

ORIGINAL RESEARCH ARTICLE

Prognostic nomogram for early-stage hepatocellular carcinoma after surgical resection: A Surveillance, Epidemiology, and End Results database-driven risk stratification model

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Abstract

While surgical resection offers favorable outcomes for early-stage hepatocellular carcinoma (HCC) patients, significant postoperative recurrence and prognostic heterogeneity remain, underscoring a lack of reliable predictive tools. Identifying robust prognostic factors is therefore essential for personalized treatment. This study aims to develop and validate a prognostic nomogram for patients with early-stage HCC after surgery using the Surveillance, Epidemiology, and End Results database (2007–2021). We retrospectively analyzed 7,090 patients with early-stage HCC (T1–2N0M0), randomly dividing them into training ($n = 4,964$) and validation ($n = 2,126$) cohorts. Key variables were selected using univariate Cox regression and least absolute shrinkage and selection operator regression to mitigate multicollinearity, followed by multivariable Cox regression to construct a model integrating diagnostic year, tumor biology, and treatment parameters. The final nomogram incorporated nine predictive variables: diagnosis year, race, socioeconomic status, tumor size, American Joint Committee on Cancer stage, alpha-fetoprotein level, fibrosis score, surgical approach, and systemic therapy timing. Hepatectomy/liver transplantation was the strongest protective factor (hazard ratio = 0.165; 95% confidence interval [CI]: 0.120–0.228). The model demonstrated strong discrimination, with C-indices of 0.724 (95% CI: 0.710–0.738) in the training cohort and 0.713 (95% CI: 0.691–0.735) in the validation cohort. Time-dependent receiver operating characteristic curves showed areas under the curve exceeding 0.70 for predicting 1-, 3-, and 5-year cancer-specific survival, and calibration plots indicated good agreement between predicted and observed outcomes. Risk stratification using a 150-point cutoff effectively distinguished high-risk patients from low-risk patients, with significantly lower 5-year survival rates (55.0% vs. 88.7%, $p < 0.001$). In conclusion, this multidimensional nomogram provides a reliable tool for individualized postoperative risk assessment and management in patients with early-stage HCC.

Keywords: Hepatocellular carcinoma; Prognostic model; SEER database; Risk stratification; Nomogram

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Citation: Liu Y, Zhou L, Liu C, Huang K. Prognostic nomogram for early-stage hepatocellular carcinoma after surgical resection: A Surveillance, Epidemiology, and End Results database-driven risk stratification model. *Cancer Plus*. 2026;8(3):025490089. doi: 10.36922/CP025490089

Received: December 2, 2025

Revised: February 1, 2026

Accepted: April 16, 2026

Published online: May 19, 2026

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1. Introduction

Hepatocellular carcinoma (HCC) ranks as a major global health challenge, being the third leading cause of cancer-related mortality worldwide. It accounts for over 900,000 new cases annually, with incidence rates demonstrating a concerning upward trajectory in most regions, driven by factors such as chronic viral hepatitis, metabolic dysfunction-associated steatotic liver disease, and environmental exposures.¹ For patients diagnosed with early-stage (T1–2N0M0) HCC, surgical resection and liver transplantation represent the primary curative-intent therapies. Despite these interventions, long-term outcomes are compromised by a high 5-year recurrence risk (50–70%) and significant heterogeneity in survival among patients.^{2,3} This prognostic variability stems not only from intrinsic tumor biology—such as histological grade, molecular subtypes, and presence of microvascular invasion⁴—but is also profoundly shaped by a complex interplay of non-anatomical determinants. These include socioeconomic disparities affecting healthcare access, variations in treatment modalities (e.g., anatomic vs. non-anatomic resection), and critical timeliness in administering multimodal therapies, including the sequence of surgery and systemic treatments.^{5,6}

The current clinical paradigm for prognostication in HCC heavily relies on staging systems such as the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging and the Barcelona Clinic Liver Cancer (BCLC) classification. These frameworks primarily emphasize anatomical tumor extent (size, number, vascular invasion) and baseline liver function.^{7,8} While providing a foundational structure for therapeutic stratification, these systems exhibit notable limitations: they are largely static, failing to seamlessly integrate dynamic advancements in treatment paradigms—such as survival gains from contemporary immunotherapy and targeted agents—or to account for socioeconomic determinants that critically influence treatment accessibility, adherence, and ultimately, patient survival.⁹ For instance, analyses of population-based registries, including the SEER database, consistently reveal that patients from lower-income backgrounds are significantly less likely to receive potentially curative surgical interventions compared to their higher-income counterparts.¹⁰ Furthermore, a substantial proportion of published prognostic models are derived from single-center, retrospective cohorts with limited sample sizes, which raises concerns regarding their generalizability, reproducibility, and robustness when applied to broader, more diverse populations.¹¹

The evolving era of precision oncology has catalyzed a shift toward the development of integrated prognostic tools

that synthesize multidimensional data. Nomograms have emerged as powerful, intuitive statistical instruments that quantify the contribution of multiple prognostic variables to generate individualized probability estimates for clinical outcomes. They have demonstrated superior predictive accuracy compared to conventional staging systems across various malignancies.¹² In HCC, while several nomograms exist, there remains a distinct gap for a comprehensive model specifically tailored to the postoperative early-stage population. An ideal tool would simultaneously encapsulate tumor biology, detailed treatment strategies (including surgical approaches and systemic therapy sequencing), socioeconomic context, and temporal trends reflecting evolving standard-of-care practices.

To address these gaps, this study leverages the large-scale, population-based Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute. This resource enables us to overcome constraints of previous studies, such as limited sample sizes and restricted variable scopes. Our primary objective is to construct and rigorously validate a multidimensional prognostic nomogram for patients with early-stage HCC following surgery. The model innovatively incorporates key, yet frequently overlooked, dimensions: the year of diagnosis (to capture temporal improvements in management), quantitative socioeconomic status indicators, and the critical timing relationship between systemic therapy and surgical intervention. We hypothesize that this integrated model will provide more accurate, individualized risk stratification for postoperative early-HCC patients. Ultimately, we aim for this tool to assist clinicians in personalizing surveillance intensity, informing adjuvant therapy decisions, and improving long-term patient outcomes through data-driven, precision management strategies.

2. Materials and methods

2.1. Data sources and case selection

This investigation accessed data from the National Cancer Institute's SEER registries (version 8.4.4), encompassing adults aged ≥ 18 years with pathologically confirmed HCC between January 2007 and December 2021. Cases meeting HCC criteria were histopathologically validated, with primary tumor localization designated as C22.0 (ICD-O-3) and histological subtypes within codes 8170–8175 (encompassing classical and special subtypes). Patients were further restricted to those classified as early-stage disease per AJCC 7th edition TNM staging (T1–2N0M0). Exclusion criteria encompassed cases with missing critical clinical data (e.g., TNM stage, tumor size, treatment details, or survival duration), postoperative survival < 1 month (to

mitigate confounding by perioperative complications), additional malignancies, ambiguous treatment records, or follow-up < 3 months. These criteria ensured data reliability and minimized potential biases. The case data screening process is illustrated in Figure 1.

2.2. Variable definitions and data handling

Feature specifications and data preprocessing steps comprised four domains: (i) demographic variables (gender, age, race, marital status, socioeconomic status); (ii) oncologic tumor attributes (maximum diameter, histological grading, AJCC tumor staging system); (iii) treatment information (surgical modality, chemotherapy, radiotherapy, timing of systemic therapy relative to surgery, and interval between diagnosis and surgery); and (iv) temporal variables (diagnostic year). AJCC staging was harmonized across SEER updates: The AJCC 6th edition staging system was used to diagnose patients from 2007 to 2009; to ensure consistency of staging data across the entire study cohort (2007–2021), we harmonized the case data from 2007 to 2009 by converting their AJCC staging from the 6th edition to align with the 7th edition criteria. Patients diagnosed between 2010–2015 were staged using the AJCC 7th edition staging system; those diagnosed in 2016–2017 were assigned to the Derived SEER Combined

Stage Group “I, II”; and 2018–2021 cases were classified under the Derived Extent of Disease 2018 Stage Group “I, II.” Cancer-specific survival (CSS) was defined as the time from diagnosis to HCC-related death. The dataset was randomly partitioned into training (70%) and validation (30%) cohorts using stratified sampling via the caret package in R software (R4.4.2, Foundation for Statistical Computing, Austria), with a fixed random seed (563) to ensure reproducibility.

2.3. Statistical analysis

This study utilized the R 4.4.2 platform, incorporating caret, tableone, survival, glmnet, and rms packages to develop a comprehensive survival prediction analysis workflow. Specifically, data cleaning, stratified sampling (7:3 training/validation set ratio), and distribution visualization were implemented via caret; baseline characteristic statistics and inter-group distribution consistency testing were performed using tableone; univariate Cox regression ($p < 0.05$) was conducted with the survival package for variable screening; least absolute shrinkage and selection operator (LASSO) regression was applied through glmnet to compress high-dimensional data and identify key predictive factors; subsequently, a multivariate Cox model was constructed using rms to generate nomograms for

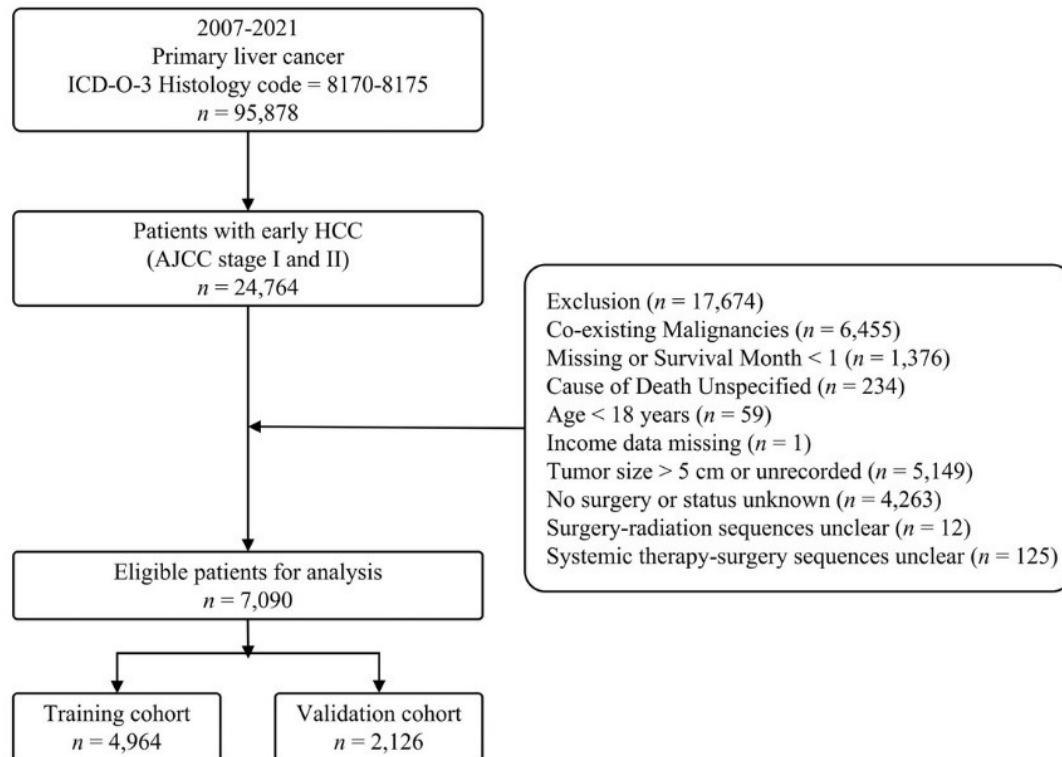


Figure 1. Patient inclusion and allocation flowchart

Abbreviations: AJCC: American Joint Committee on Cancer; HCC: Hepatocellular carcinoma.

risk stratification (low-risk/high-risk groups) and survival difference analysis (log-rank test). Model performance was evaluated using pROC and timeROC for discriminative power assessment (area under the curve [AUC] and dynamic receiver operating characteristic [ROC]); clinical net benefit was analyzed using ggDCA; survival curves were visualized, and prediction probabilities were calibrated (using the `calibrate()` function) with `survminer`. A *p*-value less than 0.05 is considered to have statistical significance.

3. Results

3.1. Baseline characteristic analysis

This study included 7,090 early-stage HCC patients, comprising a training cohort ($n=4,964$) and an internal validation cohort ($n=2,126$). Table 1 shows the cohort's median overall survival of 44 months (interquartile range: 19–83 months), with 27.1% mortality attributed to HCC-related causes. Demographic analysis revealed: 61.2% were elderly adults (≥ 60 years), 75.1% were male, 67.7% identified as White, 58.8% were currently married, and 69.4% had an annual household income between USD 60,000 and 100,000. Clinical features included 73.2% of tumors measuring > 2 and ≤ 5 cm, 65.3% classified as AJCC stage I, 46.2% with alpha-fetoprotein (AFP) positivity, and 30.7% with fibrosis scores of 5–6. Moderately differentiated tumors were the most common histologic grade (41.8%). Treatment modalities predominantly comprised hepatic resection/orthotopic liver transplantation (33.1%) and local tumor ablation (31.2%). The proportions of preoperative chemotherapy and preoperative radiation therapy were both higher than those of postoperative chemotherapy and postoperative radiation therapy. The proportion of cases with a diagnosis-to-treatment interval exceeding 60 days was 38.7%. No significant differences were observed between the two cohorts in baseline characteristics ($p > 0.05$ for all variables), ensuring robustness for subsequent model development and validation.

3.2. Prognostic variable selection

Univariate Cox regression identified 13 variables significantly associated with CSS ($p < 0.05$), including diagnostic year, ethnic composition, socioeconomic status, maximal tumor diameter, and operative procedures (Table 2). Notably, hepatic resection/orthotopic liver transplantation exhibited the strongest protective effect (hazard ratio [HR] = 0.18, 95% confidence interval [CI]: 0.15–0.21), whereas postoperative radiation therapy (HR = 2.31, 95% CI: 1.53–3.50) and chemotherapy (HR = 2.08, 95% CI: 1.73–2.48) significantly increased mortality risks. These findings may suggest that postoperative

therapies, often indicative of more advanced cases, could be confounded by other variables. LASSO regression (Figure 2) reduced dimensionality, eliminating variables such as marital status and radiation sequencing, ultimately selecting nine key predictors for multivariate analysis. The multivariate Cox regression analysis demonstrated that hepatic resection/transplantation remained the most significant protective factor (HR = 0.17, 95% CI: 0.14–0.20), corresponding to an 83% lower hazard of cancer-specific death relative to local tumor destruction. Hepatectomy also showed a significant reduction in risk (HR = 0.17, 95% CI: 0.14–0.20). Regarding chemotherapy timing, “post-chemotherapy surgery” was associated with a higher risk compared to “pre-chemotherapy surgery” (HR = 1.33, 95% CI: 1.10–1.60). Later diagnosis years were associated with reduced risk, as patients diagnosed between 2017–2021 demonstrated a 45% lower hazard than those diagnosed during 2007–2011 (HR = 0.55, 95% CI: 0.46–0.65). Additional risk factors included tumor diameter of > 2 and ≤ 5 cm (HR = 1.56, 95% CI: 1.35–1.80) and AJCC stage II (HR = 1.41, 95% CI: 1.26–1.58).

3.3. Model construction and evaluation

A nomogram predicting CSS in early-stage HCC patients undergoing surgery was developed using multivariate Cox regression analysis that incorporated nine variables (Figure 3). The model's discriminatory capacity, as evaluated using the C-index, was 0.724 (95% CI: 0.710–0.738) in the training cohort and 0.713 (95% CI: 0.691–0.735) in the validation cohort. Calibration plots (Figure 4) show slopes near unity, indicating strong congruence between predicted and observed survival probabilities. Time-dependent ROC curves demonstrated strong predictive power, with 1-, 3-, and 5-year AUCs exceeding 0.7 in both cohorts (Figure 5A and 5B). Decision curve analysis (Figure 6A and 6B) further highlighted a favorable clinical net benefit across all risk thresholds.

3.4. Risk stratification based on the model

Patients were classified into low-risk (total score ≤ 150) and high-risk (score > 150) groups using the prognostic scoring system. Kaplan–Meier survival analysis showed statistically significant differences between groups ($p < 0.001$ at all-time points) in both cohorts (Figure 7). The training cohort yielded cumulative survival rates of 90.4%, 69.0%, and 55.0% in high-risk patients and 97.6%, 92.8%, and 88.7% in low-risk patients for 1-, 3, and 5-year CSS, respectively. In the validation cohort, the corresponding values were 90.0%, 67.3%, and 54.4% compared to 97.2%, 90.3%, and 86.3% for 1-, 3, and 5-year CSS, respectively. These results underscore the model's clinical utility for personalized risk assessment and management.

Table 1. Comparison of baseline data between the training set and the validation set

Parameters	Overall (n = 7,090)	Training set (n = 4,964)	Validation set (n = 2,126)	p-value
Survival months (median [IQR])	44.00 [19.00, 83.00]	44.00 [19.00, 84.00]	44.00 [19.00, 82.00]	0.739
CSS				
Alive or dead from other causes	5,168 (72.9)	3,618 (72.9)	1550 (72.9)	1.000
Dead (attributed to this cancer)	1,922 (27.1)	1,346 (27.1)	576 (27.1)	
Year of diagnosis				
2007–2011	2,097 (29.6)	1,473 (29.7)	624 (29.4)	0.950
2012–2016	2,514 (35.5)	1,755 (35.4)	759 (35.7)	
2017–2021	2,479 (35.0)	1,736 (35.0)	743 (34.9)	
Age (years)				
<60	2,752 (38.8)	1,942 (39.1)	810 (38.1)	0.434
≥60	4,338 (61.2)	3,022 (60.9)	1,316 (61.9)	
Gender				
Male	5,327 (75.1)	3,712 (74.8)	1,615 (76.0)	0.304
Female	1,763 (24.9)	1,252 (25.2)	511 (24.0)	
Marital status				
Married	4,172 (58.8)	2,915 (58.7)	1,257 (59.1)	0.842
Single	2,661 (37.5)	1,872 (37.7)	789 (37.1)	
Unknown	257 (3.6)	177 (3.6)	80 (3.8)	
Race				
White	4,797 (67.7)	3,347 (67.4)	1,450 (68.2)	0.326
Black	739 (10.4)	511 (10.3)	228 (10.7)	
Other	1,504 (21.2)	1,075 (21.7)	429 (20.2)	
Unknown	50 (0.7)	31 (0.6)	19 (0.9)	
Income level				
<USD 60,000	958 (13.5)	684 (13.8)	274 (12.9)	0.569
USD 60,000–100,000	4,923 (69.4)	3,441 (69.3)	1,482 (69.7)	
>USD 100,000	1,209 (17.1)	839 (16.9)	370 (17.4)	

(Cont'd...)

Table 1. (Continued)

Parameters	Overall (n = 7,090)	Training set (n = 4,964)	Validation set (n = 2,126)	p-value
Tumor size				
≤2 cm	1,897 (26.8)	1,338 (27.0)	559 (26.3)	0.585
>2 and ≤5 cm	5,193 (73.2)	3,626 (73.0)	1,567 (73.7)	
Grade				
Well differentiated	1,669 (23.5)	1,184 (23.9)	485 (22.8)	0.339
Moderately differentiated	2,962 (41.8)	2,092 (42.1)	870 (40.9)	
Poorly differentiated	734 (10.4)	505 (10.2)	229 (10.8)	
Undifferentiated	38 (0.5)	29 (0.6)	9 (0.4)	
Unknown	1,687 (23.8)	1,154 (23.2)	533 (25.1)	
AJCC stage				
I	4,631 (65.3)	3,216 (64.8)	1,415 (66.6)	0.159
II	2,459 (34.7)	1,748 (35.2)	711 (33.4)	
AFP				
Negative/normal	2,505 (35.3)	1,781 (35.9)	724 (34.1)	0.288
Positive/elevated	3,277 (46.2)	2,267 (45.7)	1,010 (47.5)	
Unknown	1,308 (18.4)	916 (18.5)	392 (18.4)	
Fibrosis score				
0–4	682 (9.6)	463 (9.3)	219 (10.3)	0.443
5–6	2,180 (30.7)	1,530 (30.8)	650 (30.6)	
Unknown	4,228 (59.6)	2,971 (59.9)	1,257 (59.1)	
Surgery				
Local tumor destruction	2,211 (31.2)	1,540 (31.0)	671 (31.6)	0.839
Segmental resection	1,801 (25.4)	1,259 (25.4)	542 (25.5)	
Lobectomy	638 (9.0)	456 (9.2)	182 (8.6)	
Hepatectomy/transplant	2,348 (33.1)	1,648 (33.2)	700 (32.9)	
Unknown	92 (1.3)	61 (1.2)	31 (1.5)	

(Cont'd...)

Table 1. (Continued)

Parameters	Overall (n = 7,090)	Training set (n = 4,964)	Validation set (n = 2,126)	p-value
Surgery–radiation sequence				
No radiation	6,752 (95.2)	4,727 (95.2)	2,025 (95.2)	0.363
Radiation before surgery	243 (3.4)	165 (3.3)	78 (3.7)	
Radiation after surgery	91 (1.3)	68 (1.4)	23 (1.1)	
Radiation before and after surgery	4 (0.1)	4 (0.1)	0 (0.0)	
Chemotherapy–surgery sequence				
No chemotherapy	5,286 (74.6)	3,687 (74.3)	1,599 (75.2)	0.853
Chemotherapy before surgery	1,322 (18.6)	938 (18.9)	384 (18.1)	
Chemotherapy after surgery	410 (5.8)	289 (5.8)	121 (5.7)	
Chemotherapy before and after surgery	72 (1.0)	50 (1.0)	22 (1.0)	
Diagnosis to treatment				
≤14 days	1,771 (25.0)	1,249 (25.2)	522 (24.6)	0.764
15–30 days	739 (10.4)	512 (10.3)	227 (10.7)	
31–60 days	1,749 (24.7)	1,206 (24.3)	543 (25.5)	
>60 days	2,741 (38.7)	1,932 (38.9)	809 (38.1)	
Unknown	90 (1.3)	65 (1.3)	25 (1.2)	

Note: Data are presented in n (%) unless specified.

Abbreviations: AFP: Alpha-fetoprotein; AJCC: American Joint Committee on Cancer; CSS: Cancer-specific survival; IQR: Interquartile range.

4. Discussion

The heterogeneity of early-stage HCC leads to significant variations in postoperative survival outcomes among patients. Curative-intent resection and liver transplantation remain standard therapeutic options for early-stage HCC patients; however, recurrence rates persist at elevated levels, with over 70% of cases manifesting within the first two postoperative years.¹³

While numerous staging systems (e.g., TNM, Cancer of the Liver Italian Program, BCLC) are widely used, most were developed for non-surgical patients and lack specific

validation in surgical populations.¹⁴ Traditional models overly rely on static anatomical features (e.g., tumor size, vascular invasion) while failing to integrate tumor biological heterogeneity (e.g., differentiation grade) and dynamic non-tumor factors (e.g., socioeconomic factors and therapeutic scheduling constraints), highlighting the critical need for precision prognostic tools. Our study presents an innovative temporal nomogram model utilizing the extensive SEER dataset ($n \geq 5,000$), transcending conventional methodological limitations. By incorporating variables such as diagnosis year, median household income, and treatment sequence, the model

Table 2. Univariate and multivariate Cox regression analysis in the training set

Parameters	Univariable		Multivariable	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Year of diagnosis				
2007–2011	Reference		Reference	
2012–2016	0.71 (0.63–0.80)	<0.001	0.67 (0.59–0.75)	< 0.001
2017–2021	0.58 (0.49–0.69)	<0.001	0.55 (0.46–0.65)	< 0.001
Age (years)				
<60	Reference			
≥60	1.37 (1.23–1.54)	<0.001	–	–
Gender				
Male	Reference			
Female	0.93 (0.82–1.06)	0.27	–	–
Marital status				
Married	Reference			
Single	1.42 (1.27–1.58)	<0.001	–	–
Unknown	0.94 (0.69–1.29)	0.705	–	–
Race				
White	Reference		Reference	
Black	1.17 (0.99–1.39)	0.06	1.02 (0.86–1.20)	0.84
Other	0.76 (0.66–0.88)	<0.001	0.64 (0.55–0.74)	<0.001
Unknown	0.86 (0.41–1.81)	0.69	1.03 (0.49–2.18)	0.934
Income level				
<USD 60,000	Reference		Reference	
USD 60,000–100,000	0.86 (0.74–1.00)	0.049	0.77 (0.66–0.90)	0.001
>USD 100,000	0.64 (0.52–0.79)	<0.001	0.65 (0.53–0.81)	<0.001
Tumor size				
≤2 cm	Reference		Reference	
>2 and ≤5 cm	1.97 (1.71–2.27)	<0.001	1.56 (1.35–1.80)	<0.001

(Cont'd...)

Table 2. (Continued)

Parameters	Univariable		Multivariable	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Grade				
Well differentiated	Reference			
Moderately differentiated	1.17 (1.01–1.35)	0.032	–	–
Poorly differentiated	1.61 (1.33–1.94)	<0.001	–	–
Undifferentiated	3.05 (1.84–5.04)	<0.001	–	–
Unknown	1.22 (1.04–1.43)	0.016	–	–
AJCC stage				
I	Reference		Reference	
II	1.21 (1.09–1.35)	<0.001	1.41 (1.26–1.58)	<0.001
AFP				
Negative/normal	Reference		Reference	
Positive/elevated	1.45 (1.28–1.65)	<0.001	1.25 (1.10–1.42)	0.001
Unknown	1.37 (1.17–1.60)	<0.001	1.33 (1.13–1.56)	0.001
Fibrosis score				
0–4	Reference		Reference	
5–6	0.93 (0.75–1.14)	0.465	1.15 (0.93–1.42)	0.204
Unknown	1.29 (1.07–1.57)	0.008	1.25 (1.03–1.52)	0.026
Surgery				
Local tumor destruction	Reference		Reference	
Segmental resection	0.55 (0.48–0.62)	<0.001	0.62 (0.54–0.70)	<0.001
Lobectomy	0.55 (0.45–0.66)	<0.001	0.57 (0.47–0.69)	<0.001
Hepatectomy/transplant	0.18 (0.15–0.21)	<0.001	0.17 (0.14–0.20)	<0.001
Unknown	0.45 (0.27–0.73)	0.001	0.38 (0.23–0.62)	<0.001
Surgery–radiation sequence				
No radiation	Reference			
Radiation before surgery	0.59 (0.38–0.91)	0.016	–	–
Radiation after surgery	2.31 (1.53–3.50)	<0.001	–	–
Radiation before and after surgery	5.29 (1.32–21.18)	0.019	–	–

(Cont'd...)

Table 2. (Continued)

Parameters	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Chemotherapy–surgery sequence				
No chemotherapy	Reference			
Chemotherapy before surgery	0.69 (0.59–0.80)	<0.001	1.03 (0.87–1.21)	0.765
Chemotherapy after surgery	2.08 (1.73–2.48)	<0.001	1.33 (1.10–1.60)	0.003
Chemotherapy before and after surgery	1.20 (0.76–1.89)	0.427	1.03 (0.65–1.63)	0.895
Diagnosis to treatment				
≤14 days	Reference			
15–30 days	1.18 (0.96–1.45)	0.109	–	–
31–60 days	1.35 (1.15–1.58)	<0.001	–	–
>60 days	1.26 (1.09–1.46)	0.002	–	–
Unknown	1.40 (0.92–2.13)	0.114	–	–

Abbreviations: AFP: Alpha-fetoprotein; AJCC: American Joint Committee on Cancer; CI: Confidence interval; HR: Hazard ratio.

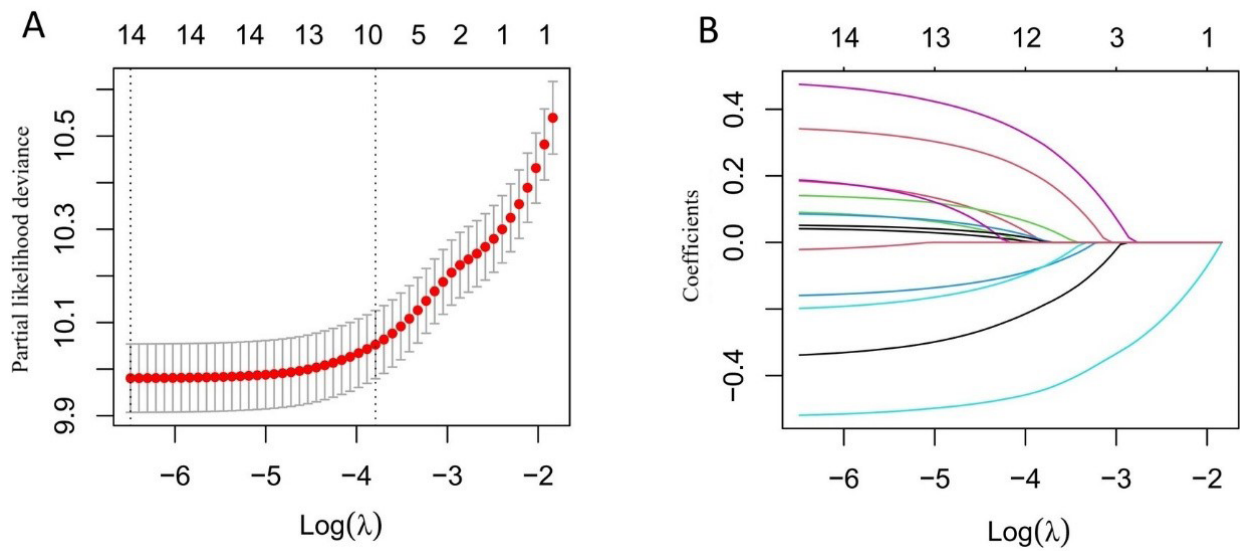


Figure 2. Least absolute shrinkage and selection operator regression. (A) Partial likelihood deviance. (B) Coefficients.

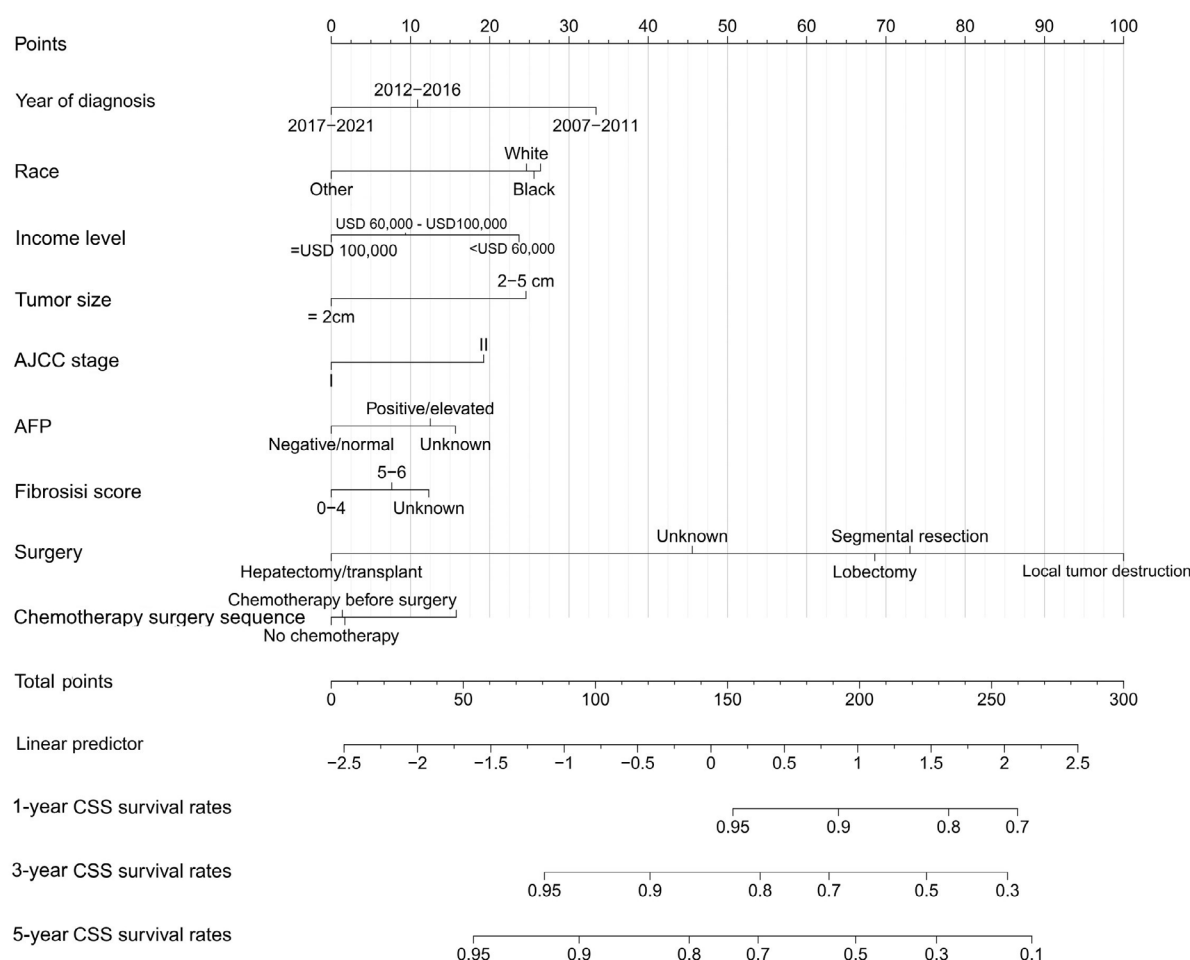


Figure 3. Nomogram for 1-, 3-, and 5-year CSS

Abbreviations: AFP: Alpha-fetoprotein; AJCC: American Joint Committee on Cancer; CSS: Cancer-specific survival.

revealed interactive effects between socioeconomic status and treatment strategies on prognosis. Statistically, the model demonstrated excellent discrimination and calibration. To further strengthen the clinical translatability and generalizability of our findings, we initiated an external validation phase through a multicenter international collaboration, involving prospective data collection from participating institutions in North America and Asia.

The results of the multidimensional analysis in this study align with other multicenter cohort studies and prospective clinical trials. Demographic characteristic analysis indicates that gender and marital status do not significantly affect the CSS of patients with early-stage HCC. The present findings align with He *et al.*'s¹⁵ observations on early-stage liver cancer prognosis. In contrast, Yan *et al.*¹⁶ reported contradictory findings: marital status (married) emerged as an independent

predictor of reduced postoperative mortality in elderly patients with AJCC stage III high-grade HCC, exhibiting enhanced survival benefits compared with non-married counterparts. This difference might be because in the high-risk postoperative population, the support from a spouse can enhance the management of complications and psychological adjustment. The analysis of racial differences further confirms the findings in previous research.^{17,18} There is no notable difference in prognosis between White and Black populations, whereas other populations have the best prognosis (HR = 0.64, 95% CI: 0.55–0.74). This survival gradient suggests that genetic susceptibility, differences in environmental exposures, and access to medical resources may jointly contribute to the racial differences in prognosis. The analysis of socioeconomic factors indicates that the mortality risk among individuals with an annual income > USD 100,000 is 35% lower than that of the lower-income group (HR = 0.65, 95% CI:

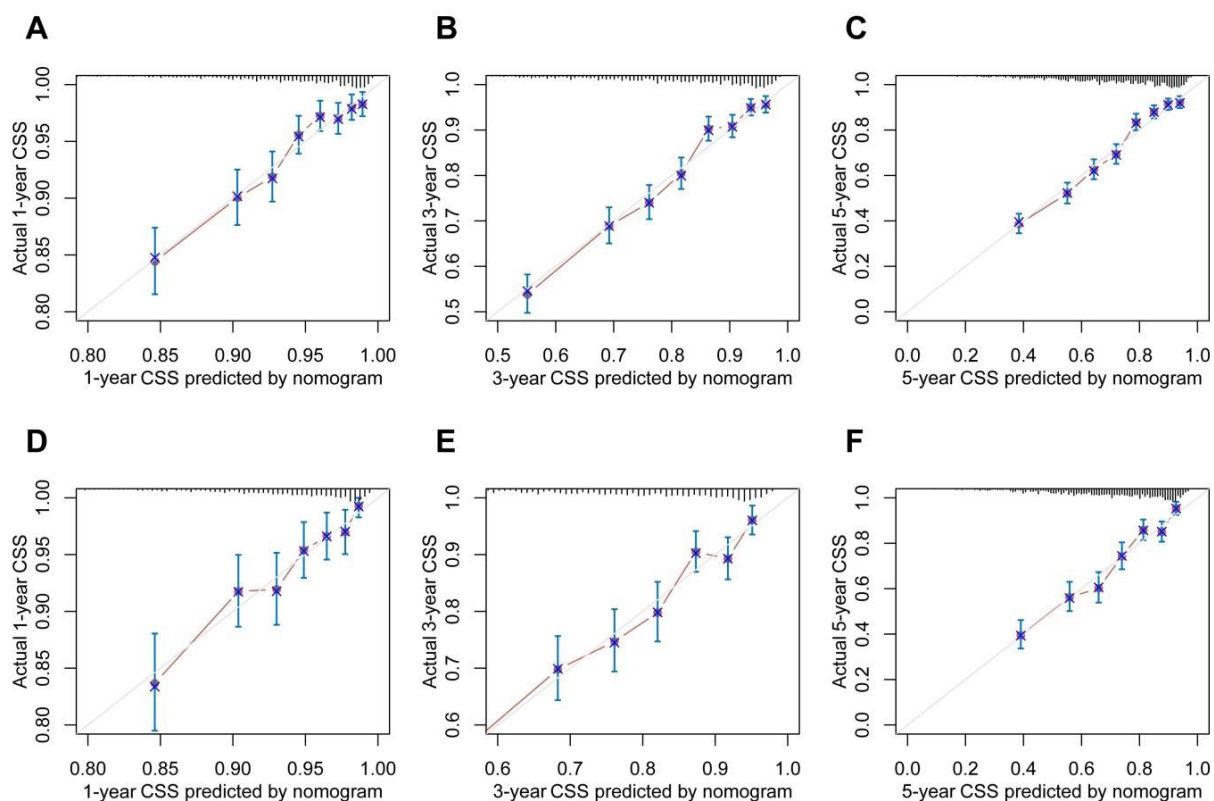


Figure 4. Calibration curves of the nomogram. (A–C) 1-, 3-, and 5-year cancer-specific survival (CSS) in the training cohort. (D–F) 1-, 3-, and 5-year CSS in the validation cohort.

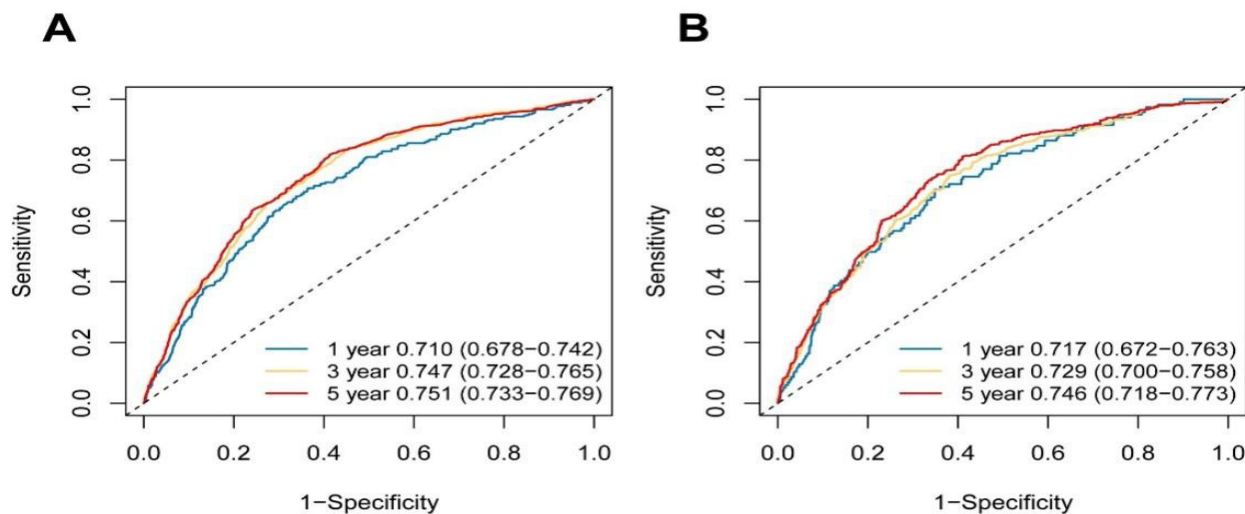


Figure 5. Receiver operating characteristic curves of the nomogram. (A) 1-, 3-, and 5-year cancer-specific survival (CSS) in the training cohort. (B) 1-, 3-, and 5-year CSS in the validation cohort.

0.53–0.81).¹⁹ This significant difference emphasizes the independent influence of economic status on the prognosis

of liver cancer. Possible mechanisms include easier access for high-income groups to high-quality medical resources, new targeted drugs, and early screening opportunities.

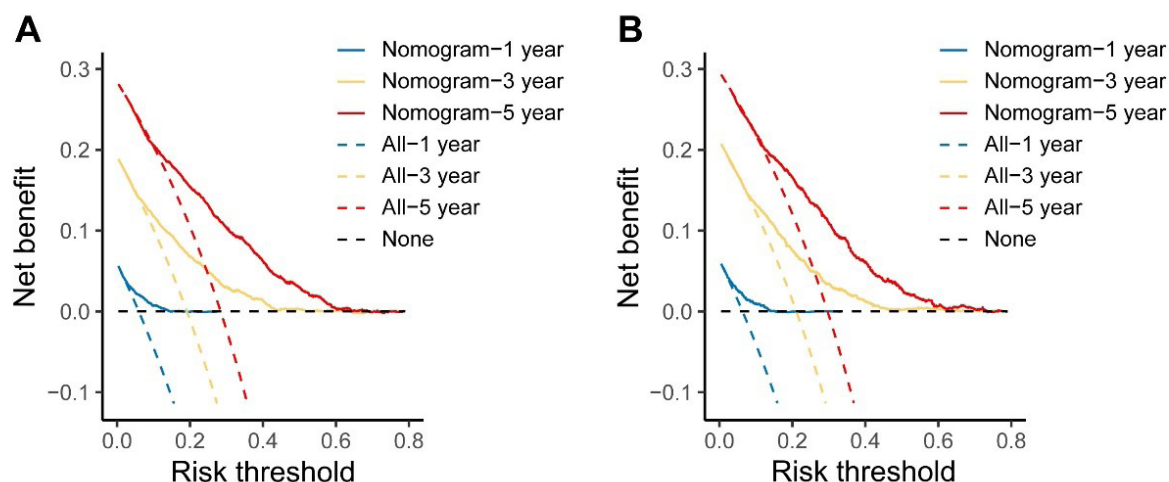


Figure 6. Decision curve analysis curves of the nomogram. (A) 1-, 3-, and 5-year cancer-specific survival (CSS) in the training cohort. (B) 1-, 3-, and 5-year CSS in the validation cohort.

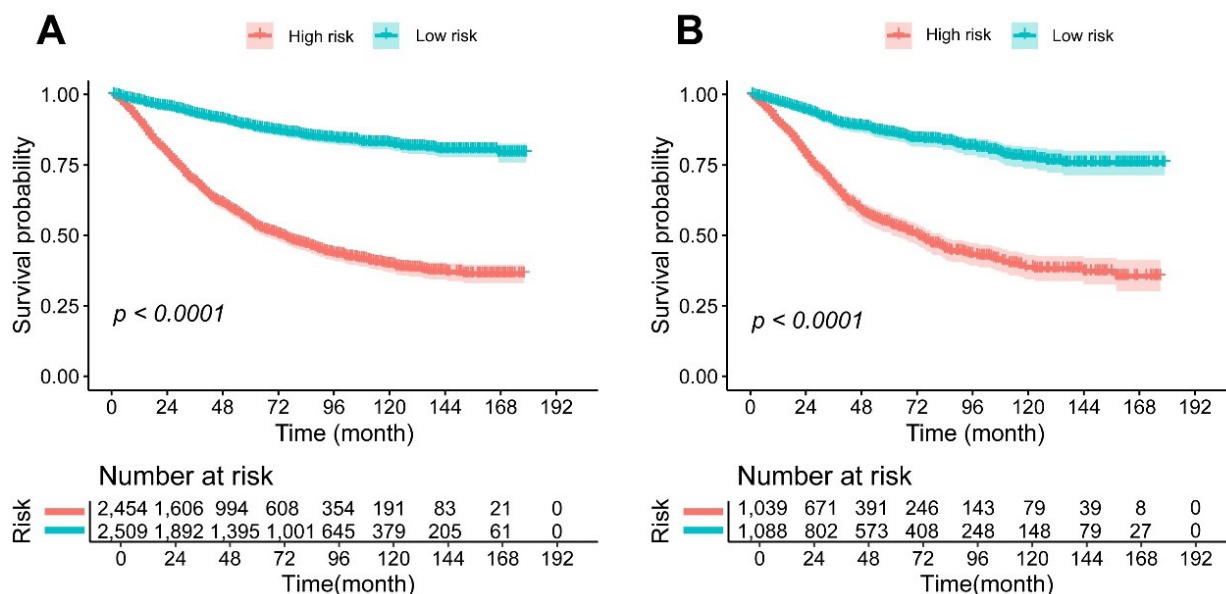


Figure 7. Kaplan-Meier curves for predicting cancer-specific survival of patients in low- and high-risk groups. (A) Training cohort. (B) Validation cohort.

Analysis of treatment modalities demonstrated that hepatectomy/liver transplantation, as the most significant protective treatment, improved patient survival by 83% (HR = 0.17, 95% CI: 0.14–0.20). Hepatic lobectomy also significantly reduced disease risk (HR = 0.57, 95% CI: 0.47–0.69). In contrast, local tumor ablation showed inferior prognostic outcomes compared to open surgery, suggesting higher risks of local recurrence or residual tumor burden, which warrants special attention to long-term quality of life—a finding highly consistent with

He *et al.*'s¹⁵ CSS prognostic study in elderly early-stage HCC patients. A retrospective study by Kim *et al.*²⁰ further supported this perspective, revealing significant differences in 5-year and 10-year recurrence-free survival between hepatectomy and ablation groups (60.6% vs. 37.5%, 39.4% vs. 25.1%, $p < 0.001$). However, several studies have reported no significant advantage of surgical resection for overall or disease-free survival in patients with early HCC.^{21,22} This underscores the necessity for personalized multidimensional evaluations. An analysis

of meta-evidence referenced in European Association for the Study of the Liver guidelines²³ demonstrated superior efficacy of laparoscopic surgery, showing a 42% reduction in local recurrence risk (relative risk = 0.58, 95% CI: 0.46–0.73) compared to ablation therapy—a conclusion strongly aligned with our findings.

Prognostic value analysis of chemotherapy timing revealed that postoperative chemotherapy (HR = 1.3279) significantly increased mortality risk compared to preoperative chemotherapy (HR = 1.0254), consistent with our previous research.²⁴ Potential mechanisms may involve stage-specific tumor biology and differential treatment tolerability: postoperative chemotherapy may exacerbate metabolic burdens due to hepatic dysfunction and immunosuppression, amplifying treatment-related toxicities, whereas preoperative chemotherapy can effectively reduce tumor volume and intraoperative metastasis risk by modulating immunosuppressive cell populations in the tumor microenvironment and inhibiting angiogenesis, thereby optimizing conditions for curative surgery. Notably, the timing of postoperative chemotherapy initiation significantly impacts outcomes. A randomized controlled trial conducted by Huang *et al.*²⁵ demonstrated that delays exceeding six weeks were associated with a higher risk of recurrence (HR = 1.52, 95% CI: 1.18–1.96). Similar observations were reported in another study on breast cancer by Chavez *et al.*,²⁶ where adjuvant chemotherapy delays > 12 weeks increased recurrence rates. These findings highlight the dynamic tumor microenvironment during the early postoperative window, underscoring the critical importance of timely intervention to control disease progression.

Pathological feature analysis revealed that AJCC stage II patients had significantly worse CSS than stage I patients (HR = 1.41, 95% CI: 1.26–1.58). This discrepancy may be attributed to the higher prevalence of microvascular invasion and satellite nodules in AJCC stage II tumors, reflecting more aggressive biological behavior.²⁷ Notably, within our model, the weight coefficient of AJCC staging was lower than local tumor destruction parameters, indicating the model prioritizes tumor invasiveness characteristics over pure anatomical staging. The prognostic value of hepatic fibrosis scoring showed that patients with Ishak 5–6 (bridging fibrosis/cirrhosis) experienced reduced CSS compared to those with Ishak 0–4. Persistent inflammation and aberrant extracellular matrix deposition can activate oncogenic signaling pathways, including transforming growth factor- β /Smad and Wnt/ β -catenin,²⁸ promoting epithelial–mesenchymal transition and immune evasion in HCC cells. Clinical analysis of AFP levels demonstrated that AFP-positive patients had worse outcomes than

their AFP-negative counterparts (HR = 1.25, 95% CI: 1.10–1.42). A multicenter retrospective cohort analysis by Chan *et al.*²⁹ confirmed that preoperative AFP $\geq$ 400 ng/mL independently predicts early postoperative recurrence (HR = 2.31). These findings underscore the need to establish biomarker-based stratified intervention strategies—in which high-risk patients with AJCC stage II disease, concomitant perivascular microinvasion with satellite lesions, Ishak 5–6 fibrosis, or AFP $\geq$ 400 ng/mL receive intensified systemic therapy at early stages.

Model performance validation demonstrated that the nomogram achieved C-index values of 0.724 (95% CI: 0.710–0.738) in the training cohort, whereas 0.713 (95% CI: 0.685–0.741) was observed in the validation cohort, significantly outperforming Yan *et al.*'s³⁰ AJCC staging model based on SEER data (training C-index = 0.552 vs. validation C-index = 0.567). Calibration curve analysis demonstrated superior concordance between predicted probabilities and observed events across datasets, validating clinical relevance. Dynamic survival analysis further supported practical applicability through time-dependent risk stratification, showing congruence between nomogram-predicted and observed 1-, 3-, and 5-year CSS rates in both cohorts. Clinical decision curve analysis demonstrated measurable net benefits (>0) across all 1-, 3-, and 5-year prognostic timeframes. ROC AUCs exceeded the 0.7 threshold in both training and validation populations. A dichotomous cutoff point (150 points) derived from nomogram total scores established a hazard stratification system validated using Kaplan–Meier analysis: the training cohort demonstrated cumulative 5-year CSS rates of 55.0% (95% CI: 48.1–61.9) in high-risk patients versus 88.7% (95% CI: 85.3–91.8) in low-risk patients ($p < 0.001$); consistent findings were observed in the validation cohort (54.4% vs. 86.3%, $p < 0.001$). This robust stratification efficacy confirms the nomogram's ability to identify high-risk populations and inform personalized follow-up strategies.

This study has several limitations. First, the SEER database lacks critical pathological parameters such as Child–Pugh liver function grading and microvascular invasion, potentially introducing bias in assessing cirrhosis-related prognostic risks. Furthermore, the absence of detailed lifestyle data, particularly information on alcohol consumption, smoking history, and other behavioral factors, represents a significant constraint, as these variables are known modifiers of HCC progression and outcomes. We acknowledge this limitation and plan to address it in future work by prospectively collecting and integrating these lifestyle variables to enhance the model's comprehensiveness.³¹ Second, the retrospective

design cannot fully eliminate residual confounding factors, particularly due to incomplete documentation of postoperative adjuvant therapy details (e.g., drug type, dosing regimen, treatment duration), which may affect accuracy in treatment efficacy evaluation. Additionally, significant limitations due to racial specificity exist: with White and Black comprising 78% of the SEER cohort, the model's predictive performance may decline substantially in Asian populations. To address these gaps, future research should focus on constructing a multimodal biomarker panel integrating radiomics features, inflammatory-immunological indices, and liver function parameters, conducting prospective, multicenter clinical trials, including the planned external validation, to validate the model's generalizability across diverse populations, including Asian cohorts.

5. Conclusion

This study overcomes the limitations of traditional anatomical staging by promoting personalized post-surgical management approaches that integrate biomarkers, socioeconomic factors, and treatment timing. Future research should aim to include lifestyle factors such as alcohol use, assess the model's performance across different populations, and conduct external validation studies at multiple medical centers. The nomogram offers a scientific basis for assessing prognosis, planning treatment, and managing follow-up care in patients with early-stage HCC.

Acknowledgments

The authors would like to express their gratitude to the National Cancer Institute for providing open access to the Surveillance, Epidemiology, and End Results (SEER) database.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

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Writing–review & editing: Yadi Liu

Ethics approval and consent to participate

This study utilized data from open-access repositories, which are exempt from ethical approval under institutional guidelines. Therefore, written informed consent was not required for the study, and all data were publicly available.

Consent for publication

Not applicable.

Availability of data

All datasets analyzed in this study are publicly available (Incidence-SEER Research Data, 17 Registries, Nov 2023 Sub (2000–2021) (<https://seer.cancer.gov/data-software/documentation/seerstat/nov2023/>)).

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