Original Article

Clinical features and prognostic factors of patients with inoperable hepatocellular carcinoma treated with chemotherapy: a population-based study

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Background: In inoperable hepatocellular carcinoma (HCC), chemotherapy is a common treatment strategy. However, there is a lack of reliable methods to predict the prognosis of patients with inoperable HCC after chemotherapy. Therefore, the aim of this study was to identify the clinical characteristics of patients with inoperable HCC and to establish and validate nomogram models for predicting the survival outcomes in this patient group following chemotherapy.

Methods: The data of patients diagnosed with HCC from the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively collected. Logistic regression analyses were used to identify potential factors for inoperability in patients with HCC. Kaplan-Meier analyses were applied to evaluate the impact of chemotherapy on prognosis. Additionally, Cox regression analyses were performed to identify the potential risk factors associated with overall survival (OS) and cancer-specific survival (CSS) in patients with inoperable HCC treated with chemotherapy. Finally, we constructed prognostic nomograms for predicting the 1- and 3-year survival probabilities.

Results: A total of 3,519 operable patients with HCC and 4,656 patients with inoperable HCC were ultimately included in this study. Logistic regression analyses revealed a significant association between patient age, gender, race, tumor, node, metastasis (TNM) stage, tumor size, pretreatment alpha fetoprotein (AFP) levels, and marital status with inoperability. Moreover, Kaplan-Meier analyses revealed a significant improvement in both OS and CSS with the administration of chemotherapy. Moreover, 1,456 patients with inoperable HCC were enrolled in the training group and 631 patients with inoperable HCC were enrolled in the validation group to develop and validate the prognostic models. Cox regression models indicated that TNM stage, tumor size, and pretreatment AFP were independent risk factors for predicting OS and CSS in patients with inoperable HCC receiving chemotherapy. These factors were subsequently integrated into the predictive nomograms.

Conclusions: We preliminarily developed survival models with strong predictive capabilities for estimating survival probabilities in patients with HCC following chemotherapy. These models hold potential for clinical application and warrant further exploration through additional studies.

Keywords: Hepatocellular carcinoma (HCC); inoperable; chemotherapy; Surveillance, Epidemiology, and End Results (SEER); nomogram

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Introduction

Liver cancer is a prevalent malignancy of the digestive system. As of 2020, it was the seventh most common cancer globally, with 905,677 newly diagnosed cases and 830,180 attributable deaths (1). Hepatocellular carcinoma (HCC) is the most prevalent histological type of liver cancer, accounting for approximately 75–85% of liver cancers (2). Various methods, including surgery, radiation therapy, and interventional treatments, can effectively address early-stage liver cancer. These approaches exhibit promising 5-year survival rates of up to 75% (3). Notably, between 14.0% and 36.7% of patients with liver cancer have metastatic disease at the time of initial diagnosis (4,5). In advanced cases, primary treatment options encompass chemotherapy, targeted therapy, radiation therapy, immunotherapy, and even palliative surgery. The prognosis for advanced HCC is particularly unfavorable, with a 3-year survival rate for palliative treatment typically ranging from 10% to 40% (6). This highlights the challenges and difficulties in treating advanced-stage liver cancer, and the outcomes can vary based on factors such as the extent of the disease, health condition, and the effectiveness of the chosen treatment modalities.

Previous studies have indicated that fewer than 20% of all patients with liver cancer are eligible for surgical intervention (7,8). Traditionally, sorafenib has been the primary treatment strategy for advanced and unresectable HCC (9). Recently, an array of alternative treatment options has emerged, including local ablation techniques such as radiofrequency ablation, percutaneous ethanol injection, cryoablation, radiotherapy/stereotactic body radiation therapy (SBRT), and microwave ablation (10-12). Moreover, strategies for the transformation to resection of unresectable HCC have also aroused considerable interest (13). In addition to this, interventional therapies have become significant in the management of intermediate and advanced liver cancer, with transarterial chemoembolization (TACE) emerging as a key approach. TACE has notably improved the prognosis of patients with inoperable late-stage HCC (14). Cytoreductive surgery remains a viable option, especially for carefully selected patients characterized by low surgical risk and robust liver function (15). In recent years, several combination approaches have been explored. Many combination approaches have been explored regarding TACE, including the pairing of TACE with radiation therapy (16,17), TACE plus Antiangiogenic Agents (sorafenib and so on), and TACE plus immune checkpoint inhibitors (ICIs) (18). In addition, immunotherapy combinations are playing an increasingly important role. ICIs with other ICIs or other drug classes including camrelizumab with rivoceranib (19), and atezolizumab with bevacizumab (20,21), had better outcomes than monotherapy such as ICIs alone or chemotherapy alone (22). Moreover, one study (23) suggests that albumin levels may be a prognostic biomarker for patients with advanced cancer receiving ICIs, with patients with lower albumin levels having a significantly higher risk of death than those with higher albumin levels.

These innovative approaches hold promise for improving treatment outcomes in cases of inoperable HCC.

Highlight box

Key findings

- We developed and validated nomogram models for predicting the overall survival (OS) and cancer-specific survival (CSS) of patients with inoperable hepatocellular carcinoma (HCC) following chemotherapy, which could accurately predict patient survival.

What is known and what is new?

- Surgical treatment is a potentially curative therapeutic strategy for patients with HCC. However, fewer than 20% of patients with HCC are eligible for potentially curative surgical resection or liver transplantation therapy due to a variety of factors. Chemotherapy is critical to improving the prognosis of those with inoperable HCC.
- In our study, Kaplan-Meier analyses revealed a significant improvement in both OS and CSS with the administration of chemotherapy. Additionally, Cox regression models revealed that tumor, node, metastasis (TNM) stage, tumor size, and pretreatment alpha fetoprotein were independent risk factors for predicting OS and CSS in patients with inoperable HCC receiving chemotherapy.

What is the implication, and what should change now?

- We identified a noteworthy association of several factors with HCC inoperability and developed survival models with a strong predictive ability to estimate survival probability in patients with HCC following chemotherapy. These models can potentially be applied in clinic and should be further explored through additional studies.

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Chemotherapy is critical to the nonsurgical management of liver cancer. In China, the FOLFOX4, a chemotherapy regimen that includes three medications: 5-fluorouracil (5-FU), leucovorin (folinic acid) and oxaliplatin, has received approval for use as a first-line treatment in cases of locally advanced and metastatic liver cancer deemed unsuitable for surgical resection or local treatment (24,25). Shim *et al.* (26) investigated the long-term follow-up outcomes of 178 patients diagnosed with HCC who had undergone combined treatment with capecitabine and cisplatin. The findings revealed an overall response rate of 19.7%, with successful control of tumor growth observed in 45.0% of the patients. They further discovered that the combination therapy of capecitabine and cisplatin demonstrated efficacy in patients with HCC with single nodules or no residual tumors in the liver. In addition, Lee *et al.* (27) reported that the combination chemotherapy of capecitabine and cisplatin had a mild antitumor effect in patients with HCC who had undergone first-line treatment for metastasis, with the associated adverse reactions being tolerable. Furthermore, a substantial phase III clinical study conducted by Qin *et al.* (24) convincingly demonstrated the survival benefits associated with systemic chemotherapy for patients with advanced liver cancer. Despite these findings, the constraints of traditional systemic chemotherapy have prompted the emergence of novel approaches for treating patients with inoperable HCC, with hepatic arterial infusion chemotherapy (HAIC) being prominent among these options. Related research (28,29) also suggest that HAIC holds promise as a treatment strategy for managing advanced HCC.

However, few large-scale studies focusing on the survival outcomes of patients with unresectable HCC following chemotherapy have been conducted. Therefore, this study aimed to identify the clinical characteristics of patients with inoperable HCC by analyzing the Surveillance, Epidemiology, and End Results (SEER) database and to develop and validate predictive models for overall survival (OS) and cancer-specific survival (CSS) in patients with inoperable HCC undergoing chemotherapy. We present this article in accordance with the TRIPOD reporting checklist (30) (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-298/rc).

Methods

Study design and data source

SEER database, the world's largest cancer database, covers approximately one-third of the population of the United States. The database offers comprehensive records of basic patient information, treatment strategies, and long-term follow-up data for patients with cancer. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

This study retrospectively collected data from the SEER database on patients diagnosed with HCC between 2010 and 2015 with a positive histology. The inclusion criteria were as follows: (I) diagnosis of HCC with a positive history; (II) the year of diagnosis between 2010 and 2015; and (III) complete survival data. Meanwhile, the exclusion criteria were as follows: (I) age <18 or >85 years; (II) presence of two or more malignancies; and (III) unknown or missing data in crucial variables such as tumor, node, metastasis (TNM) stage, pretreatment alpha fetoprotein (AFP) levels, race, marital status, cause of death, tumor size, and administration of chemotherapy.

The selection flowchart of this study is shown in *Figure 1*. Prior to extracting patient information, we obtained permission from the SEER program by signing the data-use agreement online.

Clinical characteristics

We extracted comprehensive data on the basic characteristics, pathological results, and long-term survival outcomes of all patients. Variables included age, sex, year of diagnosis, race, TNM stage, the administration of chemotherapy/surgery/radiotherapy, pretreatment AFP, tumor size, cause of death, survival months, marital status, vital status, and other relevant factors. Age was divided into groups of [18–60] and (60–85] years. Furthermore, tumor size was grouped into groups of (0–5], (5–10], and >10 cm. Lastly, marital status was classified as married and other (including separated, divorced, widowed, single, unmarried, or domestic partner).

Risk factors for inoperability in patients with HCC

According to the recommendation (code 'Reason no cancer directed surgery' in SEER) and administration of surgery, patients with HCC were divided into operable and inoperable groups. We compared the baseline variables, pathological outcomes, and treatment strategies of patients between the operable and inoperable groups. Subsequently, uni- and multivariate logistic regression analyses were used to identify the risk factors for inoperable HCC.

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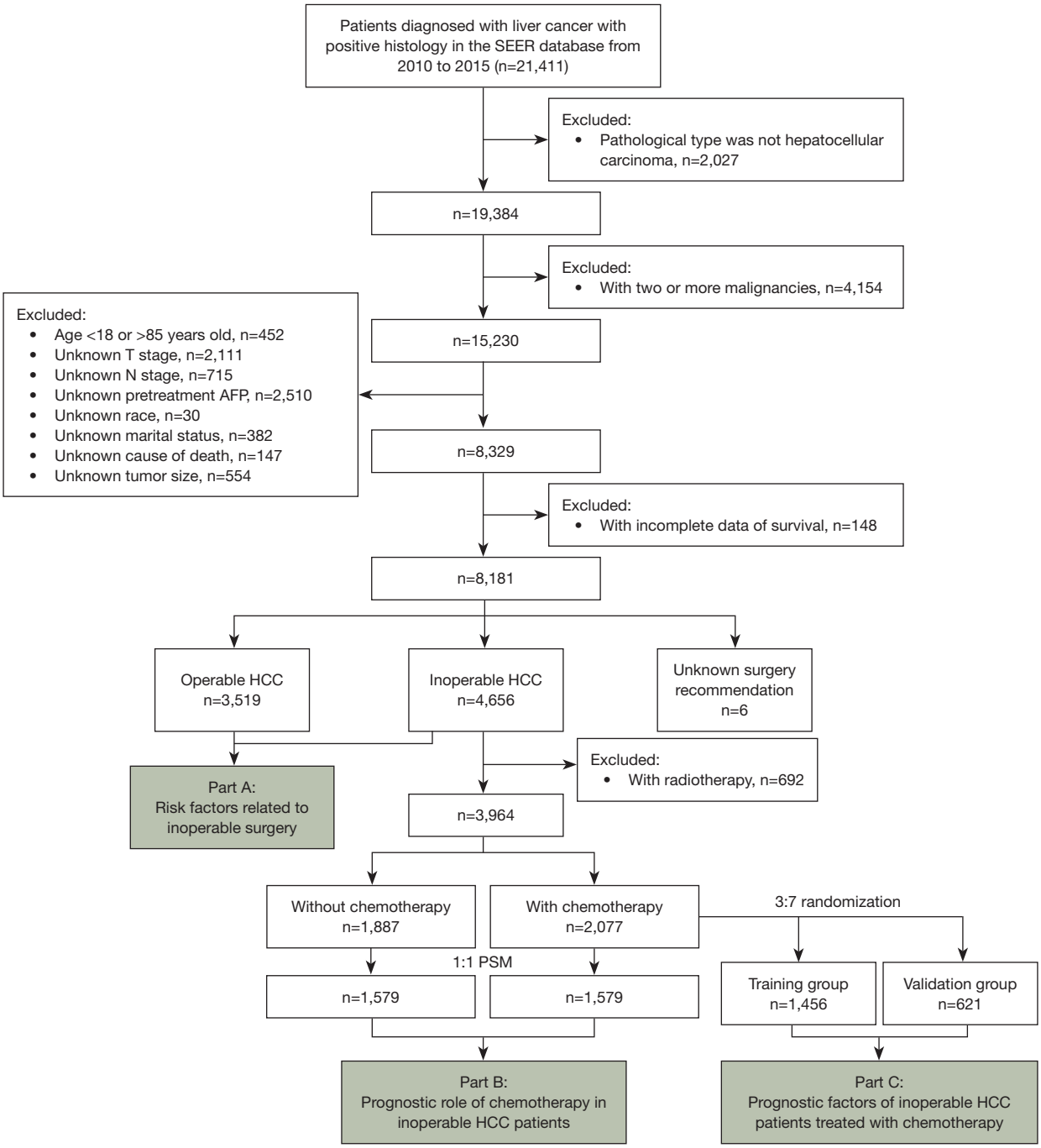

Figure 1 Flow diagram of the selection process. SEER, Surveillance, Epidemiology, and End Results; AFP, alpha fetoprotein; PSM, propensity score matching; HCC, hepatocellular carcinoma.

The prognostic role of chemotherapy in patients with inoperable HCC

All patients received adjuvant chemotherapy instead of neoadjuvant chemotherapy. Additionally, patients with the disease relapsed after surgery and chemotherapy were not included in this research. According to the administration of chemotherapy, patients with inoperable HCC were then categorized into two groups: with chemotherapy and without

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chemotherapy. We compared the baseline characteristics of the two groups and performed propensity score matching (PSM) analysis at a ratio of 1:1 using the nearest-neighbor matching method to balance the baseline data of the two groups of patients for further survival analyses. Subsequently, Kaplan-Meier (KM) analyses were constructed to identify the prognostic role of chemotherapy in patients with inoperable HCC and to create different subgroups.

Construction and validation of prognostic nomograms

Patients with inoperable HCC were randomly divided into a training group and a validation group at a ratio of 7:3 using a random count table method. Uni- and multivariate Cox regression analyses were used to identify the potential risk factors for OS and CSS in patients with inoperable HCC treated with chemotherapy. Subsequently, survival nomograms based on Cox regression analyses were constructed to predict the 1- and 3-year OS and CSS probability of patients with inoperable HCC treated with chemotherapy. The concordance index (C-index) and receiver operating characteristic (ROC) curves were employed to assess the discrimination of the nomograms in both the training and validation groups. Finally, the consistency between the expected and observed survivals was determined via calibration curves.

Statistical analysis

All statistical analyses were conducted using SPSS 23.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.1 (The R Foundation for Statistical Computing). Categorical variables are presented as numbers and percentages and were compared with the chi-square test. Continuous variables that did not adhere to a normal distribution are reported as the median with interquartile range (IQR) and were compared using the Mann-Whitney test. PSM analysis was used to balance the baseline differences between the different groups. Moreover, KM analysis was used to determine the survival benefits of chemotherapy in patients with inoperable HCC, while Cox and logistic regression analyses were used to identify the risk factors influencing prognosis or the likelihood of inoperability.

Results

Risk factors for inoperability in patients with HCC

A total of 3,519 patients with operable HCC and 4,656 patients with inoperable HCC were ultimately included in this study. As shown in *Table 1*, compared to the operable group, the inoperable group had an older age at diagnosis, a higher proportion of male patients and White patients, a later tumor stage, a larger tumor size, a higher proportion of positive pretreatment AFP, a lower proportion of married patients, and a higher proportion of patients receiving chemotherapy and radiation therapy.

Uni- and multivariate logistic regression analyses indicated several factors to be independently associated with unresectability of HCC, including higher age at diagnosis [odds ratio (OR) =1.366, 95% confidence interval (CI): 1.232–1.514; P<0.001], advanced T stage (T3 *vs.* T1: OR =3.040, 95% CI: 2.618–3.530, P<0.001; T4 *vs.* T1: OR =1.602, 95% CI: 1.204–2.131, P=0.001), advanced N stage (OR =3.858; 95% CI: 2.882–5.165; P<0.001), advanced M stage (OR =6.190; 95% CI: 4.898–7.824; P<0.001), larger tumor size {(5–10] *vs.* (0–5] cm: OR =1.925, 95% CI: 1.699–2.195, P<0.001; >10 *vs.* (0–5] cm: OR =2.149, 95% CI: 1.826–2.530, P<0.001}, positive pretreatment AFP levels (OR =1.434, 95% CI: 1.287–1.597, P<0.001), and never-married status (OR =1.414; 95% CI: 1.242–1.611; P<0.001) or single/divorced/widowed (SDW) status (OR =1.444; 95% CI: 1.273–1.683; P<0.001). On the other hand, female gender (OR =0.800; 95% CI: 0.709–0.90; P<0.001) and American Indian/Alaska Native and Asian/Pacific Islander race (OR =0.584; 95% CI: 0.513–0.665; P<0.001) were identified as protective factors against HCC unresectability (*Table 2*).

The prognostic role of chemotherapy in patients with inoperable HCC

In patients with inoperable HCC, the chemotherapy group, when compared with the no-chemotherapy group, had a lower M stage (M0: 81.70% *vs.* 77.16%; P<0.001) and a higher proportion of married patients (55.71% *vs.* 43.83%; P<0.001). Moreover, significant differences were observed in the distribution of some baseline characteristics between the two groups, including race, summary stage, T stage, American Joint Committee on Cancer (AJCC) stage, and tumor size (*Table 3*).

To assess the impact of chemotherapy on the prognosis of patients with inoperable HCC, PSM analysis was performed to mitigate potential baseline differences that could affect prognosis. As presented in Table S1, no statistically significant differences were observed in the baseline characteristics after PSM, confirming their comparability.

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Table 1 Basic characteristics of patients with operable and inoperable HCC

Variable	Operable (N=3,519)	Inoperable (N=4,656)	P value
Age (years)			<0.001
[18–60]	1,602 (45.52)	1,862 (39.99)	
(60–85]	1,917 (54.48)	2,794 (60.01)	
Sex			<0.001
Male	2,648 (75.25)	3,727 (80.05)	
Female	871 (24.75)	929 (19.95)	
Year of diagnosis			0.35
2010	569 (16.17)	687 (14.76)	
2011	558 (15.86)	736 (15.81)	
2012	548 (15.57)	732 (15.72)	
2013	570 (16.20)	795 (17.07)	
2014	597 (16.97)	843 (18.11)	
2015	677 (19.24)	863 (18.54)	
Race			<0.001
White	2,283 (64.88)	3,250 (69.80)	
Black	404 (11.48)	673 (14.45)	
Other	832 (23.64)	733 (15.74)	
Summary stage			<0.001
Localized	2,734 (77.69)	1,896 (40.72)	
Regional	681 (19.35)	1,673 (35.93)	
Distant	104 (2.96)	1,087 (23.35)	
T stage			<0.001
T1	1,999 (56.81)	1,634 (35.09)	
T2	1,047 (29.75)	894 (19.20)	
T3	387 (11.00)	1,868 (40.12)	
T4	86 (2.44)	260 (5.58)	
N stage			<0.001
N0	3,461 (98.35)	3,999 (85.89)	
N1	58 (1.65)	657 (14.11)	
M stage			<0.001
M0	3,431 (97.50)	3,617 (77.68)	
M1	88 (2.50)	1,039 (22.32)	
AJCC group			<0.001
I	1,966 (55.87)	1,328 (28.52)	
II	1,019 (28.96)	689 (14.80)	
III	407 (11.57)	1,292 (27.75)	
IV	127 (3.61)	1,347 (28.93)	
Tumor size (cm)			<0.001
(0–5]	2,482 (70.53)	1,796 (38.57)	
(5–10]	691 (19.64)	1,787 (38.38)	
>10	346 (9.83)	1,073 (23.05)	
Pretreatment AFP			<0.001
Negative	1,322 (37.57)	1,151 (24.72)	
Positive	2,197 (62.43)	3,505 (75.28)	
Marital status			<0.001
Married	2,131 (60.56)	2,400 (51.55)	
Never married	675 (19.18)	1,129 (24.25)	
SDW	713 (20.26)	1,127 (24.21)	
Chemotherapy			<0.001
No	2,380 (67.63)	2,189 (47.01)	
Yes	1,139 (32.37)	2,467 (52.99)	
Radiotherapy			<0.001
No	3,366 (95.65)	3,964 (85.14)	
Yes	153 (4.35)	692 (14.86)	

Data are shown as n (%). HCC, hepatocellular carcinoma; AJCC, American Joint Committee on Cancer; AFP, alpha fetoprotein; SDW, separated, divorced, widowed.

As shown in *Figure 2*, KM analyses revealed a significant improvement in OS and CSS among patients with inoperable HCC who received chemotherapy both before and after PSM. Additionally, survival benefits from chemotherapy for patients with inoperable HCC were observed across various subgroups (*Figure 3*).

Construction and validation of prognostic nomograms

For nomogram construction, 1,456 patients were enrolled

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Table 2 Uni- and multivariate logistic regression analyses for identifying risk factors of inoperability in patients with HCC

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years		<0.001		<0.001
[18–60]	Reference		Reference	
(60–85]	1.254 (1.148–1.370)	<0.001	1.366 (1.232–1.514)	<0.001
Sex		<0.001		<0.001
Male	Reference		Reference	
Female	0.758 (0.682–0.842)	<0.001	0.800 (0.709–0.902)	<0.001
Race		<0.001		<0.001
White	Reference		Reference	
Black	1.170 (1.023–1.339)	0.02	0.998 (0.856–1.163)	0.98
Other	0.619 (0.553–0.693)	<0.001	0.584 (0.513–0.665)	<0.001
T stage		<0.001		<0.001
T1	Reference		Reference	
T2	1.045 (0.935–1.167)	0.44	1.097 (0.972–1.239)	0.14
T3	5.905 (5.198–6.708)	<0.001	3.040 (2.618–3.530)	<0.001
T4	3.699 (2.874–4.761)	<0.001	1.602 (1.204–2.131)	0.001
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	9.804 (7.467–12.872)	<0.001	3.858 (2.882–5.165)	<0.001
M stage		<0.001		<0.001
M0	Reference		Reference	
M1	11.200 (8.965–13.991)	<0.001	6.190 (4.898–7.824)	<0.001
Tumor size (cm)		<0.001		<0.001
(0–5]	Reference		Reference	
(5–10]	3.574 (3.212–3.977)	<0.001	1.925 (1.699–2.195)	<0.001
>10	4.286 (3.742–4.908)	<0.001	2.149 (1.826–2.530)	<0.001
Pretreatment AFP		<0.001		<0.001
Negative	Reference		Reference	
Positive	1.832 (1.666–2.016)	<0.001	1.434 (1.287–1.597)	<0.001
Marital status		<0.001		<0.001
Married	Reference		Reference	
Never married	1.485 (1.328–1.661)	<0.001	1.414 (1.242–1.611)	<0.001
SDW	1.403 (1.257–1.567)	<0.001	1.444 (1.273–1.683)	<0.001

HCC, hepatocellular carcinoma; AFP, alpha fetoprotein; SDW, separated, divorced, widowed; OR, odds ratio; CI, confidence interval.

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Table 3 Comparisons between patients with inoperable HCC with and without chemotherapy treatment before PSM

Variable	With chemotherapy (N=2,077)	Without chemotherapy (N=1,887)	P value
Age, years			0.35
[18–60]	868 (41.79)	761 (40.33)	
(60–85]	1,209 (58.21)	1,126 (59.67)	
Sex			0.94
Male	1,649 (79.39)	1,500 (79.49)	
Female	428 (20.61)	387 (20.51)	
Race			0.04
White	1,436 (69.14)	1,304 (69.10)	
Black	287 (13.82)	304 (16.11)	
Other	354 (17.04)	279 (14.79)	
Summary stage			0.002
Localized	915 (44.05)	771 (40.86)	
Regional	760 (36.59)	663 (35.14)	
Distant	402 (19.35)	453 (24.01)	
T stage			0.001
T1	711 (34.23)	705 (37.36)	
T2	443 (21.33)	323 (17.12)	
T3	821 (39.53)	736 (39.00)	
T4	102 (4.91)	123 (6.52)	
N stage			0.78
N0	1,783 (85.84)	1,614 (85.53)	
N1	294 (14.16)	273 (14.47)	
M stage			<0.001
M0	1,697 (81.70)	1,456 (77.16)	
M1	380 (18.30)	431 (22.84)	
AJCC group			<0.001
I	604 (29.08)	575 (30.47)	
II	364 (17.53)	235 (12.45)	
III	581 (27.97)	516 (27.34)	
IV	528 (25.42)	561 (29.73)	
Tumor size (cm)			<0.001
(0–5]	836 (40.25)	697 (36.94)	
(5–10]	823 (39.62)	692 (36.67)	
>10	418 (20.13)	498 (26.39)	

Table 3 *(continued)*

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Table 3 *(continued)*

Variable	With chemotherapy (N=2,077)	Without chemotherapy (N=1,887)	P value
Pretreatment AFP			0.66
Negative	506 (24.36)	471 (24.96)	
Positive	1,571 (75.64)	1,416 (75.04)	
Marital status			<0.001
Married	1,157 (55.71)	827 (43.83)	
Never married	451 (21.71)	557 (29.52)	
SDW	469 (22.58)	503 (26.66)	

Data are shown as n (%). HCC, hepatocellular carcinoma; PSM, propensity score matching; AJCC, American Joint Committee on Cancer; AFP, alpha fetoprotein; SDW, separated, divorced, widowed.

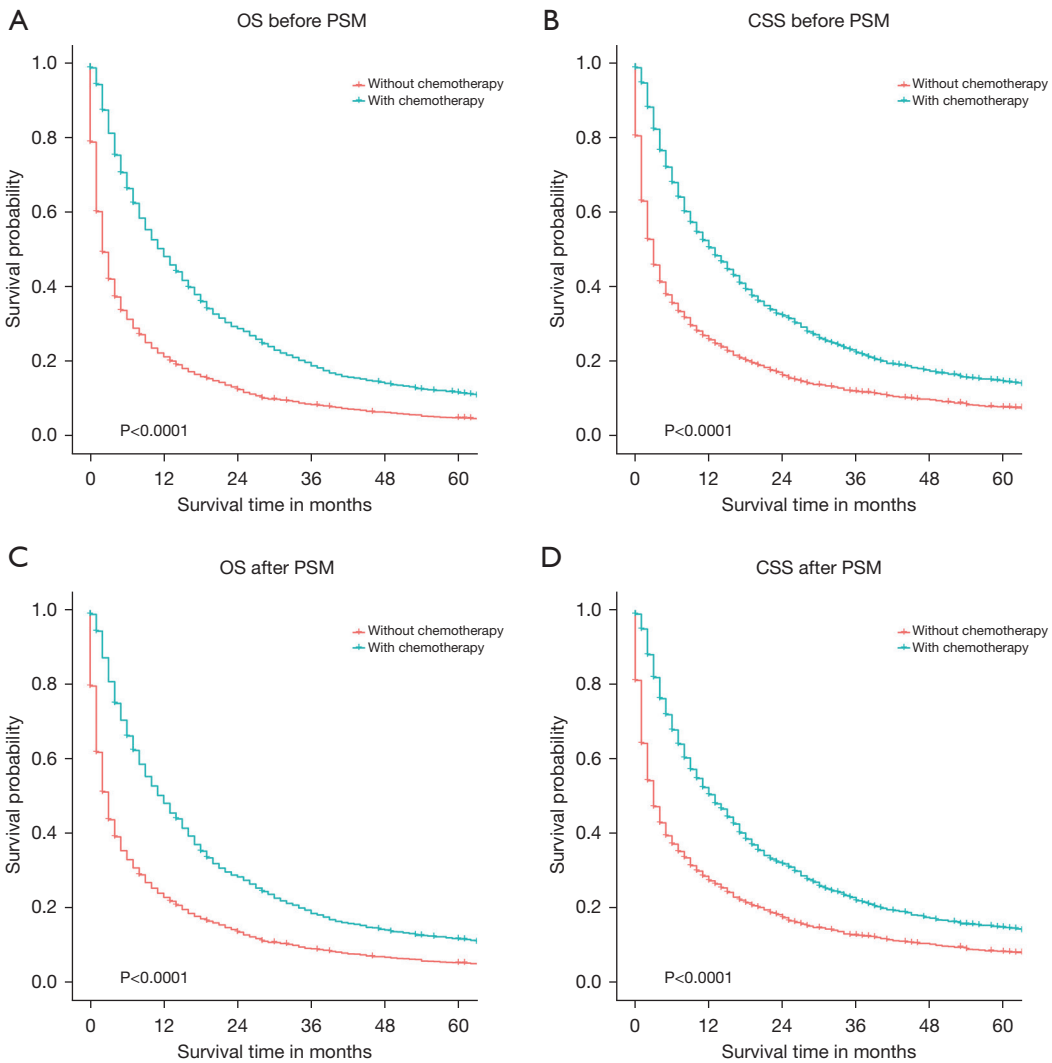

Figure 2 Kaplan-Meier survival curves for assessing the prognostic role of chemotherapy in patients with inoperable HCC. (A) OS before PSM; (B) CSS before PSM; (C) OS after PSM; (D) CSS after PSM. PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival; HCC, hepatocellular carcinoma.

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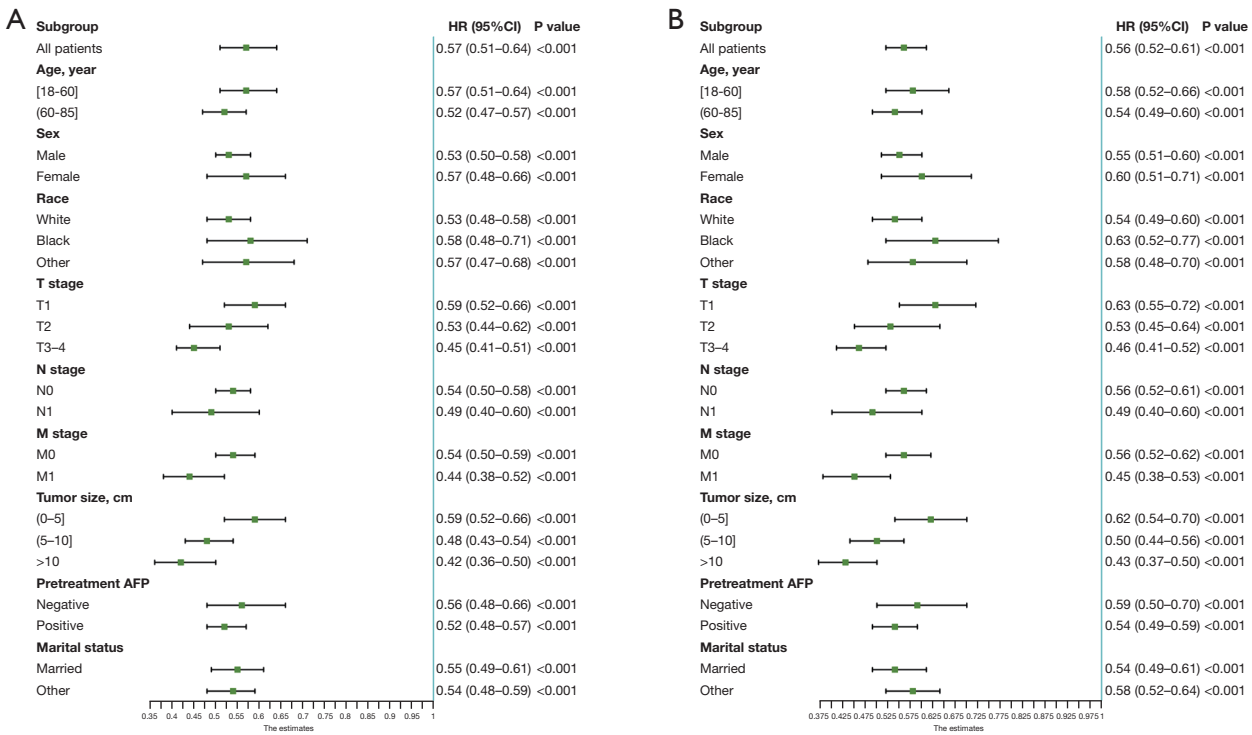

Figure 3 Forest plot for evaluating the prognostic role of chemotherapy in patients with inoperable HCC stratified by different clinical subgroups. (A) OS; (B) CSS. HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; OS, overall survival; CSS, cancer-specific survival.

in the training group and 631 in the validation group. As shown in Table S2, no significant differences were detected in the baseline characteristics between these two groups of patients.

Subsequently, TNM stage, tumor size, and pretreatment AFP were identified to be independent risk factors for OS (*Table 4*) and CSS (*Table 5*) in patients with inoperable HCC receiving chemotherapy.

We constructed the corresponding nomograms for predicting the 1- and 3-year OS and CSS probabilities (*Figure 4*). For OS, the C-index in both the training group and the validation group was 0.684. As for CSS, the C-index was 0.693 and 0.697 in the training group and the validation group, respectively. As shown in *Figure 5*, the 1- and 3-year areas under the curve (AUCs) for OS were 0.772 and 0.758 in the training group and were 0.782 and 0.774 in the validation group, respectively. Moreover, the 1- and 3-year AUCs for CSS were 0.781 and 0.771 in the training group and were 0.789 and 0.794 in the validation group, respectively (*Figure 5*). Additionally, the calibration curves demonstrated a high level of consistency between the expected and observed survivals in both the training and validation groups (*Figure 6*).

Discussion

Liver cancer, due to its high incidence and mortality rate, imposes a significant burden on society (31). Surgical treatment represents a potentially curative therapeutic strategy, offering significantly higher long-term relapse-free survival rates (40%) and 5-year survival rates (90%) compared to other alternatives in carefully selected patients with HCC (32,33). However, the eligibility for potentially curative surgical resection or liver transplantation therapy is limited to fewer than 20% of patients with HCC (7,8). This limitation is primarily attributed to factors such as multicentric tumors, vascular invasion, extrahepatic metastases, or other comorbidities. In general, determining the appropriate treatment plan for patients with liver cancer requires consideration of multiple factors, such as what is done in the Barcelona Clinic Liver Cancer staging system, which takes into account the patient's overall condition

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Table 4 Uni- and multivariate regression analyses for predicting the OS of patients with inoperable HCC treated with chemotherapy in the training group

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years		0.60		
[18–60]	Reference			
(60–85]	1.029 (0.923–1.148)	0.60		
Sex		0.71		
Male	Reference			
Female	0.975 (0.854–1.113)	0.71		
Race		0.23		
White	Reference			
Black	1.146 (0.979–1.342)	0.10		
Other	1.007 (0.872–1.163)	0.92		
T stage		<0.001		<0.001
T1	Reference		Reference	
T2	1.092 (0.940–1.268)	0.25	1.219 (1.038–1.433)	0.02
T3	2.081 (1.831–2.365)	<0.001	1.466 (1.269–1.694)	<0.001
T4	2.930 (2.263–3.793)	<0.001	1.944 (1.488–2.541)	<0.001
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	2.187 (1.878–2.547)	<0.001	1.447 (1.229–1.704)	<0.001
M stage		<0.001		<0.001
M0	Reference		Reference	
M1	2.634 (2.291–3.027)	<0.001	1.897 (1.633–2.205)	<0.001
Tumor size (cm)		<0.001		<0.001
(0–5]	Reference		Reference	
(5–10]	1.656 (1.467–1.870)	<0.001	1.381 (1.185–1.609)	<0.001
>10	2.136 (1.840–2.479)	<0.001	1.707 (1.426–2.043)	<0.001
Pretreatment AFP		<0.001		<0.001
Negative	Reference		Reference	
Positive	1.651 (1.455–1.874)	<0.001	1.541 (1.353–1.753)	<0.001
Marital status		0.40		
Married	Reference			
Other	1.048 (0.940–1.167)	0.40		

OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein.

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Table 5 Uni- and multivariate regression analyses for predicting the CSS of patients with inoperable HCC with or without chemotherapy treatment in the training group

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.62		
[18–60]	Reference			
(60–85]	1.029 (0.918–1.155)	0.62		
Sex		0.82		
Male	Reference			
Female	0.984 (0.856–1.131)	0.82		
Race		0.10		
White	Reference			
Black	1.192 (1.011–1.405)	0.04		
Other	1.062 (0.915–1.234)	0.43		
T stage		<0.001		<0.001
T1	Reference		Reference	
T2	1.115 (0.950–1.308)	0.18	1.256 (1.057–1.493)	0.01
T3	2.185 (1.909–2.502)	<0.001	1.498 (1.287–1.745)	<0.001
T4	3.086 (2.361–4.034)	<0.001	1.990 (1.508–2.628)	<0.001
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	2.203 (1.880–2.580)	<0.001	1.430 (1.207–1.695)	<0.001
M stage		<0.001		<0.001
M0	Reference		Reference	
M1	2.741 (2.373–3.165)	<0.001	1.943 (1.663–2.269)	<0.001
Tumor size (cm)		<0.001		<0.001
(0–5]	Reference		Reference	
(5–10]	1.694 (1.490–1.927)	<0.001	1.405 (1.194–1.654)	<0.001
>10	2.285 (1.956–2.668)	<0.001	1.826 (1.512–2.205)	<0.001
Pretreatment AFP		<0.001		<0.001
Negative	Reference		Reference	
Positive	1.795 (1.565–2.057)	<0.001	1.670 (1.452–1.920)	<0.001
Marital status		0.43		
Married	Reference			
Other	1.047 (0.935–1.174)	0.43		

CSS, cancer-specific survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein.

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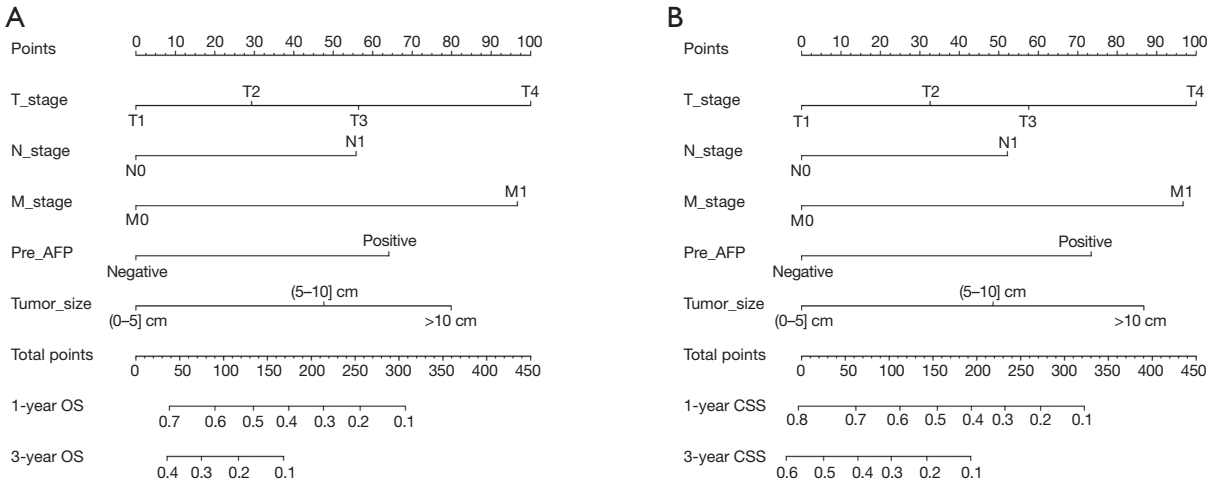

Figure 4 Prognostic nomograms of 1- and 3-year OS (A) and CSS (B) in patients with inoperable HCC treated with chemotherapy. AFP, alpha fetoprotein; OS, overall survival; CSS, cancer-specific survival.

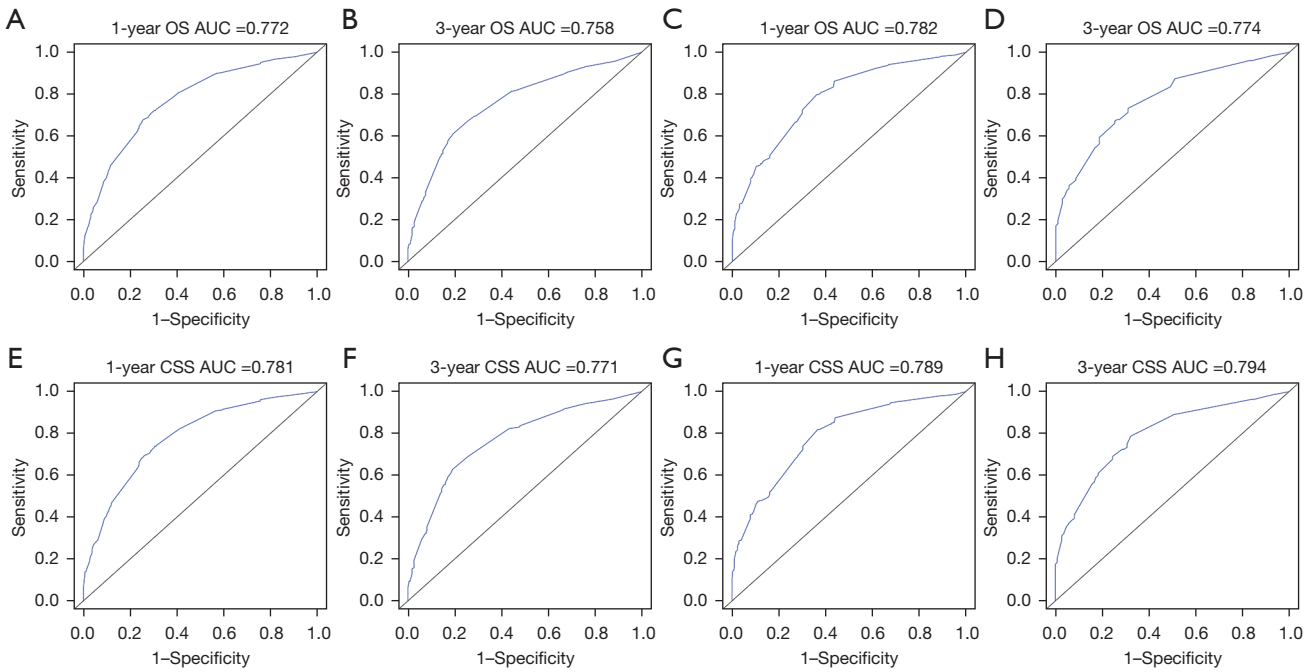

Figure 5 ROC curves of the predictive nomograms: the 1- and 3-year ROC curves of OS in the (A,B) training and (C,D) validation groups and the 1- and 3-year ROC curves of CSS in the (E,F) training and (G,H) validation groups. OS, overall survival; AUC, area under the curve; CSS, cancer-specific survival; ROC, receiver operating characteristic.

Eastern Cooperative Oncology Group performance score (ECOG PS), tumor burden (number, size, extent), liver function, and the available treatment options (34).

In the study, inoperable HCC was explored and analyzed. Research is divided into three parts, all of which are readable. Firstly, independent risk factors related to the inoperable HCC were investigated, including advanced TNM stage, positive pretreatment AFP levels and so on. The second part is about the positive prognostic value of adjuvant chemotherapy in inoperable HCC, which

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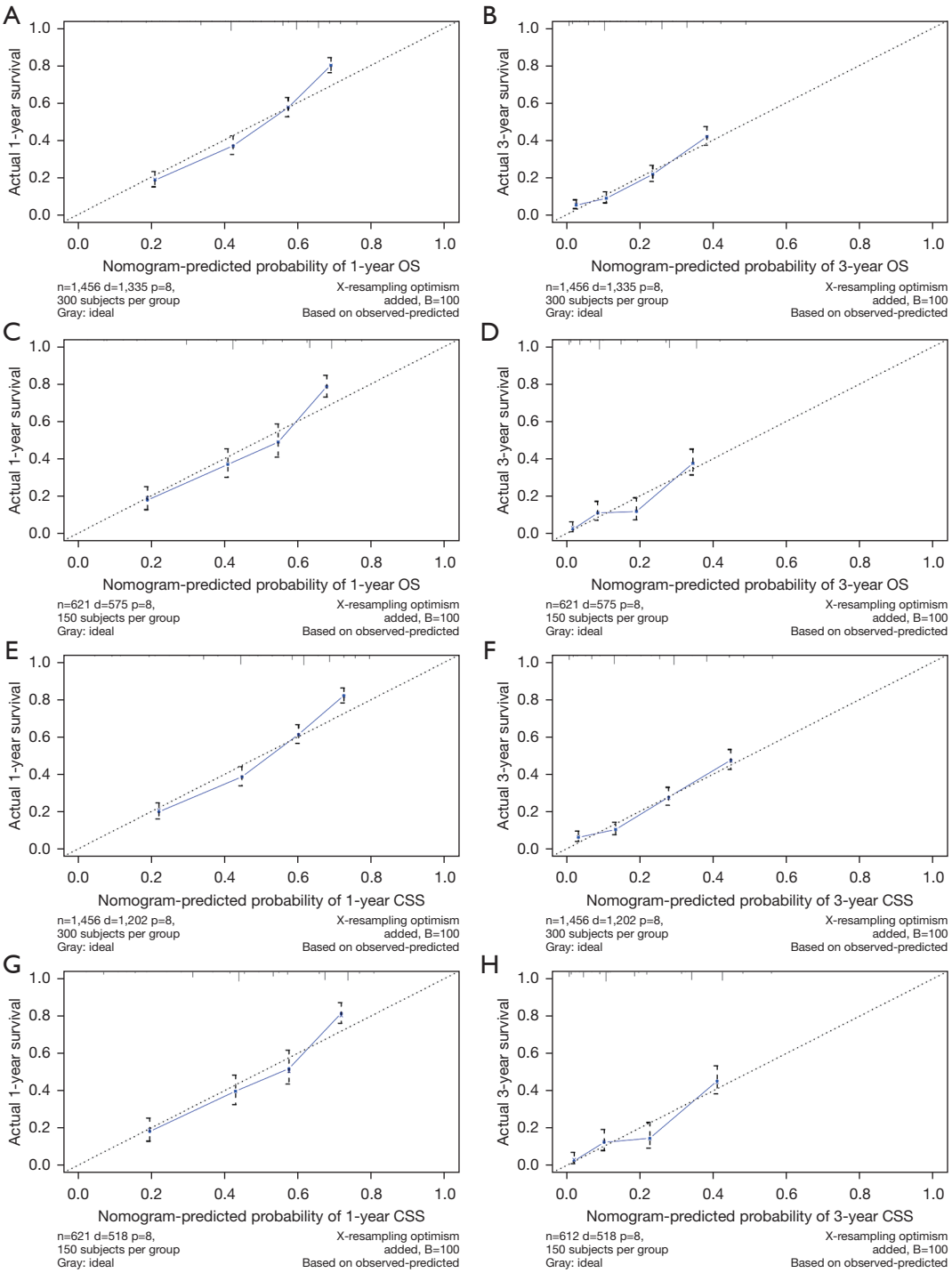

Figure 6 Calibration curves of the predictive nomograms: the 1- and 3-year calibration curves of OS in (A,B) the training and (C,D) validation groups and the 1- and 3-year calibration curves of CSS in (E,F) the training and (G,H) validation groups. OS, overall survival; CSS, cancer-specific survival.

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can significantly improve patient prognosis. Finally, we established a nomogram prediction model to estimate the survival probability of patients with inoperable HCC receiving chemotherapy, to assist doctors to make clinical decisions, especially on the use of chemotherapy. The aim of the study is to help clinicians treat patients with inoperable HCC in a reasonable way and assist them in making more informed clinical decisions.

In this study, several independent risk factors were identified as being associated with the unresectability of HCC, including higher age at diagnosis, male gender, advanced TNM stage, larger tumor size, positive pretreatment AFP levels, and a never-married or SDW status. A higher T stage indicates a larger tumor size, a greater number of tumor nodules, or invasion of critical blood vessels. Meanwhile, higher N or M stage signifies the presence of lymph node or distant metastasis. A higher TNM stage is strongly associated with the potential unresectability of the tumor. Furthermore, tumor size plays a significant role in determining unresectability. In general, large liver tumors encroach upon the hepatic blood vessels, and their proximity to the first, second, or third hepatic portal regions escalates the complexity of vascular separation during surgery, amplifying the risk of vascular rupture, bleeding, or damage. Furthermore, individuals with larger tumors often demonstrate a higher propensity for microvascular invasion and elevated tumor grading in contrast to those bearing smaller tumors (35,36). Hence, for patients afflicted with massive HCC, a meticulous preoperative assessment of the tumor's size, shape, blood supply, and relationship with neighboring tissues is pivotal for the success of surgical treatment.

Chemotherapy plays a crucial role in improving the prognosis of patients with inoperable HCC. In our study, the administration of chemotherapy was found to significantly improve both the OS and CSS across a variety of subgroups. In China, the FOLFOX4 systemic chemotherapy regimen has been approved for the first-line treatment of patients with locally advanced and metastatic liver cancer who are not suitable for surgical resection or local treatment (24,25) (level 1, grade A). Furthermore, other chemotherapy regimens have demonstrated specific therapeutic effects in advanced liver cancer, including combinations such as gemcitabine with platinum-based drugs (37) and capecitabine combined with oxaliplatin (27), among others. However, the therapeutic efficacy of single-agent chemotherapy is limited, and comprehensive treatment models combining chemotherapy with other treatment modalities have been widely developed. Asnacios *et al.* (38) conducted a prospective enrollment of 45 previously untreated patients with advanced-stage progressive HCC to investigate the therapeutic value of cetuximab in combination with gemcitabine plus oxaliplatin. The results revealed a response rate of 20%, and disease stabilization was achieved in 40% of the patients. This combination therapy appeared to be effective and was associated with manageable toxicity. The combination of chemotherapy and targeted therapy (sorafenib) has also yielded promising therapeutic efficacy and safety in patients with inoperable HCC (39,40). In recent years, the introduction of new chemotherapy regimens, such as HAIC, has alleviated the severe systemic side effects associated with traditional chemotherapy. Moreover, numerous prior studies have substantiated the efficacy of HAIC in patients with advanced or inoperable HCC (28,41,42).

The nomogram prediction model can integrate information from multiple variables to assist in estimating the probability of a certain event or outcome. It can take multiple variables into account, providing personalized predictions and aiding doctors in formulating better treatment plans, decisions, or recommendations. Some studies have explored the risk factors that affect the prognosis of patients with HCC. Wang *et al.* (43) devised a model aimed at predicting the OS in AFP-negative patients with HCC. Their findings revealed that several independent risk factors have a significant impact on OS, including body mass index, tumor stage, distant metastasis, hepatitis B surface antigen, albumin, gamma-glutamyl transpeptidase, and lactate dehydrogenase. Additionally, it is worth noting that this predictive model demonstrates superior predictive value over the TNM staging system. Tang *et al.* (44) identified radiomics score, satellite lesions, vascular invasion, anatomical resection, and bilirubin level as independent predictors of OS in patients with HCC combined with cholangiocarcinoma.

However, there is currently a lack of evidence regarding factors that can predict the effectiveness of chemotherapy. We developed a predictive model to forecast the prognosis of patients with inoperable HCC treated with chemotherapy. This model was established using the outcomes of Cox regression analysis, with the included variables being TNM stage, tumor size, and pretreatment AFP. Liu *et al.* (2) investigated the relationship between chemotherapy and the risk factors affecting survival in HCC. Their findings revealed that AJCC TNM stage, tumor size, AFP, and surgical options were significantly correlated with OS and CSS in patients with HCC who underwent chemotherapy.

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The conclusions of their study were in line with our research. However, it should be mentioned that their study included all patients with HCC, while our study specifically focused on patients with inoperable HCC. Carr *et al.* (45) analyzed the data of 967 patients with unresectable and untransplantable HCC confirmed by biopsy. The results indicated that patients with normal AFP levels had a longer survival duration than those with elevated AFP levels. Large HCCs often present challenges in prognosis, as they are frequently associated with vascular invasion and the development of multiple satellite lesions, contributing to an unfavorable prognosis (46-48). In addition, several studies (49-51) have found a large tumor size to be associated with poor survival in patients with HCC treated with TACE. However, Yamasaki *et al.* (52) reported that tumor size was not an independent factor influencing the outcomes of patients with advanced HCC treated with HAIC.

In the next five years, with the increase in the number of inoperable HCC patients, the improvement of therapeutic efficacy and the optimization of prognosis have become urgent challenges for doctors. As a result, survival prediction model becomes an excellent auxiliary method. However, it should be mentioned that the future treatment methods will be updated and improved, including but not limited to the combination therapy we mentioned above, such as ICIs combined chemotherapy, TACE combined chemotherapy, etc. In the future, we need to timely update the indicators of the survival prediction model and the way of establishing the model to satisfy the different kinds of treatment. However, chemotherapy still plays an important role in the treatment of inoperable HCC, so our study may still have value and provide researchers with certain help in the future. Some limitations to our study should be mentioned. First, we employed a retrospective design with data collected from a public database, and selection bias was inevitable. Moreover, the SEER database lacks critical variables such as liver function parameters (liver enzymes, bilirubin levels, albumin levels), comorbid conditions (jaundice, ascites, hepatic encephalopathy), and imaging data. Finally, the details of the chemotherapy regimens, including information on specific drugs and administration methods, were not clearly outlined. Prospective and randomized controlled studies are needed to verify our findings.

Conclusions

We first explored the independent risk factors influencing the inoperability of patients with HCC. Subsequently, we confirmed that chemotherapy can improve the prognosis of patients with inoperable HCC. Finally, we developed survival models with a strong predictive capability for estimating the survival probabilities of patients with HCC undergoing chemotherapy. These models hold considerable potential for use in clinic and merit further investigation in future research.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-298/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-298/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality

Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Liu M, Xu M, Tang T. Association between chemotherapy and prognostic factors of survival in hepatocellular carcinoma: a SEER population-based cohort study. Sci Rep 2021;11:23754.
3. El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 2008;134:1752-63.
4. Shuto T, Hirohashi K, Kubo S, et al. Treatment of adrenal metastases after hepatic resection of a hepatocellular carcinoma. Dig Surg 2001;18:294-7.
5. Katyal S, Oliver JH 3rd, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000;216:698-703.
6. Cabrera R, Nelson DR. Review article: the management of hepatocellular carcinoma. Aliment Pharmacol Ther 2010;31:461-76.
7. Guan YS, Liu Y. Interventional treatments for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2006;5:495-500.
8. Gaba RC, Lokken RP, Hickey RM, et al. Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy. J Vasc Interv Radiol 2017;28:1210-1223.e3.
9. Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol 2017;67:999-1008.
10. Bae SH, Park HC. Local modalities for inoperable hepatocellular carcinoma: radiofrequency ablation versus stereotactic body radiotherapy. Ann Transl Med 2018;6:S3.
11. Zeng H, Su K, Chen X, et al. A propensity score matching study on survival benefits of radiotherapy in patients with inoperable hepatocellular carcinoma. Sci Rep 2023;13:6879.
12. Gylstorff S, Wilke V, Kraft D, et al. Selective Internal Radiotherapy Alters the Profiles of Systemic Extracellular Vesicles in Hepatocellular Carcinoma. Int J Mol Sci 2023;24:12512.
13. Liang C, He Z, Tao Q, et al. From Conversion to Resection for Unresectable Hepatocellular Carcinoma: A Review of the Latest Strategies. J Clin Med 2023;12:7665.
14. Murata S, Mine T, Sugihara F, et al. Interventional treatment for unresectable hepatocellular carcinoma. World J Gastroenterol 2014;20:13453-65.
15. Nagashima J, Okuda K, Tanaka M, et al. Prognostic benefit in cytoreductive surgery for curatively unresectable hepatocellular carcinoma - comparison to transcatheter arterial chemoembolization. Int J Oncol 1999;15:1117-23.
16. Shui Y, Yu W, Ren X, et al. Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. Radiat Oncol 2018;13:188.
17. Kang J, Nie Q, DU R, et al. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Mol Clin Oncol 2014;2:43-50.
18. Rizzo A, Ricci AD, Brandi G. Trans-Arterial Chemoembolization Plus Systemic Treatments for Hepatocellular Carcinoma: An Update. J Pers Med 2022;12:1788.
19. Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet 2023;402:1133-46.
20. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-73.
21. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
22. Rizzo A, Ricci AD, Brandi G. Immune-based combinations for advanced hepatocellular carcinoma: shaping the direction of first-line therapy. Future Oncol 2021;17:755-7.
23. Guven DC, Sahin TK, Erul E, et al. The association between albumin levels and survival in patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. Front Mol Biosci 2022;9:1039121.
24. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 2013;31:3501-8.
25. Qin S, Cheng Y, Liang J, et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. Oncologist 2014;19:1169-78.
26. Shim JH, Park JW, Nam BH, et al. Efficacy of combination chemotherapy with capecitabine plus cisplatin in patients with unresectable hepatocellular carcinoma.

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Cancer Chemother Pharmacol 2009;63:459-67.
27. Lee JO, Lee KW, Oh DY, et al. Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. Ann Oncol 2009;20:1402-7.
28. Hendi M, Mou Y, Lv J, et al. Hepatic Arterial Infusion Chemotherapy Is a Feasible Treatment Option for Hepatocellular Carcinoma: A New Update. Gastrointest Tumors 2021;8:145-52.
29. Iwamoto H, Shimose S, Shirono T, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma in the era of chemo-diversity. Clin Mol Hepatol 2023;29:593-604.
30. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015;162:55-63.
31. Huang DQ, Mathurin P, Cortez-Pinto H, et al. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol 2023;20:37-49.
32. Mancuso A, Perricone G. Hepatocellular Carcinoma and Liver Transplantation: State of the Art. J Clin Transl Hepatol 2014;2:176-81.
33. Cauchy F, Fuks D, Belghiti J. HCC: current surgical treatment concepts. Langenbecks Arch Surg 2012;397:681-95.
34. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
35. Pawlik TM, Delman KA, Vauthey JN, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 2005;11:1086-92.
36. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
37. Taïeb J, Bonyhay L, Golli L, et al. Gemcitabine plus oxaliplatin for patients with advanced hepatocellular carcinoma using two different schedules. Cancer 2003;98:2664-70.
38. Asnacios A, Fartoux L, Romano O, et al. Gemcitabine plus oxaliplatin (GEMOX) combined with cetuximab in patients with progressive advanced stage hepatocellular carcinoma: results of a multicenter phase 2 study. Cancer 2008;112:2733-9.
39. Richly H, Henning BF, Kupsch P, et al. Results of a Phase I trial of sorafenib (BAY 43-9006) in combination with doxorubicin in patients with refractory solid tumors. Ann Oncol 2006;17:866-73.
40. Richly H, Schultheis B, Adamietz IA, et al. Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma: results from a phase I extension trial. Eur J Cancer 2009;45:579-87.
41. Tsai WL, Lai KH, Liang HL, et al. Hepatic arterial infusion chemotherapy for patients with huge unresectable hepatocellular carcinoma. PLoS One 2014;9:e92784.
42. Song MJ. Hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma. World J Gastroenterol 2015;21:3843-9.
43. Wang X, Mao M, He Z, et al. Development and Validation of a Prognostic Nomogram in AFP-negative hepatocellular carcinoma. Int J Biol Sci 2019;15:221-8.
44. Tang YY, Zhao YN, Zhang T, et al. Comprehensive radiomics nomogram for predicting survival of patients with combined hepatocellular carcinoma and cholangiocarcinoma. World J Gastroenterol 2021;27:7173-89.
45. Carr BI, Pancoska P, Branch RA. Tumor and liver determinants of prognosis in unresectable hepatocellular carcinoma: a large case cohort study. Hepatol Int 2009;4:396-405.
46. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg 2002;194:592-602.
47. Yeh CN, Lee WC, Chen MF. Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung memorial hospital. Ann Surg Oncol 2003;10:1070-6.
48. Choi GH, Han DH, Kim DH, et al. Outcome after curative resection for a huge (>OR =10 cm) hepatocellular carcinoma and prognostic significance of gross tumor classification. Am J Surg 2009;198:693-701.
49. Yoshioka H, Sato M, Sonomura T, et al. Factors associated with survival exceeding 5 years after transcatheter arterial embolization for hepatocellular carcinoma. Semin Oncol 1997;24:S6-29-S6-37.
50. Poon RT, Ngan H, Lo CM, et al. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. J Surg Oncol 2000;73:109-14.
51. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for

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unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461-9.
52. Yamasaki T, Kimura T, Kurokawa F, et al. Prognostic factors in patients with advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy. J Gastroenterol 2005;40:70-8.

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