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ORIGINAL ARTICLE

Retrospective Study

Conditional survival probability of distant-metastatic hepatocellular carcinoma: A population-based study

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Abstract

BACKGROUND

The prognosis of many patients with distant metastatic hepatocellular carcinoma (HCC) improved after they survived for several months. Compared with traditional survival analysis, conditional survival (CS) which takes into account changes in survival risk could be used to describe dynamic survival probabilities.

AIM

To evaluate CS of distant metastatic HCC patients.

METHODS

Patients diagnosed with distant metastatic HCC between 2010 and 2015 were extracted from the Surveillance, Epidemiology and End Results database. Univariate and multivariate Cox regression analysis were used to identify risk factors for overall survival (OS), while competing risk model was used to identify risk factors for cancer-specific survival (CSS). Six-month CS was used to calculate the probability of survival for an additional 6 mo at a specific time after initial diagnosis, and standardized difference (d) was used to evaluate the survival differences between subgroups. Nomograms were constructed to predict CS.

RESULTS

Positive α-fetoprotein expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis were independent risk factors for actual OS and CSS through univariate and multivariate analysis. Actual survival rates decreased over time, while CS rates gradually increased. As for the 6-month CS, the survival difference caused by chemotherapy and radiotherapy gradually disappeared over time, and the survival difference caused by lung metastasis reversed. Moreover, the influence of age and gender on survival gradually appeared. Nomograms were fitted for patients who have lived for 2, 4 and 6 mo to predict 6-month conditional OS and

CSS, respectively. The area under the curve (AUC) of nomograms for conditional OS decreased as time passed, and the AUC for conditional CSS gradually increased.

CONCLUSION
CS for distant metastatic HCC patients substantially increased over time. With dynamic risk factors, nomograms constructed at a specific time could predict more accurate survival rates.

Key Words: Conditional survival; Hepatocellular carcinoma; Distant metastasis; Prognosis; Nomogram

Core Tip: Distant metastatic hepatocellular carcinoma (HCC) patients demonstrate high hazard ratios for death in the first few months, which makes survival estimates at the time of initial diagnosis inaccurate. Conditional survival (CS) which takes into account changes in survival risk could be used to describe dynamic survival probabilities. We conducted a population-based study to assess CS for distant metastatic HCC patients. Compared with actual survival rate for HCC patients which gradually decreased after initial diagnosis, CS rate substantially increased over time. With dynamic risk factors, nomograms were constructed to predict more accurate CS at different time after initial diagnosis.

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DOI: https://dx.doi.org/10.4251/wjgo.v15.i11.1874

INTRODUCTION

Primary liver cancer was the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906 000 new cases and 830 000 deaths[1]. Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, accounting for 75%–85% of the cases. HCC represents a growing health threat with annual mortality rates increasing by 2%–3% per year from 2003 to 2012 and a 43% increase in the rate of death from 2000 to 2016 in the USA[2,3]. Due to high metastatic potential, 14.0%–36.7% of HCC patients already had extrahepatic metastasis at the time of initial diagnosis, and the incidence of distant metastases in patients with HCC was about 13.5% [4-7]. The prognosis in HCC patients with extrahepatic metastasis was poorer than the prognosis of early-stage patients. Over the past three decades, the outcome of patients with advanced HCC has substantially improved due to better selection of appropriate treatments and advances in effective treatment[8-10]. For example, the small molecule targeted drug of sorafenib has been shown to extend life expectancy by nearly 3 mo[11,12]. However, extrahepatic metastatic HCC patients still have poor survival with a median expected survival time of only 6–8 mo or a 25% survival rate at 1 year[13].

With high mortality rate and poor prognosis, distant metastatic HCC patients would demonstrate high hazard ratios for death in the first few months, which makes survival estimates at the time of initial diagnosis inaccurate. Conditional survival (CS) is a concept that takes into account changes in survival risk and could be used to describe dynamic survival probabilities[14]. Previous studies have reported CS of breast cancer, glioma, lung cancer, colorectal cancer and other cancers[15-19]. CS studies of HCC patients have also been published, but these studies did not categorize the patients according to clinical stage[20-22]. As distant metastatic HCC patients have poorer survival than those in early stage, the CS estimates would also be different. Therefore, a study of dynamic CS analysis in patients with distant metastatic HCC is meaningful.

In this study, we calculated the dynamic survival probability for patients with distant metastatic HCC using data from the Surveillance, Epidemiology and End Results (SEER) database. Moreover, nomograms were constructed to predict CS of distant metastatic HCC patients at different time after initial diagnosis.

MATERIALS AND METHODS

Data collection

Data of primary diagnosed HCC patients from 2010 to 2015 were retrieved from the SEER database Program 17 registries (https://seer.cancer.gov/). Data were included following these criteria: (1) Age> 18 years; (2) patients were pathologically diagnosed with stage IVB HCC; (3) HCC was the only primary cancer; and (4) complete follow-up and survival data. Patients were excluded if the diagnosis was made only at autopsy. Those patients with incomplete American Joint Committee on Cancer (AJCC) staging, α-fetoprotein (AFP) expression information, and unknown death reason were all excluded. Marital status included married (married and having domestic partner), single (never married), and separated (separated, divorced or widowed). The tumor size mentioned in this study referred to the size of the primary tumor.

Surgery referred to surgery of the primary site.

Statistical analysis

In this study, overall survival (OS) was defined as the time from the start of randomized treatment to death due to any reason, and cancer-specific survival (CSS) was defined as the time from the start of randomized treatment to death due to a specific disease. Univariate and multivariate Cox regression model were built to evaluate associations between features and OS, while Fine–Gray competing risk regression model was used to assess associations between features and CSS. Survival analysis was performed using the Kaplan–Meier method. Cumulative incidence function curves were used to describe difference of mortality probability in subgroups.

CS analysis was applied to assess the possibility of additional survival for patients who have survived for specific months. Here, an additional 6-months' survival (CS6) was calculated as: CS6 = S(x + 6)/S(x), which means CS6 among patients who have survived 2 mo from the date of diagnosis was calculated by dividing the survival at 8 mo by the survival at 2 mo. Based on variables selected by the multivariate Cox regression model and the competing risk model, nomograms for OS and CSS were fitted to estimate the CS6 of distant metastatic HCC patients, respectively. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to evaluate the performance of these nomograms.

Differences in CS among subgroups were calculated using the standardized differences (d) method, with the formula below[23]

$$d = (P2 - P1)/\sqrt{[P(1 - P)]}$$

The value of standardized differences can be divided into four conditions: $|d| < 0.1$ shows no difference in each group; $0.1 \leq |d| < 0.3$ shows a small difference; $0.3 \leq |d| < 0.5$ shows a moderate difference; and $|d| \geq 0.5$ shows a significant difference. A significance level of $P < 0.05$ was used in all analyses. The statistical analysis was conducted using R software (packages: survival, cmprsk, rms, and timeROC).

RESULTS

Clinicopathological characteristics

A total of 1502 patients were included in the study (Table 1). The median age of these patients was 61 years (interquartile range: 56–68 years), 81.89% were male, and 65.11% of the patients were white. About half of the patients (49.40%) were married. Most patients were diagnosed with positive AFP expression (84.29%) and had a primary tumor size > 5 cm (72.70%). For TNM staging, > 50% patients were diagnosed in the T3 stage (n = 783, 52.13%), and > 60% were diagnosed without lymph nodes metastasis (N0, n = 1031, 68.64%). Consistent with previous study, lung metastasis (n = 553, 36.82%) was more frequent than other distant metastasis sites, including bone (n = 430, 28.63%) and brain (n = 27, 1.80%). Over half of the patients received chemotherapy, while few received primary-site surgery (n = 82, 5.46%) and radiotherapy (n = 302, 20.11%). The median survival time was only 4 (range, 1–117) mo, and 1457 (97.0%) patients died during the follow-up time and 1379 (94.65%) of them died because of HCC.

Table 1 Clinical and pathological characteristics distribution of distant metastatic hepatocellular carcinoma patients

Characteristics	*n*	%
Age, yr		
< 55	299	19.91
55-65	656	43.68
≥ 65	547	36.42
Gender		
Male	1230	81.89
Female	272	18.11
Race		
White	978	65.11
Black	237	15.78
Other	287	19.11
Marital status		
Single	405	26.96
Married	742	49.40

Separated	355	23.64
AFP expression		
Positive	1266	84.29
Negative	236	15.71
Tumor size		
≤ 5 cm	410	27.30
> 5 cm	1092	72.70
T stage		
T1	337	22.44
T2	216	14.38
T3	783	52.13
T4	166	11.05
N stage		
N0	1031	68.64
N1	471	31.36
Surgery		
No	1420	94.54
Yes	82	5.46
Chemotherapy		
No/unknown	691	46.01
Yes	811	53.99
Radiotherapy		
No/unknown	1200	79.89
Yes	302	20.11
Lung metastasis		
No	949	63.18
Yes	553	36.82
Bone metastasis		
No	1072	71.37
Yes	430	28.63
Brain metastasis		
No	1475	98.20
Yes	27	1.80
Survival status		
Alive	45	3.00
Other cause death	78	5.19
Cancer specific death	1379	91.81
Total	1502	100

AFP: Alpha-fetoprotein.

Comparison of OS and CSS

The 2-, 6- and 12-month OS rates were 64.14%, 32.79% and 17.48%, while the 2-, 6- and 12-month CSS rates were 65.89%, 34.77% and 19.16%, respectively (Figure 1). From the results of univariate analysis: positive AFP expression, tumor size (> 5 cm), higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung

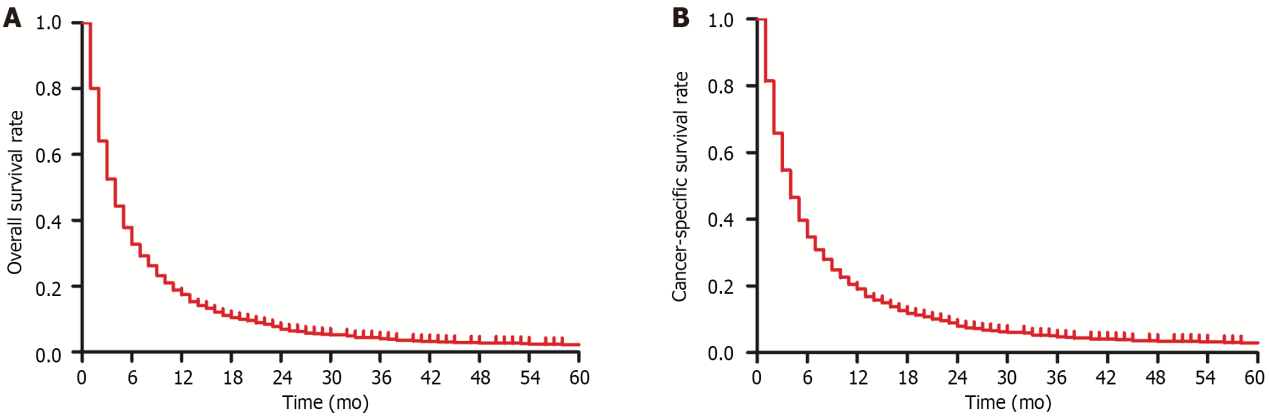

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Figure 1 Kaplan–Meier survival curve of overall survival and cancer-specific survival. A: Overall survival; B: Cancer-specific survival.

metastasis were risk factors for OS, and these factors were also risk factors for CSS through the Gray's test (Supplementary Table 1; Supplementary Figures 1 and 2). Race was also identified to be associated with CSS through the Gray's test. For multivariate analysis, positive AFP expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, lung metastasis, and bone metastasis were independent risk indicators of OS, and they were also independent risk indicators of CSS through the competing risk model (Table 2). Bone metastasis was only identified as a risk factor in multivariate analysis, which may have been influenced by radiotherapy. Patients with bone metastasis who received radiotherapy had better survival rates and less cancer-specific mortality rates before 22 mo compared with patients without bone metastasis and bone metastatic patients without radiotherapy (Supplementary Figure 3).

Comparison of actual and CS

Actual OS and CSS rates since initial diagnosis and their corresponding CS are presented in Supplementary Tables 2 and 3. Among patients surviving at 2, 4 and 6 mo after diagnosis, the probability of OS at 12 mo was 27.25%, 39.39% and 53.31%, respectively. Among patients surviving at 2, 4 and 6 mo after diagnosis, the probability of CSS at 12 mo was 29.08%, 41.20% and 55.11%, respectively. The actual survival and 6-month CS are shown in Figures 2A and B. The actual survival rates decreased over time for OS and CSS, while the CS rates gradually increased.

According to d of conditional OS, risk factors could be categorized into three groups (Table 3): (1) $|d| > 0.1$, which means risk factors remained to be significant over time [AFP expression (negative *vs* positive), tumor size (> 5 cm *vs* ≤ 5 cm), T stage (T3 *vs* T1, T4 *vs* T1), N stage (N1 *vs* N0), and primary-site surgery (Yes *vs* No)]; (2) $|d| > 0.1 \rightarrow |d| < 0.1$, which means the influence caused by risk factors gradually decreased [race (other race *vs* black race), chemotherapy (Yes *vs* No/unknown), and radiotherapy (Yes *vs* No/unknown)]; and (3) $d < -0.1 \rightarrow d > 0.1$, which means the difference in survival caused by risk factors reversed over time [lung metastasis (Yes *vs* No)]. As for conditional CSS, risk factors could be also divided into three groups according to *d* value (Table 4): (1) $|d| > 0.1$, which means risk factors remained to be significant over time [AFP expression (negative *vs* positive), tumor size (> 5 cm *vs* ≤ 5 cm), T stage (T3 *vs* T1, T4 *vs* T1), N stage (N1 *vs* N0), and primary-site surgery (Yes *vs* No)]; (2) $|d| > 0.1 \rightarrow |d| < 0.1$, which means the influence caused by risk factors gradually decreased [race (other race *vs* black race), chemotherapy (Yes *vs* No/unknown), and radiotherapy (Yes *vs* No/unknown)]; and (3) $d < -0.1 \rightarrow d > 0.1$, which means the difference in survival caused by risk factors reversed over time [lung metastasis (Yes *vs* No)]. In addition, differences in conditional OS and CSS caused by age (55-65 *vs* < 55, ≥ 65 *vs* < 55) and gender (male *vs* female) gradually appeared over time ($|d| < 0.1 \rightarrow |d| > 0.1$).

Nomograms for CS

Prognostic relevance of features varied at different time since the initial diagnosis. Based on multivariate Cox regression model at different time points, three nomograms for 6-month conditional OS were fitted for patients who have lived for 2, 4 or 6 mo (Supplementary Table 4 and Figure 3). AUC for these nomograms gradually decreased over time: AUC was 0.679 for patients who survived 2 mo (Figure 3A); 0.663 for patients who survived 4 mo (Figure 3B); and 0.655 for patients who survived 6 mo (Figure 3C). The characteristics included in the nomogram changed with time, and AFP expression, tumor size, and primary-site surgery were prognostic indicators for all the three models.

Similarly, based on competing risk models at different time points, three nomograms for 6-month conditional CSS were conducted for patients who have lived for 2- 4 or 6 mo (Supplementary Table 5 and Figure 4). The value of AUC of the ROC curves gradually increased over time, and the AUCs for patients who survived 2, 4 and 6-mo were 0.659, 0.663 and 0.664, respectively (Figures 4A–C). AFP expression, tumor size, and primary-site surgery were still prognostic indicators that were included in all the models, while T stage was associated with 6-month conditional CSS for patients who lived for 2 or 4 mo.

Table 2 Multivariate analyses of factors associated with overall survival and cancer-specific survival

Characteristics	Overall survival		Cancer-specific survival	
	HR	*P* value	HR	*P* value
Age, yr				
< 55				
55-65	1.03 (0.89-1.19)	0.67	0.98 (0.85-1.13)	0.78
≥ 65	1.09 (0.94-1.26)	0.27	1.02 (0.88-1.19)	0.77
Gender				
Female				
Male	1.1 (0.96-1.26)	0.18	1.07 (0.93-1.24)	0.35
Race				
Black				
White	1.03 (0.89-1.2)	0.67	1.09 (0.93-1.27)	0.29
Other	1.12 (0.93-1.34)	0.23	1.2 (0.99-1.45)	0.063
Marital status				
Married				
Single	1.00 (0.88-1.14)	0.96	0.95 (0.83-1.08)	0.42
Separated	0.93 (0.82-1.07)	0.31	0.86 (0.75-0.99)	0.038
AFP expression				
Negative				
Positive	1.35 (1.17-1.56)	5.02E-05	1.33 (1.16-1.52)	5.70E-05
Tumor size				
> 5 cm				
≤ 5 cm	0.86 (0.74-1.00)	0.057	0.97 (0.83-1.13)	0.69
T stage				
T1				
T2	1.15 (0.95-1.39)	0.16	0.98 (0.8-1.2)	0.85
T3	1.27 (1.1-1.46)	1.03E-03	1.24 (1.07-1.42)	3.30E-03
T4	1.27 (1.04-1.54)	0.18	1.29 (1.07-1.56)	7.30E-03
N stage				
N0				
N1	1.19 (1.06-1.33)	3.89E-03	1.12 (0.99-1.27)	0.062
Surgery				
No				
Yes	0.42 (0.32-0.54)	7.65E-12	0.51 (0.41-0.64)	1.50E-09
Chemotherapy				
No/unknown				
Yes	0.59 (0.53-0.66)	1.42E-21	1.39 (1.25-1.56)	2.40E-09
Radiotherapy				
No/unknown				
Yes	0.71 (0.61-0.83)	1.40E-05	1.25 (1.09-1.42)	9.00E-04
Lung metastasis				
No				

Yes	1.36 (1.22-1.52)	9.97E-08	1.29 (1.15-1.45)	1.60E-05
Bone metastasis				
No				
Yes	1.22 (1.07-1.39)	3.76E-03	1.24 (1.08-1.41)	1.70E-03
Brain metastasis				
No				
Yes	0.97 (0.65-1.44)	0.89	0.96 (0.61-1.5)	0.85

AFP: α-fetoprotein; HR: Hazard ratio.

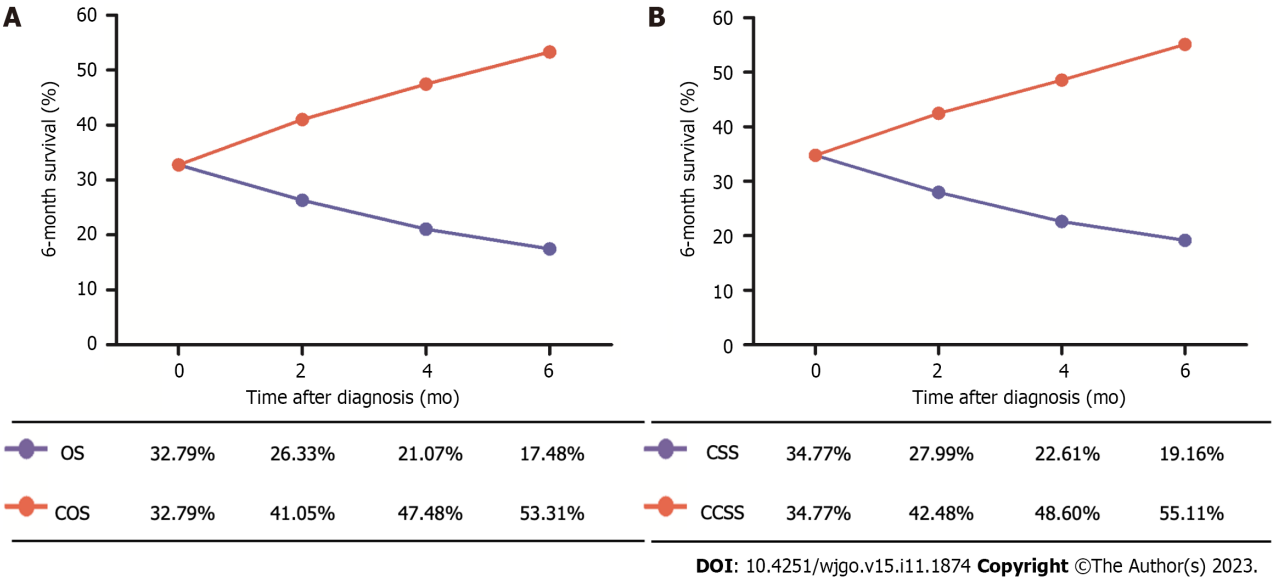

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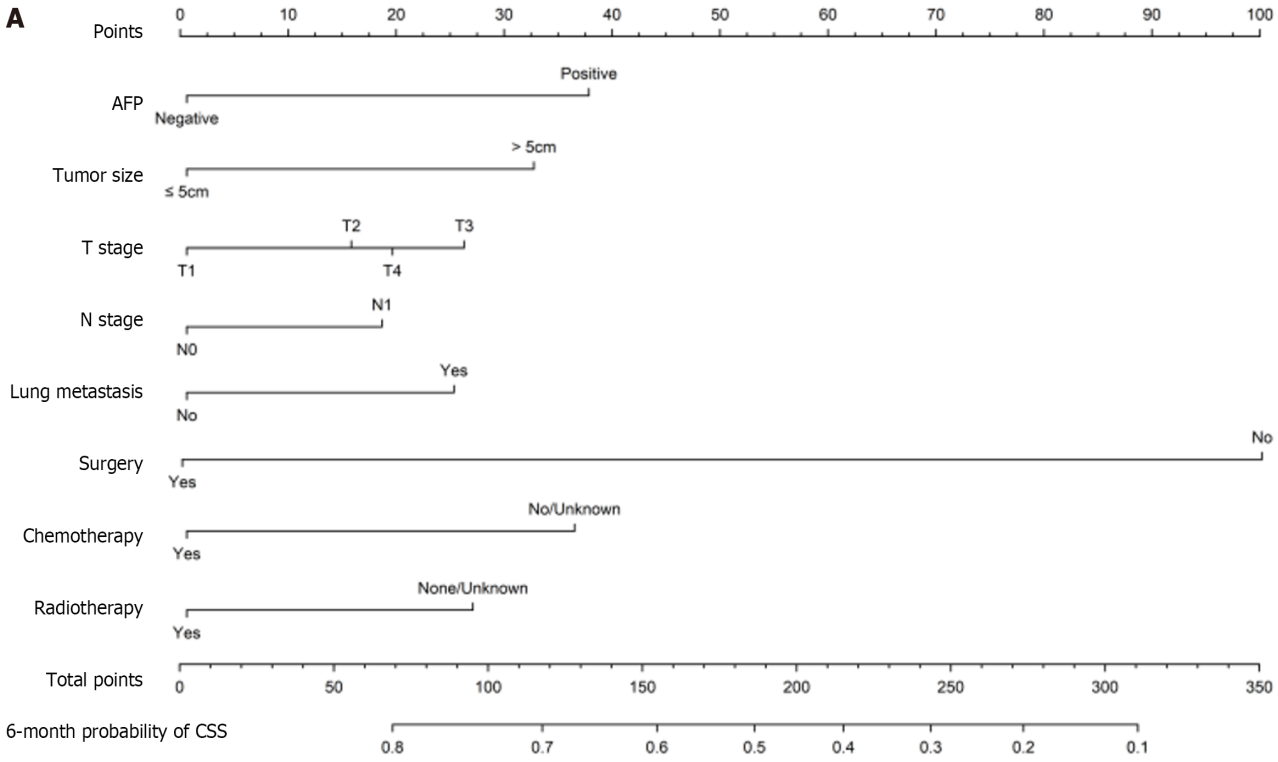
Figure 2 Conditional survival relative to actual survival. A: Conditional overall survival relative to actual overall survival; B: Conditional cancer-specific survival relative to actual cancer-specific survival. OS: Overall survival; COS: Conditional overall survival; CSS: Cancer specific survival; CCSS: Conditional cancer specific survival.

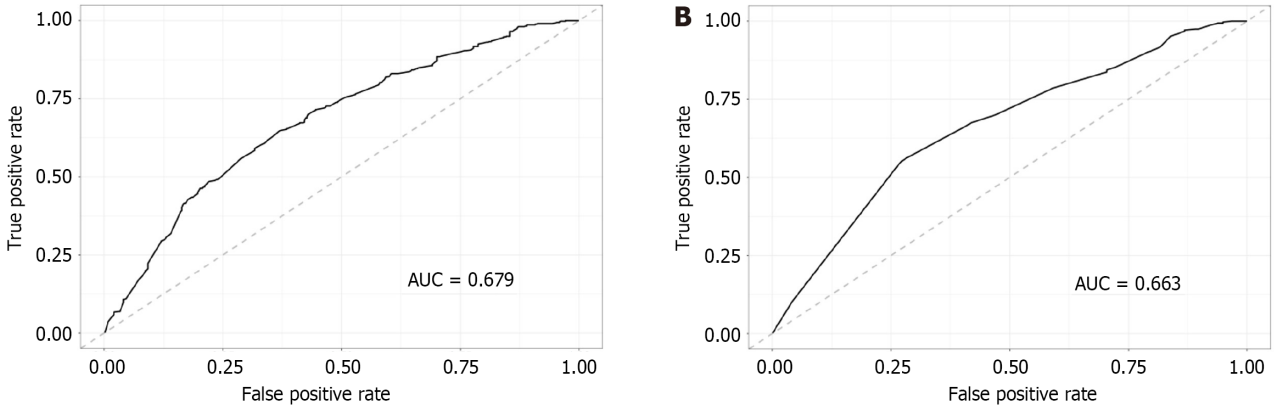
DISCUSSION

As one of the leading causes of cancer-related death worldwide, HCC is usually diagnosed at late and advanced stages [24]. While previous studies have concentrated on predicting prognosis for HCC patients, only a few have focused on distant metastatic HCC patients. Former studies on the prognosis of metastatic HCC have identified risk factors including older age, male gender, high T stage, low degree of tumor differentiation, N1 stage, non-primary site surgery, no chemoradiotherapy, larger tumor size, no radiotherapy, and multi-organ metastasis, while high T stage, N1 stage, non-primary site surgery, no chemotherapy, and no radiotherapy were also independent risk factors in our study[25,26].

Attributing to the characteristics of poor prognosis and high mortality rate, the predictive model that was constructed at the time of initial diagnosis would be influenced by patients who died in the first few months. Actual survival did not reflect how prognosis changed over time. Therefore, CS would provide patients with survival probabilities at a specific time since prognosis was adjusted for the time the patient had already survived[27]. There were several reports regarding CS of HCC, including a study that also used the data from SEER[22]. As reported in this study, the conditional OS improved from 8.4% to 44.1% for the AJCC stage IVB group during the first 5 years after initial diagnosis, and the conditional CSS improved from 12.1% to 66.7% in the AJCC stage IVB group. However, only 3.1% of distant metastatic HCC patients achieved a 5-year survival[28]. Thus, a 5-year CS could not reflect the survival situation for distant metastatic HCC patients and these patients should be separated from patients with early-stage HCC. Since 1 year survival rate was 17.48% for distant metastatic HCC patients in this study, we adopted a 6-month CS analysis, which was more suitable.

Compared with actual survival, which demonstrated a downward trend, conditional OS and CSS demonstrated upward trends over time. Survival rate for patients who had already lived for 6 mo to survive an additional 6 mo was 53.31%, while 12-month OS rate of the whole cohort was only 17.48% calculated at initial diagnosis. In subgroup analysis, risk factors of positive AFP expression, tumor size (> 5 cm), T stage (T3 and T4), N1 stage, and non-primary-site surgery maintained a substantial and stable effect on CS, while survival differences among races, chemotherapy groups, and radiotherapy groups decreased over time. Disparities in detection and treatment were linked to survival differences


A
Points
0 10 20 30 40 50 60 70 80 90 100
AFP
Positive
Negative
Tumor size
> 5cm
≤ 5cm
T stage
T2 T3
T1 T4
N stage
N1
N0
Lung metastasis
Yes
No
Surgery
No
Yes
Chemotherapy
No/Unknown
Yes
Radiotherapy
None/Unknown
Yes
Total points
0 50 100 150 200 250 300 350
6-month probability of CSS
0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1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0.75
0.50
0.25
0.00
AUC = 0.679
0.00 0.25 0.50 0.75 1.00
False positive rate
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True positive rate
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AUC = 0.663
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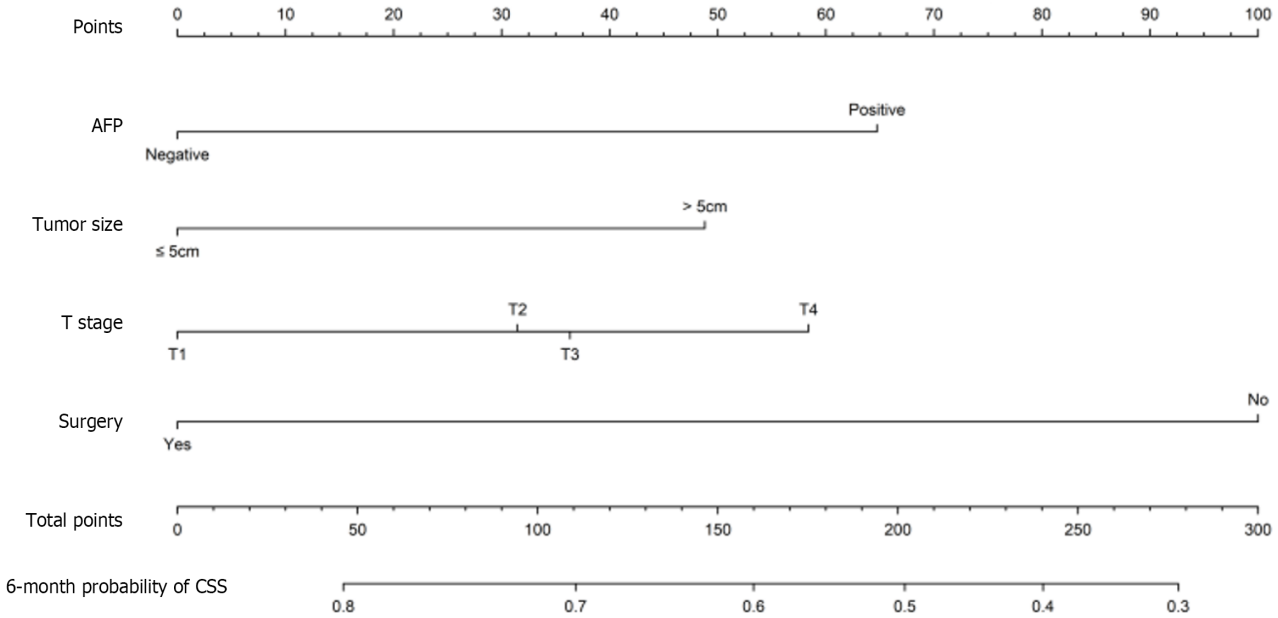
False positive rate


Points
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AFP
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Tumor size
> 5cm
≤ 5cm
T stage
T2 T4
T1 T3
Surgery
No
Yes
Total points
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6-month probability of CSS
0.8 0.7 0.6 0.5 0.4 0.3

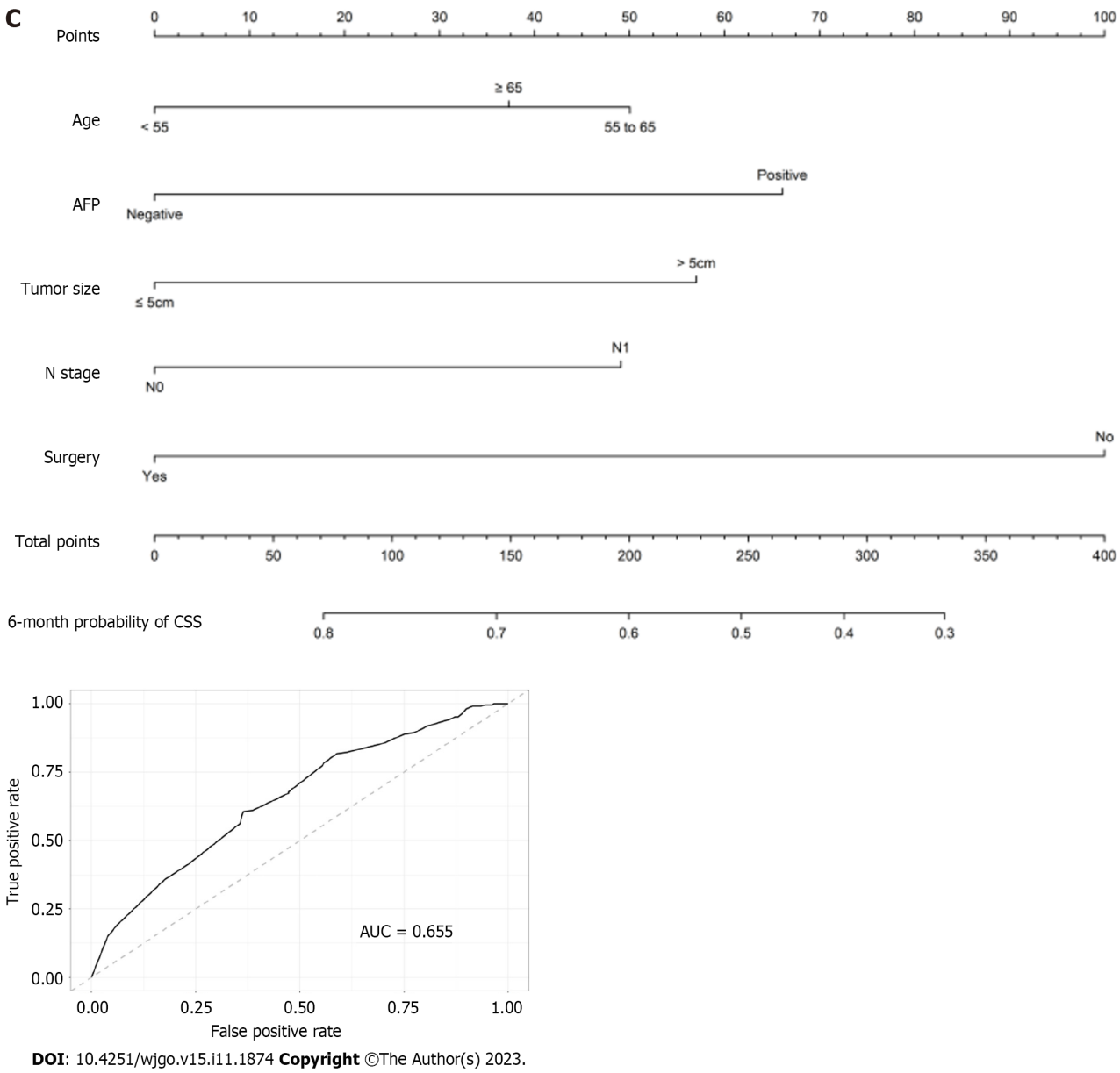

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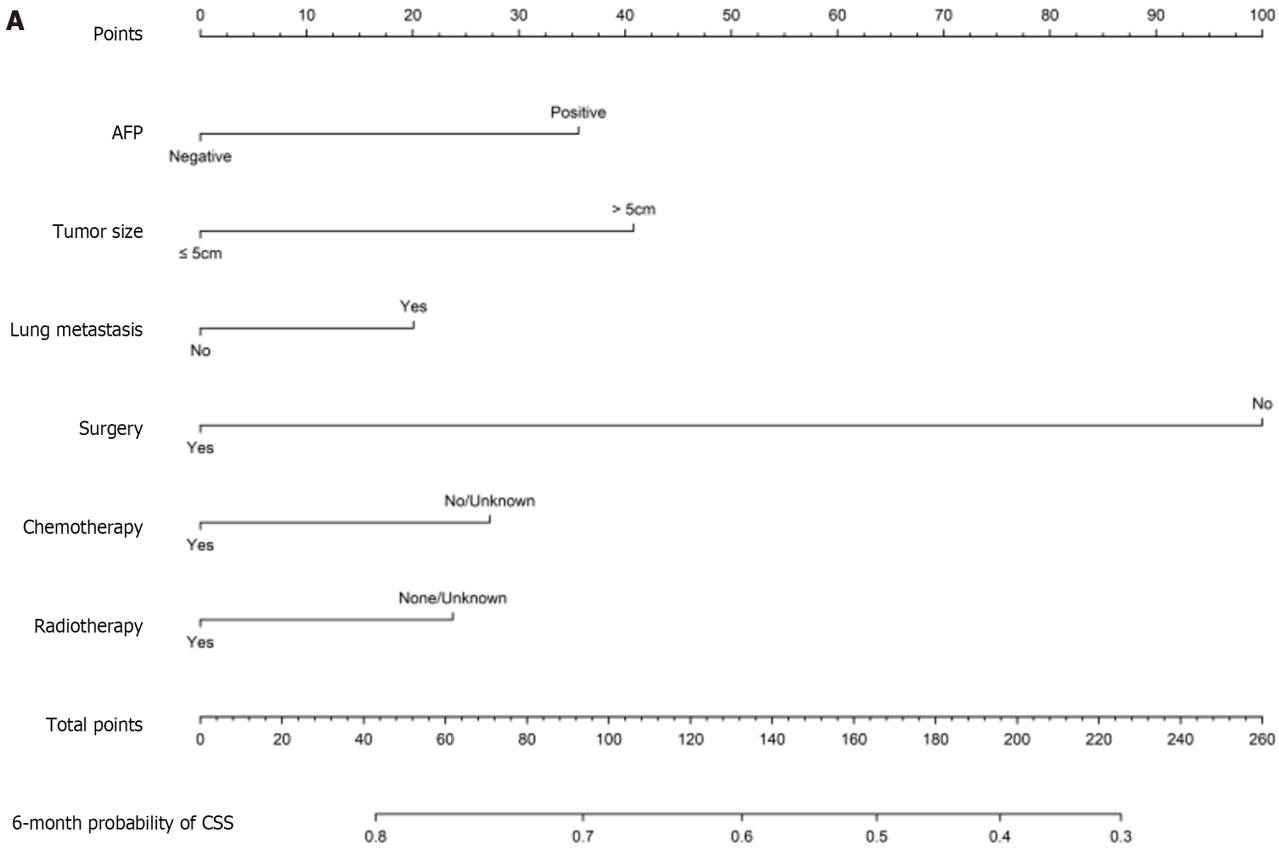
Figure 3 Nomograms and receiver operating characteristic curves for 6-mo conditional overall survival among patients having survived.
A: 2 mo; B: 4 mo; C: 6 mo. OS: Overall survival; AFP: α-fetoprotein; AUC: Area under the curve; CSS: Cancer specific survival.

among ethnic groups, but their impact diminished over time[29]. Chemotherapy and radiotherapy were considered to be protective factors for survival at initial diagnosis, and they may provide benefit in the first few months. However, as time goes by, their influence decreases gradually. This may be due to the difference in molecular pathology and resistance that appeared 10 mo following the initial diagnosis. Also, patients who had a poorer condition could not tolerate chemotherapy and radiotherapy at the initial diagnosis and had a shorter survival time, so poor conditions may explain worse survival for some non-chemotherapy or non-radiotherapy patients. Lung metastasis showed a reversed effect on CS over time, which was an unfavorable indicator for survival at initial diagnosis and became a protective factor when patients survived for 12 mo. This may partly be because patients with the ability to live beyond 12 mo had better molecular pathological features and health status. The influence of age groups and genders on survival did not appear until 10 mo after initial diagnosis, and older patients had a poorer prognosis because of their poorer health status. The survival difference was not significant in the first few months for different age groups attributing to the high mortality, but it would become significant after 10 mo. Similarly, females have a higher CS rate than males, and sex disparities may be caused by factors including sex-related biological factors, and gender-related environmental and behavioral factors[30-34]. Patients with bone metastasis had better CS rate compared to those without bone metastasis before the first 12 mo, which may be because many patients with bone metastasis received radiotherapy[35]. The findings that followed the result that patients with bone metastasis who received radiotherapy had a better OS and CSS in the first few months compared with patients without bone metastasis also suggest the effectiveness of radiotherapy in HCC patients with bone metastasis.


A
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AFP
Positive
Negative
Tumor size
> 5cm
≤ 5cm
Lung metastasis
Yes
No
Surgery
No
Yes
Chemotherapy
No/Unknown
Yes
Radiotherapy
None/Unknown
Yes
Total points
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6-month probability of CSS
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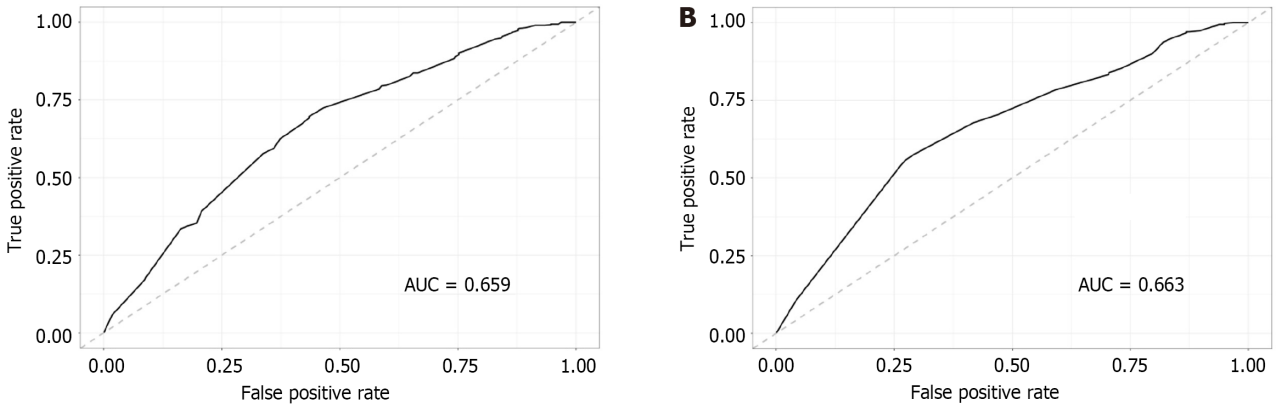
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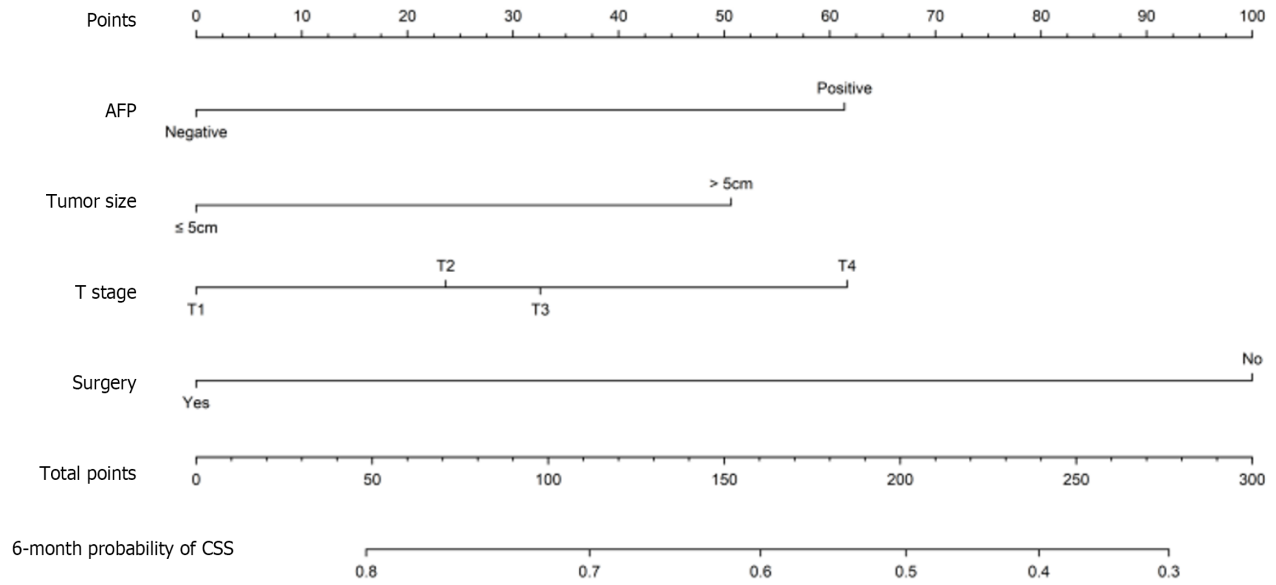
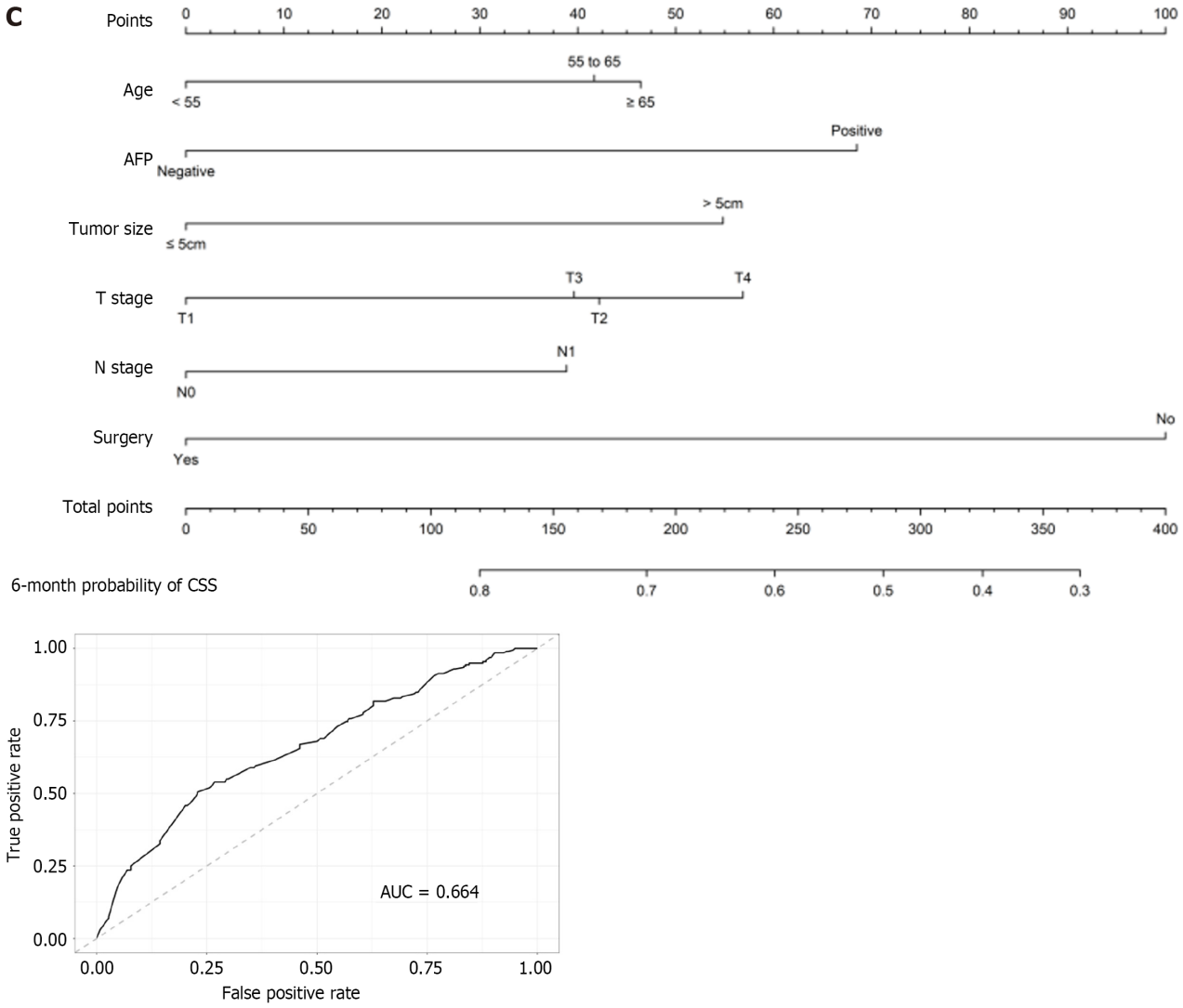
0.75
0.50
0.25
0.00
AUC = 0.659
0.00 0.25 0.50 0.75 1.00
False positive rate
B
True positive rate
1.00
0.75
0.50
0.25
0.00
AUC = 0.663
0.00 0.25 0.50 0.75 1.00
False positive rate


Points
0 10 20 30 40 50 60 70 80 90 100
AFP
Positive
Negative
Tumor size
> 5cm
≤ 5cm
T stage
T2
T4
T1
T3
Surgery
No
Yes
Total points
0 50 100 150 200 250 300
6-month probability of CSS
0.8 0.7 0.6 0.5 0.4 0.3



DOI: 10.4251/wjgo.v15.i11.1874 **Copyright** ©The Author(s) 2023.

Figure 4 Nomograms and receiver operating characteristic curves for 6-mo conditional cancer-specific survival among patients having survived. A: 2 mo; B: 4 mo; C: 6 mo. CSS: Cancer specific survival; AFP: α-fetoprotein; AUC: Area under the curve.

Nomograms are useful tools combining tumor-related risk factors to estimate and predict the survival rate of different patients[36]. We constructed nomograms for 6-month CS at 2, 4 and 6 mo after initial diagnosis. These nomograms may help to predict dynamic survival for distant metastatic HCC survivors with greater accuracy. As risk indicators for survival kept changing as time passed, the features fitted in the nomograms also changed. AFP expression, tumor size, and primary-site surgery were included in all the nomograms, which was consistent with previous nomogram studies on HCC[37,38]. The value of AUC gradually decreased in nomograms for conditional OS, while the value of AUC showed a gradual and slight increase in models for conditional CSS. This may be explained by the fact that as time passes, the increased death rate for other causes led to a diminished effect of these clinicopathological factors on OS, but they kept their influence on CSS. These nomograms may help assess patients' survival rates at different times. They can be used to remind clinicians and family members that more continued surveillance and care should be given to patients with lower CS rates. Furthermore, if patients have survived for a certain number of months, they may have a better prognosis, and the therapeutic goals and strategies can be more positive for them.

There were several limitations to our study. First, the research was a retrospective analysis with higher selection biases. Second, there was a lack of important features such as liver function, carcinoembryonic antigen, and vascular invasion that were not available in the SEER database, especially liver function, which was significant in the survival of HCC patients. Due to incomplete data, grade and fibrosis score were also not included in the analysis, which limited the ability of the nomogram to assess relevant survival. Third, the SEER database provided disease information at initial diagnosis, and so the metastasis events that occurred in the later survival time could not be recorded. We used data on HCC patients who were diagnosed from 2010 to 2015, and the treatment may have improved in the years since; for example, the occurrence of combination therapy, which includes immunotherapy and molecular targeted therapy, limited the use of our CS nomograms on these patients. For example, as the first small oral molecular targeted medicine, sorafenib successfully prolonged the OS of advanced HCC patients, and the novel programmed cell death 1 checkpoint inhibitor nivolumab could be used for patients who have disease progression or unacceptable adverse effects with sorafenib[39,

Table 3 Six-month conditional overall survival rates of patients with distant-metastatic hepatocellular carcinoma

Characteristics	Overall survival (months after diagnosis)							
	0	*d*	2	*d*	4	*d*	6	*d*
Overall	32.79		41.05		47.48		53.31	
Age, yr								
< 55	30.69		42.39		59.26		64.45	
55-65	33.86	0.07	39.96	-0.05	44.03	-0.30	45.78	-0.37
≥ 65	32.64	0.04	41.65	-0.02	49.58	-0.19	56.99	-0.15
Gender								
Female	34.64		43.92		52.4		55.63	
Male	32.38	-0.05	40.42	-0.07	46.37	-0.12	52.75	-0.06
Race								
Black	33.03		41.07		48.04		51.95	
White	34.35	0.03	42.77	0.03	48.1	0.001	54.56	0.05
Other	27.17	-0.12	34.55	-0.13	44.34	-0.07	49.06	-0.06
Marital status								
Married	32.59		40.58		46.51		54.99	
Single	32.99	0.01	42.24	0.03	51.3	0.10	52.08	-0.06
Separated	32.96	0.01	40.71	0.00	45.57	-0.02	51.27	-0.07
AFP expression								
Positive	30.77		38.99		44.09		49.63	
Negative	43.69	0.28	50.46	0.23	62.1	0.36	67.32	0.35
Tumor size								
≤ 5 cm	38.43		50.31		62.75		60.63	
> 5 cm	30.67	-0.17	37.48	-0.26	39.59	-0.46	49.85	-0.22
T stage								
T1	39.82		49.18		56.84		60.72	
T2	36.94	-0.06	49.78	0.01	57	0.003	55.68	-0.10
T3	28.86	-0.23	34.84	-0.29	41.77	-0.30	49.69	-0.22
T4	31.63	-0.17	40.2	-0.18	33.72	-0.46	46.16	-0.29
N stage								
N0	34.58		43.29		50.08		57.11	
N1	28.87	-0.12	35.65	-0.16	40.76	-0.19	43.26	-0.28
Surgery								
No	30.65		38.31		44.61		50.83	
Yes	69.51	0.83	73.97	0.73	74.6	0.60	71.93	0.42
Chemotherapy								
No/unknown	21.54		35.16		46.49		52.55	
Yes	42.34	0.44	44.13	0.18	47.92	0.03	53.61	0.02
Radiotherapy								
No/unknown	28.85		38.14		45.8		53	
Yes	48.42	0.42	49.72	0.24	50	0.08	54.05	0.02
Lung metastasis								

No	38.7		44.51		48.12		51.58	
Yes	22.59	-0.34	33.02	-0.23	45.71	-0.05	58.48	0.14
Bone metastasis								
No	31.33		39.55		46.72		53.91	
Yes	36.41	0.11	44.54	0.10	49.19	0.05	51.94	-0.04
Brain metastasis								
No	32.85		41.08		47.44		53.15	
Yes	29.63	-0.07	38.89	-0.04	50	0.05	62.5	0.19

0, 2, 4, 6 refer to the months that patients have survived since initial diagnosis. AFP: α-fetoprotein; d: Standardized differences.

40]. These are important factors that should be taken into consideration in the predictive model. We used the 7th edition of the AJCC staging system for HCC as the most up-to-date AJCC staging system for these patients was inaccessible. The Barcelona Clinic Liver Cancer classifications for HCC was also not present in our study. Finally, although the constructed nomograms were internally validated, they also need external validation.

CONCLUSION

Positive AFP expression, higher T stage (T3 and T4), N1 stage, non-primary-site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis were independent risk factors for actual OS and CSS through univariate and multivariate analysis. Actual survival rates decreased over time, while CS rates gradually increased. With dynamic risk factors, nomograms constructed at different time would provide more accurate CS.

Table 4 Six-month conditional cancer-specific survival rates of patients with distant-metastatic hepatocellular carcinoma

Characteristics	Cancer-specific survival (months after diagnosis)							
	0	*d*	2	*d*	4	*d*	6	*d*
Overall	34.77		42.48		48.6		55.11	
Age, yr								
< 55	32.05		43.36		53.19		66.41	
55-65	36	0.08	41.63	-0.04	45.44	-0.16	42.52	-0.48
≥ 65	34.79	0.06	43.05	-0.01	50.09	-0.06	56.97	-0.19
Gender								
Female	36.67		45.76		54.64		58.38	
Male	34.35	-0.05	41.77	-0.08	47.24	-0.15	54.33	-0.08
Race								
Black	36.22		43.24		49.22		55.84	
White	36.31	0.00	44.26	0.02	49.36	0.00	56.34	0.01
Other	28.31	-0.17	35.2	-0.16	44.84	-0.09	50.3	-0.11
Marital status								
Married	34.01		41.82		47.37		55.74	
Single	35.15	0.02	43.06	0.03	52.07	0.09	54.74	-0.02
Separated	36	0.04	43.25	0.03	47.46	0.00	54.23	-0.03
AFP expression								
Positive	32.75		44.94		45.3		51.21	
Negative	45.67	0.27	51.74	0.14	62.82	0.35	70	0.38

Tumor size								
≤ 5 cm	40.79		51.88		64.07		62.94	
> 5 cm	32.51	-0.17	38.86	-0.26	42.46	-0.43	51.42	-0.23
T stage								
T1	41.66		50.32		57.88		62.8	
T2	40.4	-0.03	51.47	0.02	59.43	0.03	57.77	-0.10
T3	30.68	-0.23	36.49	-0.28	42.85	-0.30	51.69	-0.22
T4	32.82	-0.19	40.66	-0.20	38.16	-0.39	46.15	-0.33
N stage								
N0	36.48		44.7		51.36		62.39	
N1	31.00	-0.12	37.11	-0.15	41.57	-0.20	44.53	-0.36
Surgery								
No	32.69		39.81		45.84		52.64	
Yes	69.51	0.77	73.97	0.69	74.6	0.58	73.6	0.42
Chemotherapy								
No/unknown	24.05		37.52		48.05		56.21	
Yes	43.68	0.41	45.05	0.15	48.87	0.02	54.64	-0.03
Radiotherapy								
No/unknown	30.92		39.7		47.66		55.55	
Yes	49.75	0.40	50.72	0.22	51	0.07	54.05	-0.03
Lung metastasis								
No	40.69		46.02		49.33		53.7	
Yes	24.4	-0.34	34.24	-0.24	46.61	-0.05	59.18	0.11
Bone metastasis								
No	33.52		41.03		48.1		55.99	
Yes	37.84	0.09	45.87	0.10	49.79	0.03	53.21	-0.06
Brain metastasis								
No	34.83		42.5		48.59		54.78	
Yes	31.91	-0.06	42.48	-0.0004	48.61	0.0004	64.46	0.19

0, 2, 4, 6 refer to the months that patients have survived since initial diagnosis. AFP: α-fetoprotein; d: Standardized differences.

ARTICLE HIGHLIGHTS

Research background

Distant metastatic hepatocellular carcinoma (HCC) patients have poor survival rates, while some of them who have survived for several months may have a better prognosis than the prediction at initial diagnosis. Conditional survival (CS) could provide patients with survival probabilities at a specific time since the prognosis would be adjusted for the time the patient had already survived.

Research motivation

In this study, we evaluated actual survival and CS of distant metastatic HCC patients.

Research objectives

This study aimed to evaluate the CS of distant metastatic HCC patients and construct nomograms to predict CS at different times.

Research methods

We used Cox regression analysis to identify risk factors for overall survival (OS) and the competing risk model to identify

risk factors for cancer-specific survival (CSS). Six-month CS was used to calculate the probability of survival for an additional 6 mo at a specific time after the initial diagnosis. We used standardized differences to evaluate the survival differences between subgroups. Nomograms were constructed to predict CS.

Research results

Using univariate and multivariate analysis, we found positive α-fetoprotein expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis to be independent risk factors for actual OS and CSS. We found that actual survival rates decreased over time, while CS rates gradually increased. The influence of chemotherapy and radiotherapy on survival gradually disappeared over time; the influence of age and gender on survival gradually appeared; and the influence of lung metastasis reversed. The area under the curve (AUC) of nomograms for conditional OS decreased as time passed, and the AUC for conditional CSS gradually increased.

Research conclusions

Actual survival rates decreased over time, while CS rates gradually increased. With dynamic risk factors, nomograms constructed at different time would provide more accurate CS.

Research perspectives

CS could be used to evaluate the dynamic survival rates for distant metastatic HCC patients.

FOOTNOTES

Author contributions: Shi J conceived and designed the study; Yang YP and Guo CJ collected the data, developed the analytic pipeline; Yang YP, Gu ZX, and Hua JJ led the analysis, generated the tables and figures, and wrote the manuscript; Yang YP, Guo CJ, and Zhang JX verified and processed the underlying data; and all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed by the Medical Ethics Committee of the Second Hospital of Jilin University; all our data comes from a public database (the SEER database) and needs no ethical approval.

Informed consent statement: As the study only involved retrospective chart reviews, informed written consents were not required in accordance with institutional IRB policy.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All of the data used in this study were downloaded from a public database (the SEER database).

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