–0.446 | < 0.001 |
| Lobectomy | 0.021 | 0.001–0.113 | < 0.001 | 0.078 | 0.033–0.168 | < 0.001 |
| Surgery but the specific operation unknown | NA | NA | NA | 0.647 | 0.138–2.610 | 0.555 |
| **Radiotherapy (%)** | | | | | | |
| No/Unknown | Ref | | | Ref | | |
| Yes | 0.081 | 0.041–0.146 | < 0.001 | 0.345 | 0.284–0.419 | < 0.001 |
| **Chemotherapy (%)** | | | | | | |
| No/Unknown | Ref | | | Ref | | |
| Yes | 0.149 | 0.113–0.196 | < 0.001 | 0.165 | 0.144–0.189 | < 0.001 |
| AJCC: American Joint Commission on Cancer | | | | | | |
| HCC: hepatocellular carcinoma | | | | | | |
| CI: confidence interval | | | | | | |

# 3.3 Nomogram construction

Based on the independent and significant risk factors identified by multivariate logistic regression analysis, we developed independent predictive models to predict the probability of early death in patients with advanced HCC, and presented them as nomograms (**Figure 2 A and B**). In the nomograms, the total points can be obtained by adding up the points for each risk factor, and then the probability of early death can be estimated. For example, a 70-year-old stage IVB patient with lung metastasis of HCC, histological grade III, AFP positive, and only received chemotherapy, had an early death probability of about 50%.

# 3.4 Performance and validation of nomograms

The C-index of the nomograms of early death in stage IVA and IVB patients were 0.828 (95% CI: 0.807-0.849) and 0.789 (95% CI: 0.768-0.810) respectively. **Figure 3 A and B** showed the ROC curve of the nomograms of early death prediction for patients with stage IVA and stage IVB HCC. In stage IVA patients, the area under the ROC curve (AUC) was 0.816 (95% CI: 0.795- 0.837); in stage IVB patients, the ROC curve (AUC) was 0.771 (95% CI: 0.750- 0.792), indicating that the nomograms had desirable predictive ability. The calibration curve was used to evaluate the true compliance of the model. All the calibration curves were close to the 45° line (**Figure 3 C and D**). Internal verification was carried out through bootstrapping (1000 re-samplings) and cross-validation (k=10). In stage IVA patients, the results indicated that the C-index after bootstrapping and cross-validation were 0.819 (95% CI: 0.798-0.840) and 0.816 (95% CI: 0.795-0.837) respectively; in stage IVB patients, the C-index after bootstrapping and cross-validation were 0.785 (95% CI:0.764-0.0.806) and 0.784 (95% CI: 0.763-0.805) respectively. **Table 4** illustrated the C-index after internal validation, which showed that after internal validation, the predicted value was still highly corresponded with the actual value.

**Table 4** The C-index after bootstrapping and cross-validation of nomograms for advanced HCC.

| | Nomogram | After internal verification |
|---|---|---|
| **Bootstrapping (1000re-samplings)** | | |
| AJCC Stage IVA | 0.828 | 0.819 |
| AJCC Stage IVB | 0.789 | 0.785 |
| **Cross validation(k=10)** | | |
| AJCC Stage IVA | 0.828 | 0.816 |
| AJCC Stage IVB | 0.789 | 0.784 |
| AJCC: American Joint Commission on Cancer | | |
| HCC: hepatocellular carcinoma | | |
| C-index: concordance index | | |

# 3.5 Clinical utility

The DCA decision curve was used to evaluate the clinical applicability of the nomograms. **Figure 4 A and B** have shown that, in stage IVA patients, the net benefit rate was 1.0%~78%; in stage IVB patients, it was

1.0%~85%. Therefore, the nomograms we constructed can well assist clinicians to evaluate early death of patients with advanced HCC accurately.

# 4 Discussion

Globally, the incidence of liver cancer is relatively high. Although improvements in treatment techniques and strategies in recent years have markedly improved the cancer-specific survival (CSS) and overall survival (OS) of liver cancer, the long-term survival rate of liver cancer is still extremely low[21]. The 1-year, 3-year, 5-year overall survival rates were 60.5%, 27.6%, and 8.4%, respectively[22]. However, early death, which was defined as death within 3 months after the initial diagnosis, was more likely to appear in advanced HCC. In this study, the data in the SEER database showed that among patients with stage IVA and IVB, the incidence of early death was 44.6% and 62.8%, respectively. At present, most studies were based on the exploration of early hepatocarcinoma and the long-term survival rate of patients, while there were few studies on the early death of patients with advanced HCC. Therefore, developing a series of prediction tools to identify the risk factors and predict the probability of early death to guide clinical treatment is quite valuable.

Although the AJCC staging system has been commonly used in the prognosis assessment of primary liver cancer, it had certain limitations as some crucial risk factors such as age, gender, race, histological grade, and treatment solutions were not included. The innovation of our research lies in the development of nomograms for early death of advanced HCC for the first time that includes the above risk factors. Nomogram is a straightforward and accessible visual tool, which has been widely used for malignant tumor risk and prognosis assessment in recent years[23]. Its simplicity and intuitiveness are conducive to busy clinicians to identify high-risk patients faster and more accurately, and then choose precise and individualized treatment plans. The SEER database has the characteristics of a large sample size and complete patient follow-up information. Therefore, the nomograms based on the SEER database were more exact and stable[24, 25].

In this study, regardless of stage IVA or stage IVB patients, age was significantly associated with early death, which was consistent with the results of previous studies[26, 27]. From the SEER database data and the existing research, it is obvious that HCC is more likely to occur in male[28], however, gender was not a risk factor for early death of advanced HCC patients. In stage IVA patients, the probability of early death in male and female patients was 45% and 42%, and that of patients in male and female with stage IVB was 63% and 64%, respectively. Also, the results showed that race and marital status were not the risk factors for early death of patients. Except for the above demographic characteristics, the research also showed that in patients with stage IVA, larger tumor size, higher histological grade, AFP positive, higher fibrosis scores, T3 ~ 4 stage, and patients who had not received surgery, radiotherapy, or chemotherapy were in the higher risk of early death. In patients with stage IVB, higher histological grade, AFP positive, T3 ~ 4 stage, N1 stage, bone metastasis, lung metastasis, and those without surgery, radiotherapy, or chemotherapy tended to suffer an early death.

It has been reported that tumor size was an independent risk factor for HCC recurrence and death after HCC resection. Taking 5 cm as the boundary, the 5-year recurrence-free survival (RFS) and overall survival (OS) rates in the ≤ 5 cm group were 38.3% and 61.5%, while those in the > 5 cm group were 25.1% and 59.9%[29]. However, our study showed that tumor size was not a risk factor for early death in patients with stage IVB. This may be because stage IVB HCC was mostly due to the recurrence of early liver cancer after surgery. At this time, the disease progressed rapidly, and the tumor size may have less impact on the early death of patients. Our research also illustrated that, in stage IVB patients, fibrosis score was also not a risk factor for early death. Liver fibrosis was a chronic inflammatory process, and it has been reported that liver fibrosis had no effect on OS and RFS until developed into liver cirrhosis[30]. However, stage IVB HCC had the characteristics of rapid progression and extensive invasiveness, and cirrhosis had no chance to develop, which might be why fibrosis score was not a risk factor for early death in patients with stage IVB. [31]. The brain was one of the most likely sites for metastasis in patients with advanced HCC[32–34], but the results in our research did not show that brain metastasis was significantly associated with early death of patients. This might be relevant to the small number of brain metastasis in liver cancer and the insufficient sample size.

Nowadays, liver cancer has entered a multimodal diagnosis and treatment era. In addition to clinically commonly used ultrasound, magnetic resonance imaging, and computed tomography, tumor markers were also playing a momentous role in the diagnosis of liver cancer[35]. Tumor markers that contribute to the diagnosis of HCC include alpha-fetoprotein (AFP) heterogeneity, Glypican-3, osteopontin, Des-γ-carboxyprothrombin, Golgi protein-73, abnormal pro-thrombin, and heat shock protein[36]. Among them, AFP is the most widely accepted serum biomarker for the diagnosis of HCC, however, the specificity and sensitivity of this tumor marker were 72–90% and 39–65%, respectively. Besides, the early diagnosis efficiency of AFP was only 9–32%, and cholangiocarcinoma did not express AFP, which limited its clinical use[37, 38]. Therefore, if these newly discovered tumor markers can be combined with epidemiology and clinical pathology, it will help establish a more accurate prediction model to guide the individualized treatment of HCC.

Sorafenib is currently considered to be the standard frontline therapy for advanced HCC. However, a great number of adverse events mainly including gastrointestinal or skin diseases have been found in patients taking sorafenib. In some severe cases, sorafenib can cause high blood pressure and abdominal pain, leading to interruption of treatment[39]. Even so, only approximately 30% of patients with advanced HCC can benefit from sorafenib, and these people usually develop drug resistance within 6 months[40]. Therefore, for the treatment of advanced HCC, it is urgent to explore new drugs and further understand the process of tumor resistance.

It is still controversial whether HCC patients with lymph node invasion should accept surgery treatment. However, in this study, the outcome indicated that surgery had an important effect on the improvement of early death in advanced HCC. Moreover, previous studies have stressed that surgery had beneficial value for advanced HCC patients, especially for that with regional lymph node invasion[41]. Therefore, although the guidelines recommend targeted therapy as the frontline treatment for advanced HCC, it might be more

targeted at patients with stage IVB. For patients with stage IVA who only had regional lymph node metastasis, surgery might also be a better treatment option. However, considering a small number of patients undergoing surgery in our study, it might be more prudent to set strict indications for surgery in advanced HCC based on the clinical conditions of the patients. Furthermore, large-scale prospective studies are required to prove the surgical value of advanced HCC.

Inevitably, there are several limitations in this study. First, although the SEER database provides a large enough sample size, it still lacks some potential risk factors, which may be related to early death, such as the specific location of regional lymph node metastasis, the patients' past medical history, adverse habits (drinking and smoking history), postoperative tumor remnants, the specific methods of radiotherapy and chemotherapy, and other tumor markers other than AFP. Second, the SEER database has limitations in HCC tumor staging; the AJCC staging system lacks some important prognostic information, including Child-Pugh classification and the patients' performance status, which makes it not widely endorsed for HCC. It is possible that the patients in our research may include Child-Pugh class C, who were in Barcelona Clinic Liver Cancer (BCLC) stage D disease, and surgery, radiotherapy, and chemotherapy were not recommended. Third, as a retrospective study, selection bias caused by censoring data is unavoidable. Last, although internal verification suggested that the nomograms had good predictive capabilities, it still requires multiple centers and large sample size data for external verification to avoid overfitting.

# 5 Conclusion

In conclusion, based on the large sample size provided by the SEER database, we identified the risk factors for early death of patients with advanced HCC and developed nomograms. Internal verification suggested that the nomograms had excellent accuracy. These nomograms may help oncologists and clinicians identify risk factors and probability of early death more quickly and accurately, so as to formulate more precise individualized treatment plans to improve the patients' survival probability and quality of life.

# Abbreviations

HCC: hepatocellular carcinoma;

SEER: Surveillance, Epidemiology, and End Results;

C-index: concordance index;

ROC: receiver operating characteristic;

AUC: area under the curve;

DCA: decision curve analysis;

TACE: Transcatheter Arterial Chemoembolization;

SRP: Surveillance Research Program;

NCI: National Cancer Institute;

DCCPS: Division of Cancer Control and Population Sciences;

ICD-O-3: International Classification of Tumor Diseases Third Edition;

OR: odds ratio

CI: confidence interval;

CSS: cancer-specific survival;

OS: overall survival;

RFS: recurrence-free survival;

AFP: alpha-fetoprotein;

AJCC: American Joint Commission on Cancer;

BCLC: Barcelona Clinic Liver Cancer.

# Declarations


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### Availability of data and materials

The original data for this study is obtained from the SEER database. The detailed website can be found at: https://seer.cancer.gov/data/. More specific data used in this study are available from the authors upon reasonable request and with permission of the SEER database.

### Ethics approval and consent to participate

All experimental protocols were approved by the National Cancer Institute (USA) to obtain research data on cancer patients (reference number 17461-Nov2020). This study was in line with the 1964 Helsinki Declaration and subsequent amendments or similar ethical standards.

### Competing interests

All authors declare that they have no competing interests.

### Consent for publication

Not applicable.

### Authors' contributions

HDZ and YWZ contributed to the study design and literature search. HDZ, HD, WJX, and PCZ completed the data analysis. HDZ, XLD, SWL, XQ, and YZ generated and improved the figures and tables. HDZ and XLD completed the manuscript. YWZ and MY proofread the manuscript. All authors contributed to the article and approved the submitted version.


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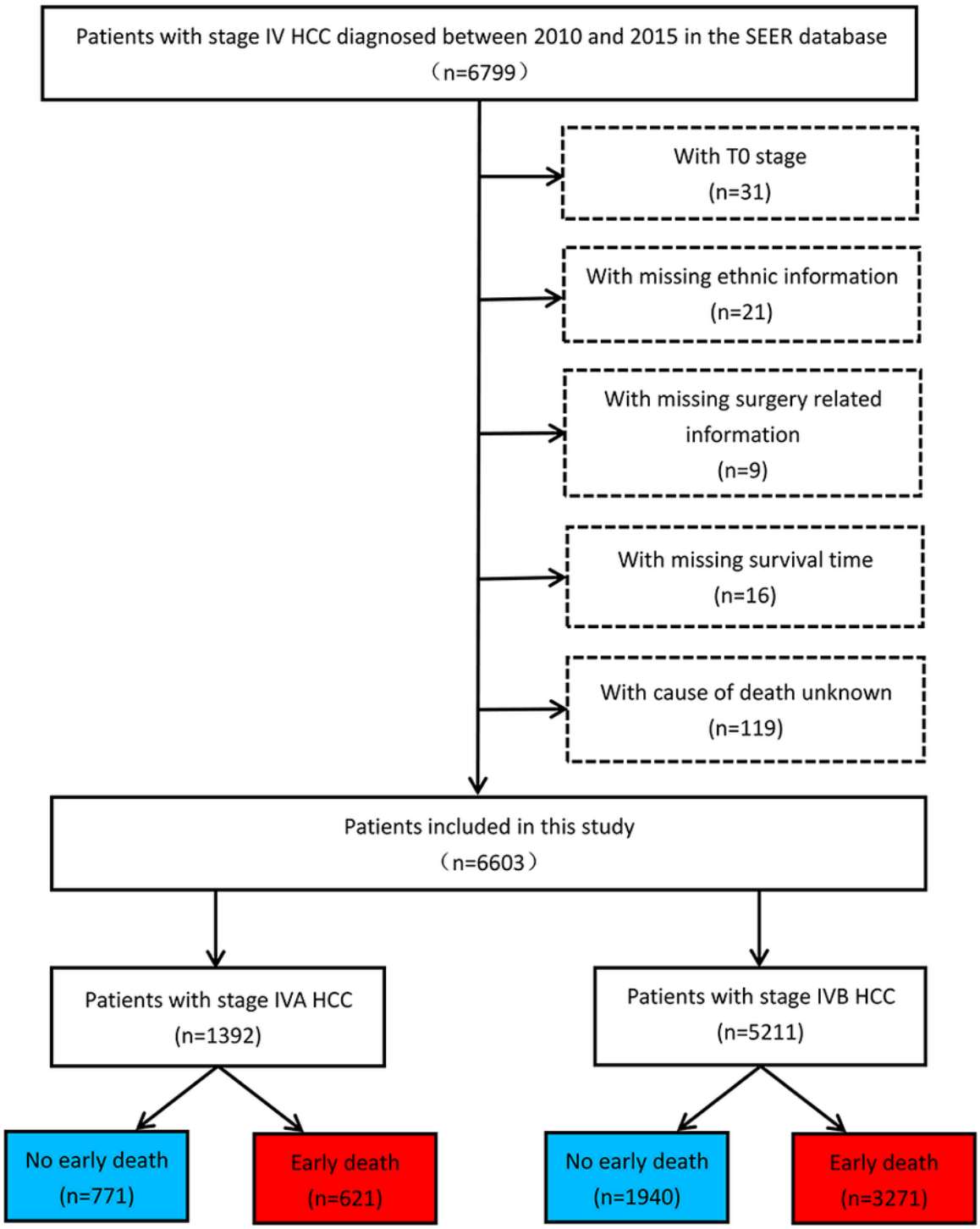
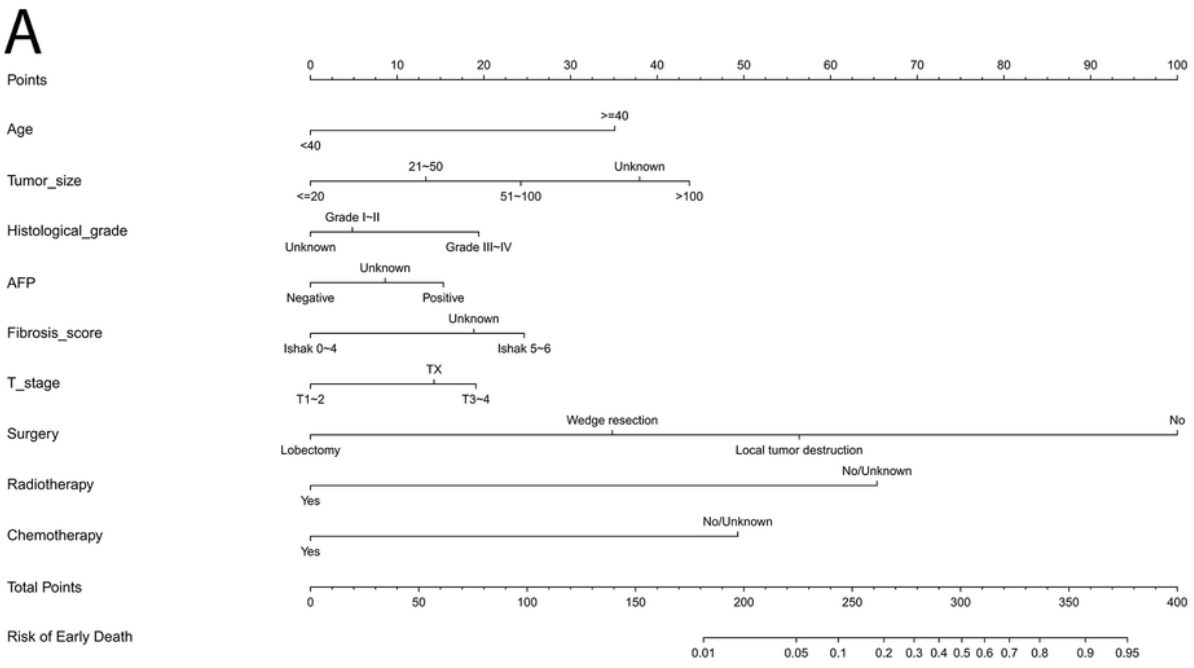
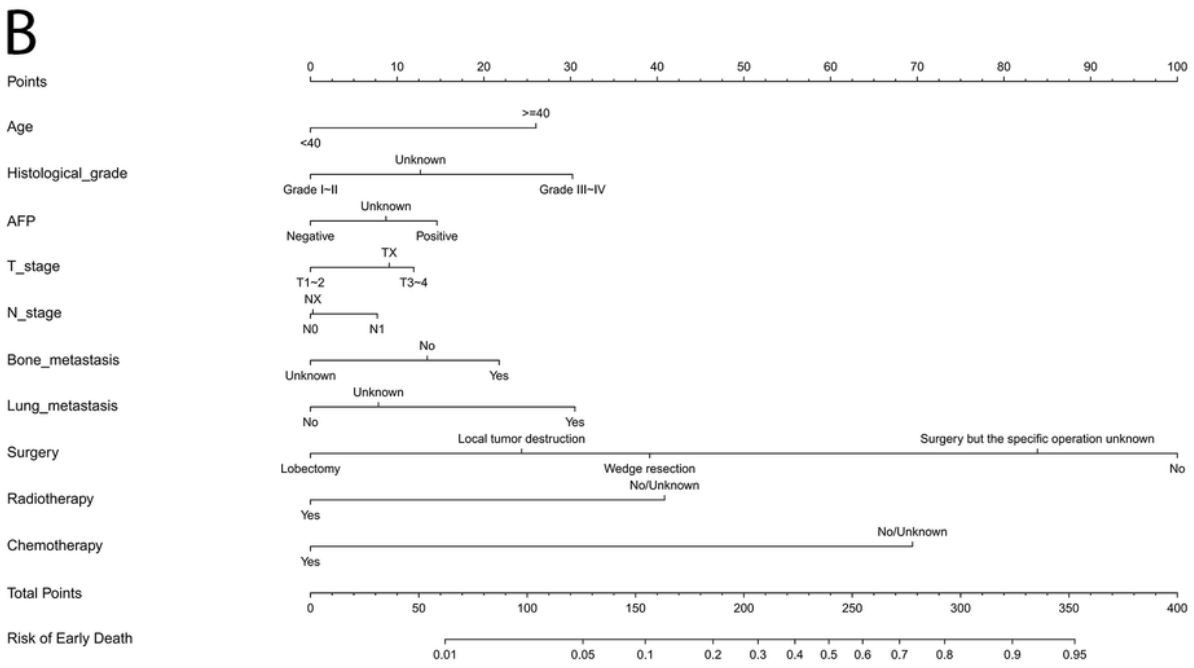
# Figures




## Figure 1

Patient selection flowchart. After a rigorous screening process, 6603 patients were finally screened out, of which 1392 were in stage IVA and 5,211 were in stage IVB. 621 patients occurred early death in stage IVA, and 3271 patients in stage IVB suffered early death. Abbreviations: HCC, hepatocellular carcinoma.




## Figure 2

**A and B** The nomograms of early death in patients with advanced HCC. **(A)** stage IVA, enrolling in 9 risk factors; **(B)** stage IVB, enrolling in 10 risk factors. Abbreviations: alpha-fetoprotein.

## Figure 3

**A and B** The receiver operating characteristic (ROC) curve for the nomograms. **(A)** stage IVA; **(B)** stage IVB. **C and D** The calibration curves plots for the nomograms (bootstrapping, 1000 re-samplings). **(C)** stage IVA; **(D)** stage IVB. Abbreviations: AUC, area under the curve.

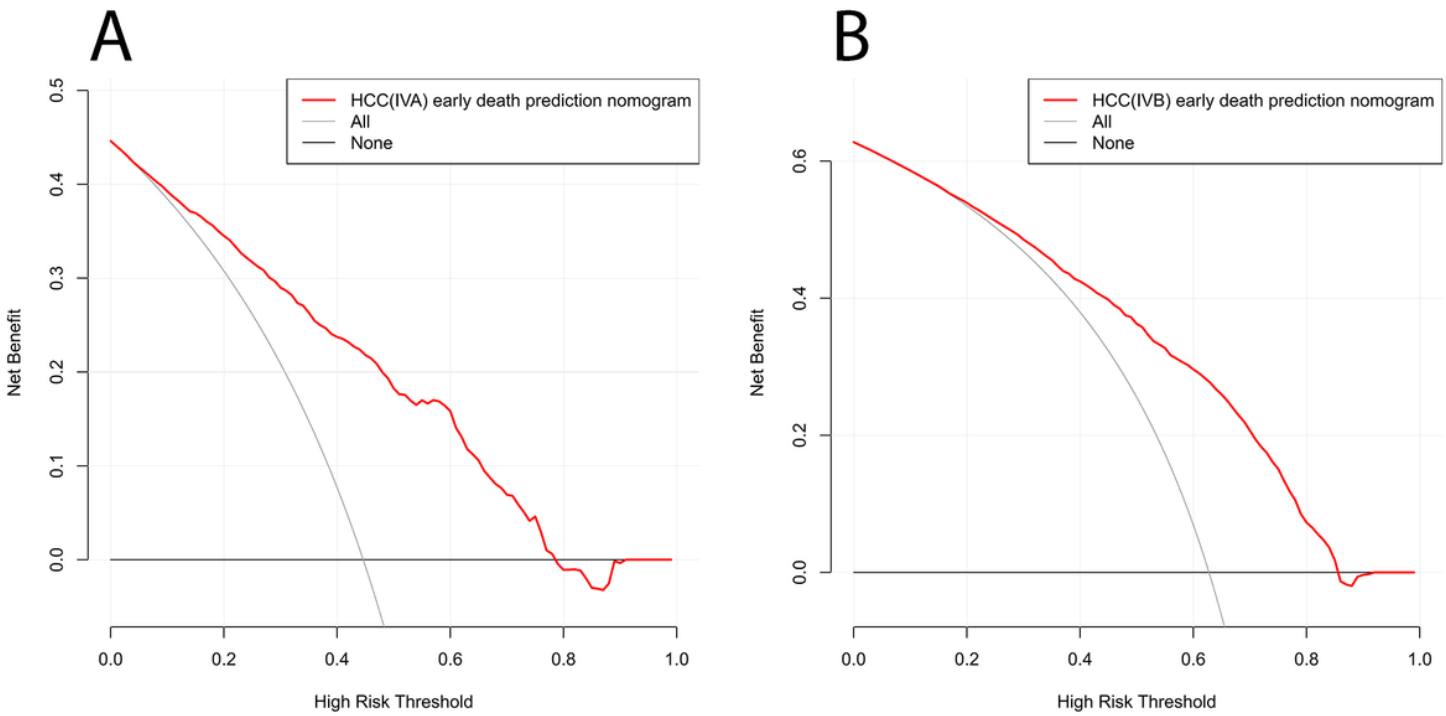



**Figure 4**

**A and B** The decision curve analysis (DCA) for the nomograms. **(A)** stage IVA; **(B)** stage IVB. Abbreviations: HCC, hepatocellular carcinoma.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.xlsx
- TableS2.xlsx