Prognostic nomogram for hepatocellular carcinoma with fibrosis of varying degrees

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Abstract

Background To investigate prognostic value of varying degrees of liver fibrosis in hepatocellular carcinoma (HCC) patients and establish an effective prognostic nomogram. Methods Eligible HCC patients with different degrees of fibrosis between 2004 and 2015 were matched from the Surveillance, Epidemiology, and End Results (SEER) database using propensity score matching (PSM). Prognostic value was evaluated using Kaplan-Meier and Cox hazard analysis. The nomogram on variables selected by multivariate analyses was established and subjected to internal validation. The predictive accuracy of nomograms was tested by concordance index (C-index) and calibration. Results HCC patients with advanced fibrosis/ cirrhosis was correlated with poor survival than those with none/moderate fibrosis in all patients [HR: 1.111, 95%CI (1.042-1.185); p=0.001] and in the PSM cohort [HR: 1.131, 95%CI (1.032-1.240); p=0.009]. Multivariate analysis of propensity-matched cohort revealed that age more than 63, higher fibrosis score, AJCC stage T3-4, distant metastasis (M1), Tumor size ≥1, vascular invasion and elevated AFP level were independent factors. The nomogram integrating these factors offers an effective prognostic prediction for HCC patients (C-index 0.749, 95%CI: 0.735~0.763) relative to AJCC 7th edition (0.727) and TNM (0.73). The calibration plots suggested optimal agreement between nomogram prediction and actual observation. Conclusions Increased fibrosis was an independent risk factor for HCC survival. The prognostic nomogram integrating fibrosis score offers a more accurate prediction.

Background

Hepatocellular carcinoma (HCC) ranks the fifth most common cancer, with up to 10% of cancer-related mortality worldwide and 70% -100% of cumulative risk of recurrence within 5 years after surgery [1-3]. The majority (70%-90%) of HCCs arises with advanced fibrosis and cirrhosis as a consequence of various etiologies [4]. Liver fibrosis is a protective wound healing response to chronic liver damage and becomes fibrous scar and cirrhosis when injury persists [5]. Often leading to hepatic dysfunction, fibrosis and cirrhosis was considered as a premalignant state that increased the HCC risk and development [6]. However, the effect of different fibrosis severities for liver fibrosis on HCC prognosis remains controversial.

Currently, there are two surgical staging systems, namely the Tumor-Node-Metastasis (TNM) from the Liver Cancer Study Group of Japan (LCSGJ) and the American Joint Committee on Cancer (AJCC) staging system. The 7^{th} edition of AJCC staging system adopting TNM classification is a commonly used staging systems and maintains the prognostic power for HCC patients [7]. Unfortunately, its application is not completely satisfactory for individual patients, especially for patients with advanced HCC [8]. One possible explanation for this imperfection lies in its failure to incorporate some other important characteristics such as age and sex in survival prediction. Nomogram is an effective and convenient statistical tool for prognostic prediction by combining all these factors and it has been developed in a variety of cancer types [9-11].

Through this SEER analysis, we aimed to evaluate the effect of different fibrosis degrees on HCC prognosis and to establish for the first time a prognostic nomogram integrating fibrosis score and other independent variables to predict HCC survival. Our model will provide precise prognostic information for clinicians in clinical practice.

Methods

Patients selection and Data extraction

We performed a retrospective cohort analysis by querying the SEER database (https://seer.cancer.gov/) for patients diagnosed with HCC [International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology codes 8170-8175 for HCC and site code C22.0 for liver] between 2004 and 2015.

HCC patients younger than 18 years, those whose survival time and fibrosis score were unavailable, patients with the same ID number, patients diagnosed before 2004, patients with no evidence of primary cancer were excluded. Fibrosis score, also called Ishak score, was classified as F0-4 [code 0, fibrosis scores 0-4 (none to moderate fibrosis)] and F5-6 [code 1, fibrosis scores 5-6 (severe fibrosis or cirrhosis)]. We compared patients with none to moderate fibrosis (F0-4) to patients with severe fibrosis or cirrhosis (F5-6). AFP level was described using code10 (positive/elevated), code 20 (Negative/normal; within normal limits) and others. Considering in only sparse number of included patients whose tumor size were more than 3 or 5 cm, we described tumor size as less than 1cm (code 0-991), greater than 1cm (code 992-996) or other. We classified vascular invasion as absent, minor invasion (code200/350/370/380/400/520/550), major invasion (code 630/635/660) and other.

Statistical analysis

As previously described [12], 1:1 propensity score matching (PSM) analysis was carried out to minimize the selection bias and balance the baseline covariates between F0-4 and F5-6 group. After matching, covariate balance was tested and no covariates exhibiting a large imbalance indicated the adequacy of the constructed propensity score. Statistical analysis from SEER database was performed using SPSS 19.0 software. Continuous variables were presented as mean ± standard deviation (SD) and was analyzed using unpaired t test. Chi-square or Fisher's exact test was used to compare categorical variables. Survival curves were generated by Kaplan–Meier method (log-rank test). Significant factors affecting survival in univariable analysis were further determined by multivariable Cox regression analysis. The prognostic nomogram based on variables of multivariate analyses was established using the rms package in R project. The predictive accuracy and discriminative ability were determined by using concordance index (C-index) and calibration curve. A threshold of $P < 0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics

According to the eligibility criteria, a total of 8119 patients diagnosed with HCC between 2004 and 2015 were identified from the SEER database. Of these, 2295 patients were in F0-4 group and 5824 patients were in F5-6 group (Figure 1). Patients with advanced fibrosis and cirrhosis were more frequently categorized as younger (61.76±9.54, p=0.000) and male (p=0.027) patients, in AJCC T1-T2 stage (p 0.0001), had no lymph node metastasis (p=0.0065), had no distant metastasis (p=0.0002), had positive AFP level (p 0.0001). In contrast, patients with none/ moderate fibrosis were more frequently classified as older and female patients, in AJCC stage T3-T4, with negative AFP level. Since the comparison of different degrees of liver fibrosis is subject to possible confounding induced by differences in baseline characteristics, we performed PSM to generate 1:1 pairs of patients. The matched groups consisted of 1660 F0-4 and 1563 F5-6 patients diagnosed with HCC (Figure 1). The covariates between the two groups were well-balanced and showed no significant differences at baseline (p 0.05 for all; Table 1 and figure 2A, 2B).

Increased fibrosis progression correlated with poor prognosis of HCC patients

In entire cohort of patients, the overall survival (OS) rate was significantly higher in patients of F0-4 group than those in F5-6 group (1-, 3-, 5-year cumulative OS rates were 65.8%, 44.5% and 33.9% *vs* 62.3%, 41.2% and 32.0%, respectively). Patients with advanced fibrosis/cirrhosis showed unfavorable prognosis (p=0.029) (figure 2C). The median overall survival (OS) time was longer in patients of F0-4 group than that of F5-6 group (27 versus 23 months) (Table 2). After one-to-one PSM, the 1-, 3-, 5-year cumulative OS rates were 70.6%, 49.6 and 37.6% in F0-4 group and 65.8%, 47.7% and 34. 7% in F5-6 group, respectively. The median OS time was again longer in patients of F0-4 group than that of F5-6 group (36 versus 28 months). Patients with advanced fibrosis/cirrhosis also showed unfavorable prognosis (p=0.028) (figure 2D). In univariate analysis of all matched patients, age (p=0.000), sex (p=0.008), primary tumor (p=0.000), lymph node metastasis (p=0.000), distant metastasis (p=0.000), vascular invasion (p=0.000), AFP level (p=0.000), fibrosis score (p=0.028) and tumor size (p=0.000) were closely associated with OS (Table 2). The multivariate Cox proportional hazards analysis for those factors showing significance by univariate analysis showed that advanced fibrosis/ cirrhosis (HR:1.131, 95%CI: 1.032-1.240, p=0.009), age more than 63 (HR: 1.365, p=0.000), AJCC stage T3-4 (HR: 1.810, p=0.000), distant metastasis (M1) (HR: 3.460, p=0.000), tumor size ≥1cm (HR: 2.536, p=0.000), minor vascular invasion (HR: 1.202, p=0.05), major vascular invasion (HR: 2.321, p=0.000) as well as elevated AFP level (HR: 1.511, p=0.000) were independent risk factors for increased mortality rate (Table 3).

Predictors of survival among advanced fibrosis/cirrhosis patients

Using multivariate analysis, predictors of survival among advanced fibrosis/cirrhosis patients were performed. As shown in Table 4, advanced fibrosis/cirrhosis patients whose age older than 63-year old demonstrated worse survival (HR: 1.480, 95%CI: 1.297-1.689, p=0.000). In advanced fibrosis/cirrhosis patients, AJCC stage T3-4 (HR: 1.900, 95%CI: 1.477~2.444, p=0.000), distant metastasis (M1) (HR: 3.270, 95%CI: 2.297-4.655, p=0.000), Tumor size ≥1cm (HR: 2.809, 95%CI: 2.152~3.668, p=0.000) and major vascular invasion (HR: 2.457, 95%CI: 1.819-3.319, p=0.000) were associated with worse survival. Negative

AFP HCC patients demonstrated better survival than positive patients (HR: 0.702, 95%CI: 0.594~0.831, p=0.000).

Prognostic Nomogram construction and validation

The prognostic nomogram integrated all significant independent factors for survival in multivariate analyses (Figure 3A). The C-index for survival prediction was 0.749 (95%CI: 0.735~0.763). In addition, the calibration plot for the probability of survival at 1, 3 and 5 year presented an optimal agreement between the prediction by nomogram and actual observation (Figure 3B). Thirty percent of all cohort was randomly generated by R software to make internal validation. The C-index of internal validation of the nomogram was 0.761 (95%CI 0.736~0.786), calibration curves also showed good agreement between prediction and observation in 1-, 3- and 5-year OS (Figure 3C). These results indicated the nomogram that integrated fibrosis score with other factors of age, AJCC T stage, distant metastasis, tumor size, vascular invasion and AFP level was reliable for survival prediction of HCC patients.

Comparison between nomogram and single independent factors/ conventional staging systems

The larger of the C-index represented a more accurate the predictive model. The C-index of the prognostic nomogram was larger than the AJCC 7th edition, the AJCC TNM staging system, and single independent factors. For the nomogram of primary cohort, the C-index for survival prediction was 0.749 (95%CI: 0.735~0.763), which was higher than AJCC 7th edition (C-index 0.727), AJCC TNM stage (C-index 0.73), tumor size (C-index 0.506), vascular invasion (C-index 0.509), AFP (C-index 0.55), and age (C-index 0.536) (p□0.05). For internal validation of the nomogram, the C-index was 0.761 (95%CI 0.736~0.786), which was also higher than AJCC 7th edition (C-index 0.732), AJCC TNM stage (C-index 0.742), tumor size (C-index 0.502), vascular invasion (C-index 0.520), AFP (C-index 0.539), and age (C-index 0.534) (p□0.05). Taken together, these results suggest that the nomogram was useful and reliable predicting model for survival of patients with HCC relative to the AJCC 7th edition and AJCC TNM stage system.

Discussion

In this study, we demonstrated that advanced fibrosis/ cirrhosis was independently associated with HCC survival and for the first time established and internally validated a fibrosis score-based nomogram for HCC survival prediction. This prognostic model integrating fibrosis score was reliable, robust and practical for HCC patients.

HCC is closely associated with liver fibrosis and its end-stage, cirrhosis, with about 80–90% of HCC patients having underlying fibrosis and approximately one in three cases with liver cirrhosis will develop HCC in their lifetime. The incidence rate of HCC within 5 years in patients with advanced liver fibrosis/ cirrhosis ranges from 5% to 30% [6, 13]. However, the impact of fibrosis score on survival outcome in HCC has yet been reached [14-17]. Therefore, a better understanding of the role of fibrosis score in HCC prognosis and a nomogram constructed to include fibrosis score may provide more-accurate prognostic prediction for HCC patients.

Fibrosis score is also called Ishak score. AJCC classifies fibrosis scores as none to moderate fibrosis and severe fibrosis or cirrhosis. To eliminate selection bias, we categorized the entire study population into groups with different degrees of fibrosis (none/ moderate fibrosis and advanced fibrosis/ cirrhosis) using the propensity score analyses. No significant difference in factors of age, sex, AJCC TNM stage, AFP level, tumor size and vascular invasion indicated the patients of both groups was well-balanced. Previously, Noda et al found no significantly association between liver fibrosis and OS of HCC patients (p=0.1185) [18]. Also, Suh et al found no significant difference in OS between mild and severe fibrosis (P = 0.267) [14]. However, our results revealed that advanced fibrosis/ cirrhosis provided worse survival than none/ moderate fibrosis. In addition, severe fibrosis/ cirrhosis was an independent risk factor for OS. This finding was consistent with a recent meta-analysis by Zhang et al and the study by Toyoda et al [19, 20]. The discrepancies may be partly attributed to the different criteria of enrolling patients. Noda et al evaluated the effect of different degrees of fibrosis on the prognosis of non-viral HCC patients [18]. Suh et al investigated the influence of liver fibrosis on prognosis only for HCC with Child-Pugh grade A and a single HCC <5 cm [14]. Appropriately 70% HCC patients were afflicted with hepatitis virus infection [6]. Child-Pugh class B and HCV positivity were also associated with the poor prognosis of HCC [21]. Our study synthetically explored the relationship between fibrosis score and clinical prognosis of HCC.

In the multivariate analyses, besides fibrosis score, age more than 63, AJCC stage T3-4, distant metastasis (M1), tumor size ≥1cm, minor and major vascular invasion, and elevated AFP level were identified as independent predictors for poor prognosis of HCC, which was in agreements with previous studies [8, 22-25]. Consistency with previous studies [25, 26], sex and lymph node metastasis failed to stratify survival in our study. In addition, we used multivariate analysis to identify predictors of survival among advanced fibrosis/cirrhosis patients and the results showed that advanced fibrosis/cirrhosis patients whose age older than 63-year old demonstrated worse survival. In advanced fibrosis/cirrhosis patients, AJCC stage T3-4, distant metastasis (M1), Tumor size ≥1cm, major vascular invasion and positive AFP level were associated with worse survival. Subsequently, we developed a nomogram that incorporated the predictors to predict the patients' survival. The C-index of our nomogram and internally validated nomogram was 0.749 and 0.761, which was higher than AJCC 7^{th} edition (entire cohort: 0.727, validation cohort: 0.732) and AJCC TNM staging system (entire cohort: 0.730, validation cohort: 0.742). The calibration plot for the 1-, 3-, or 5-year probability of survival showed an optimal agreement between the prediction by the nomogram and actual observation in both the entire cohort and validation cohort.

Our study has several limitations that may affect the results to some extent. Firstly, the nomogram was constructed based on data from the SEER databases, which lacked the record of HCC etiology (e.g. viral status), liver function index, Child-Pugh class or severity of portal hypertension and performance status. Therefore, the predictive accuracy of our nomogram failed to be compared with Barcelona Clinic Liver Cancer (BCLC) scoring system [27]. Secondly, large amount of data was unclear. This represented a strong limitation to conclusion on survival and the established nomogram. Thirdly, it is well-known that HBV suppression with nucleos(t)ide analogues and HCV eradication with direct-acting antivirals (DAAs) or with pegylated interferon have a significant impact on hepatic decompensation and ultimately on survival of patients with HCC. For the same reasons, another critical point is the lack of data on HCC

treatment received by patients, that could significantly affect survival. Fourthly, although PSM was applied to minimize the potential bias, the retrospective nature of this study made it hard to avoid other biases caused by some confounding factors. A further validation from prospective or randomized control trials were required. Finally, this analysis was performed based on a database and validated internally. Therefore, externally validations with more patients from other institutions or study groups were warranted.

Conclusions

Our study proposed that HCC patients with advanced fibrosis/cirrhosis had a poor outcome than those with lower degrees of fibrosis. We established a reliable and superior nomogram based on fibrosis score and other independent risk factors to predict the prognosis of patients with HCC.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Abbreviations

HCC, Hepatocellular carcinoma; AJCC, American Joint Committee on Cancer; DCA, decision curve analysis; OS, overall survival; TNM, Tumor-Node-Metastasis; LCSGJ, the Liver Cancer Study Group of Japan; C-index, concordance index; BCLC, Barcelona Clinic Liver Cancer.

Author's contributions

SYC conceived and designed the study. RZ, JC, YYJ and JW performed the statistical analysis. RZ and SYC analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declared no conflict of interests.

Availability of data and materials

The datasets generated during the current study are publicly archived from SEER database (https://seer.cancer.gov/) and are available from the corresponding author on reasonable request.

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Tables

Table 1 The baseline characteristics of HCC patients with different fibrosis scores after PSM.

riable	Before PSM			After PSM		
	F0-4 (n=2295)	F5-6 (n=5824)	P value	F0-4 (n=1660)	F5-6 (n=1563)	P value
an age (SD)	63.84±12.13	61.76±9.54	0.000	63.54±9.62	63.43±9.24	0.248
:, n						
le	1742	4555	0.027	1320	1254	0.614
nale	553	1269		340	309	
:C T, 7th ed, n						
T2	922	2707	< 0.0001	729	705	0.755
T4	361	762		201	180	
known	1012	2355		730	678	
:C N, 7th ed, n						
	1211	3283	0.0065	909	869	0.721
	72	197		19	14	
known	1012	2344		732	680	
:C M, 7th ed, n						
	1175	3250	0.0002	890	844	0.950
	143	387		47	46	
known	977	2187		723	673	
P, n						
sitive/elevated	1217	3531	< 0.0001	958	911	0.749
gative	648	1411		432	413	
:lear	430	882		270	239	
nor size, n						
:m	2091	5262	0.3470	1583	1492	0.896
m	7	12		0	0	
:lear	197	550		77	71	
scular invasion, n						
sent	920	2219	< 0.0001	761	713	0.909
nor invasion	284	399		138	120	
jor invasion (code)/635/660)	185	475		91	87	
known	906	2731		670	643	

AFP, Alpha Fetoprotein; AJCC, American Joint Committee on Cancer; PSM, propensity score matching.

Table 2 Univariate analysis of prognostic factors associated with overall survival (OS) after propensity score matching

Variable	Before PSM			After PSM		
	All patients	Survival time (months) median (95%CI)	P value	All patients	Survival time (months) median (95%CI)	P value
Group, n						
F0-4	2295	27(23.999-30.001)	0.029	1660	36(32.191-39.809)	0.028
F5-6	5824	23(21.465-24.535)		1563	28(24.265-31.735)	
Age, n						
≤63	4695	30(27.516-32.484)	0.000	1692	40(35.293-44.707)	0.000
63	3424	20(18.51-21.49)		1531	25(22.395-27.605)	
Sex, n						
Male	6297	24(22.491-25.509)	0.025	2574	30(26.955-33.045)	0.008
Female	1822	27(23.862-30.138)		649	37(29.635-44.365)	
AJCC T, 7th ed, n						
T1-T2	3629	44(39.689-48.311)	0.000	1434	56	0.000
T3-T4	1123	7(6.046-7.954)		381	9(7.077-10.923)	
Unclear	3367	19(17.365-20.635)		1408	22(19.305-24.695)	
AJCC N, 7th ed, n						
N0	4494	32(29.665-34.335)	0.000	1778	42(37.736-46.264)	0.000
N1	269	4(3.095-4.905)		33	4(1.908-6.092)	
Unclear	3356	20(18.367-21.633)		1412	22(19.307-24.693)	
AJCC M, 7th ed, n						
M0	4425	33(30.567-35.433)	0.000	1734	42(37.38-46.62)	0.000
M1	530	3(2.494-3.506)		93	4(3.191-4.809)	
Unclear	3164	21(19.190-22.81)		1396	23(20.243-25.757)	
Vascular invasion, n						
Absent	3139	52(47.312-56.688)	0.000	1474	59(49.969-68.031)	0.000
Minor	683	30(25.482-34.518)		258	36(24.221-47.779)	
Major	660	4(3.281-4.719)		178	7(4.961-9.039)	
Unclear	3637	17(15.722-18.278)		1313	17(14.85-19.15)	
AFP, n						
Positive/elevated	4748	19(17.785-20.215)	0.000	1869	23(20.536-25.464)	0.000
Negative	2059	47(41.161-52.839)		845	57(48.156-65.844)	
Unclear	1312	21(17.714-24.286)		509	25(19.72-30.28)	
Tumor size, n						
≤1cm	7353	30(28.238-31.762)	0.000	3075	35(32.288-37.712)	0.000
1cm	19	13(0-27.348)		0	-	
Unclear	747	2(1.568-2.432)		148	2(1.069-2.931)	

AFP, Alpha Fetoprotein; AJCC, American Joint Committee on Cancer; OS, overall survival; PSM, propensity score matching.

Table 3 Multivariate analysis of factors predictive of patients' overall survival after propensity score matching.

Variable	Before PSM		After PSM	
	HR (95%CI)	p Value	HR (95%CI)	p Value
Group F5-6 (versus F0-4)	1.111(1.042-1.185)	0.001	1.131 (1.032-1.240)	0.009
Age（63）versus ≤63）	1.447(1.366-1.533)	0.000	1.365(1.243-1.498)	0.000
Sex Female (versus male)	0.917(0.856-0.983)	0.014		
AJCC T, 7th ed, n (%)	1.683(1.517~1.867)	0.000	1.810(1.517~2.159)	0.000
T3-4 (versus T1-2)				
AJCC N, 7th ed, n (%)	1.364(1.168-1.594)	0.000		
N1 (versus N0)				
AJCC M, 7th ed	2.328(2.068-2.621)	0.000	3.460(2.705-4.424)	0.000
M1(versus M0)				
Tumor size ≥1cm	1.417(0.837~2.399)	0.194	2.536(2.096~3.068)	0.000
(versus <1cm)				
Vascular invasion Minor	1.267(1.132-1.418)	0.000	1.202(1.000-1.445)	0.050
(versus none)				
Vascular invasion Major	2.401(2.134-2.701)	0.000	2.321(1.885-2.857)	0.000
(versus none)				
AFP Negative (versus Positive/elevated)	0.670(0.622~0.721)	0.000	0.662(0.587-0.746)	0.000

AFP, Alpha Fetoprotein; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

Table 4 Multivariate analysis of factors predictive of patients' overall survival in advanced fibrosis/ cirrhosis HCC group.

Variable	HR (95%CI)	p Value
Age 63versus ≤ 63	1.480(1.297-1.689)	0.000
Derived AJCC T, 7th ed, n (%)	1.900(1.477~2.444)	0.000
T3-4 (versus T1-2)		
Derived AJCC M, 7th ed	3.270(2.297-4.655)	0.000
M1(versus M0)		
Tumor size ≥1cm	2.809(2.152~3.668)	0.000
(versus 1cm)		
Vascular invasion Minor	1.200(0.918-1.569)	0.181
(versus none)		
Vascular invasion Major	2.457(1.819-3.319)	0.000
(versus none)		
AFP Negative (versus Positive/elevated)	0.702(0.594~0.831)	0.000

AFP, Alpha Fetoprotein; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval.

Figures

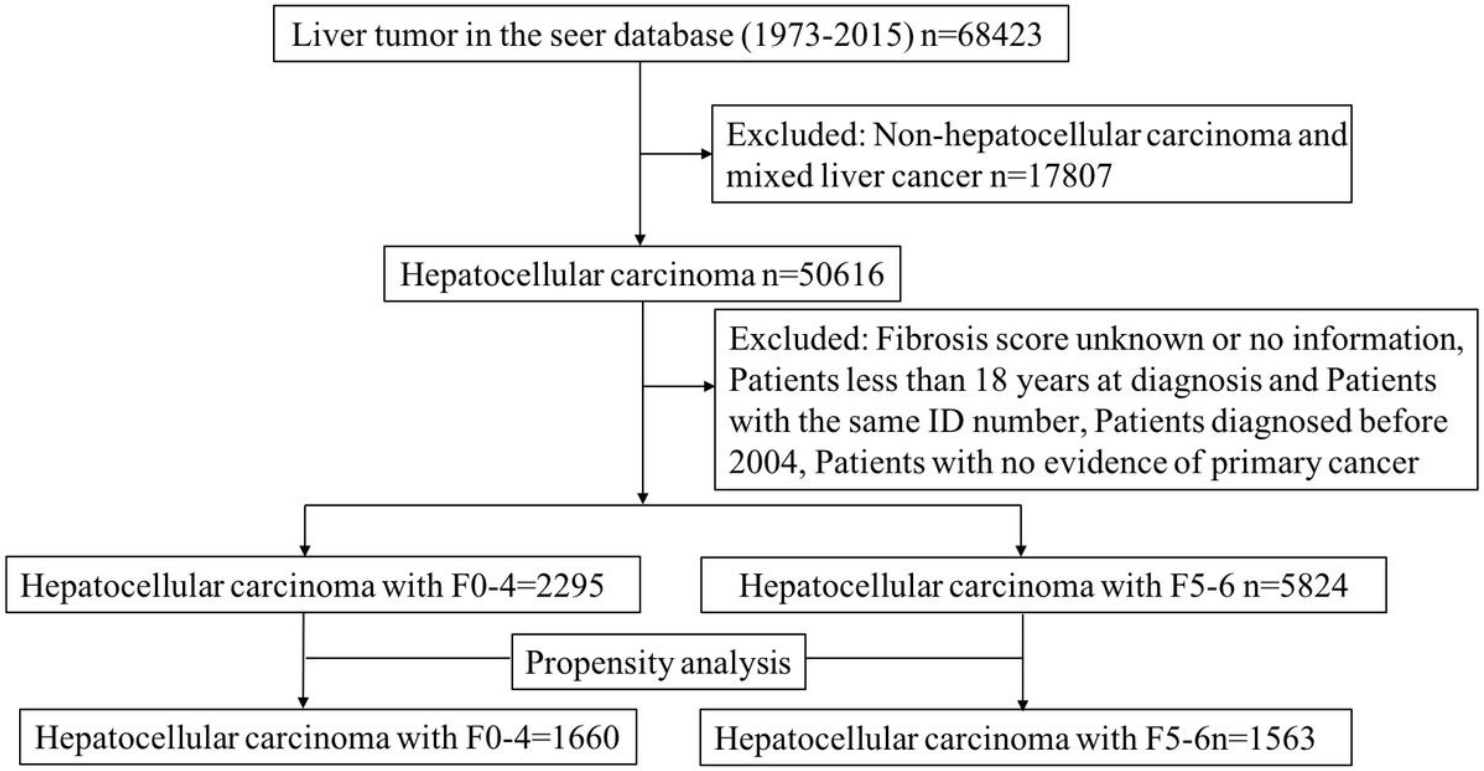

Figure 1

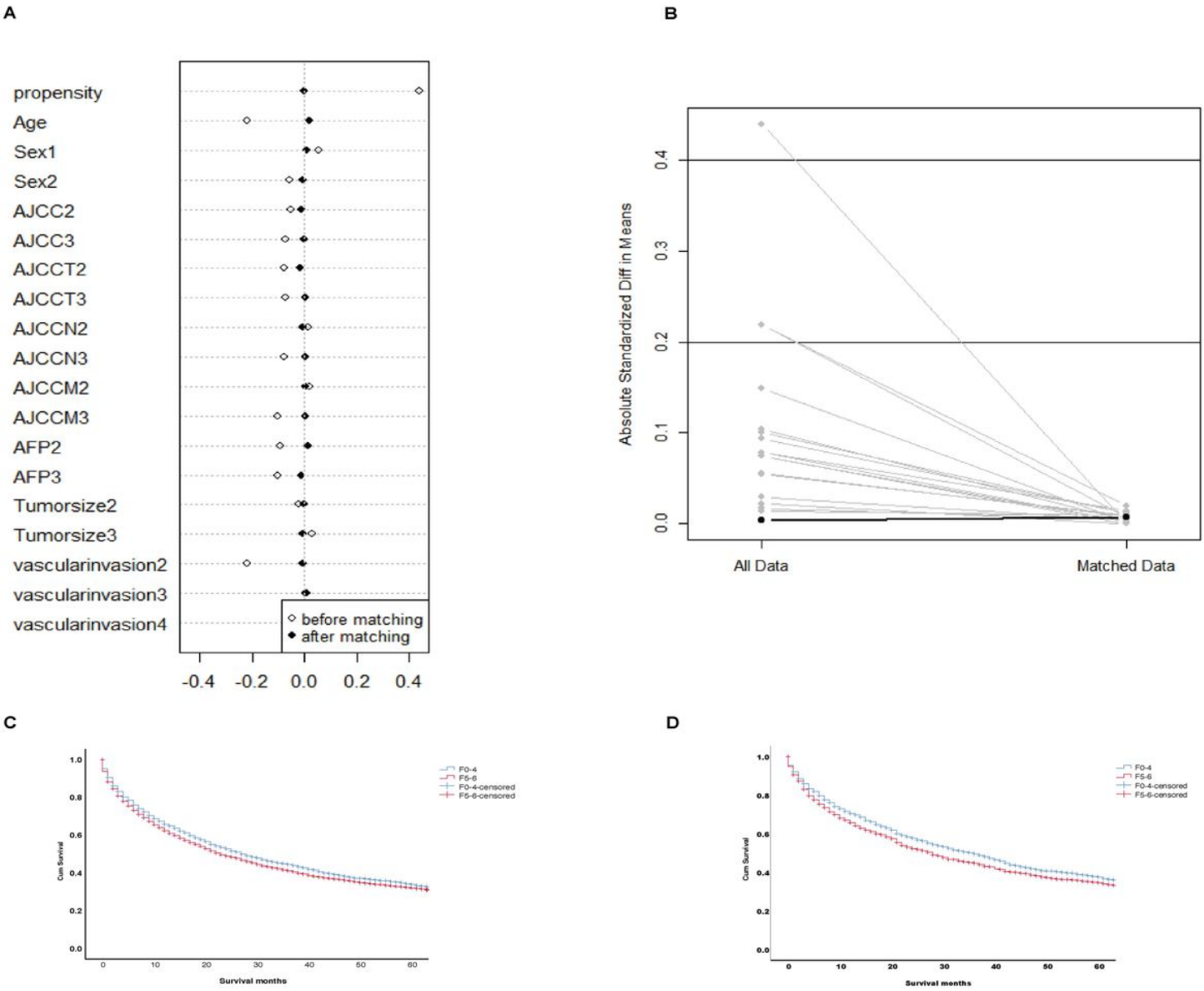
A
propensity
Age
Sex1
Sex2
AJCC2
AJCC3
AJCCT2
AJCCT3
AJCCN2
AJCCN3
AJCCM2
AJCCM3
AFP2
AFP3
Tumorsize2
Tumorsize3
vascularinvasion2
vascularinvasion3
vascularinvasion4
before matching
after matching
-0.4 -0.2 0.0 0.2 0.4
B
Absolute Standardized Diff in Means
0.0 0.1 0.2 0.3 0.4
All Data
Matched Data
C
F0-4
F5-6
F0-4-censored
F5-6-censored
Cum Survival
Survival months
D
F0-4
F5-6
F0-4-censored
F5-6-censored
Cum Survival
Survival months

Figure 2

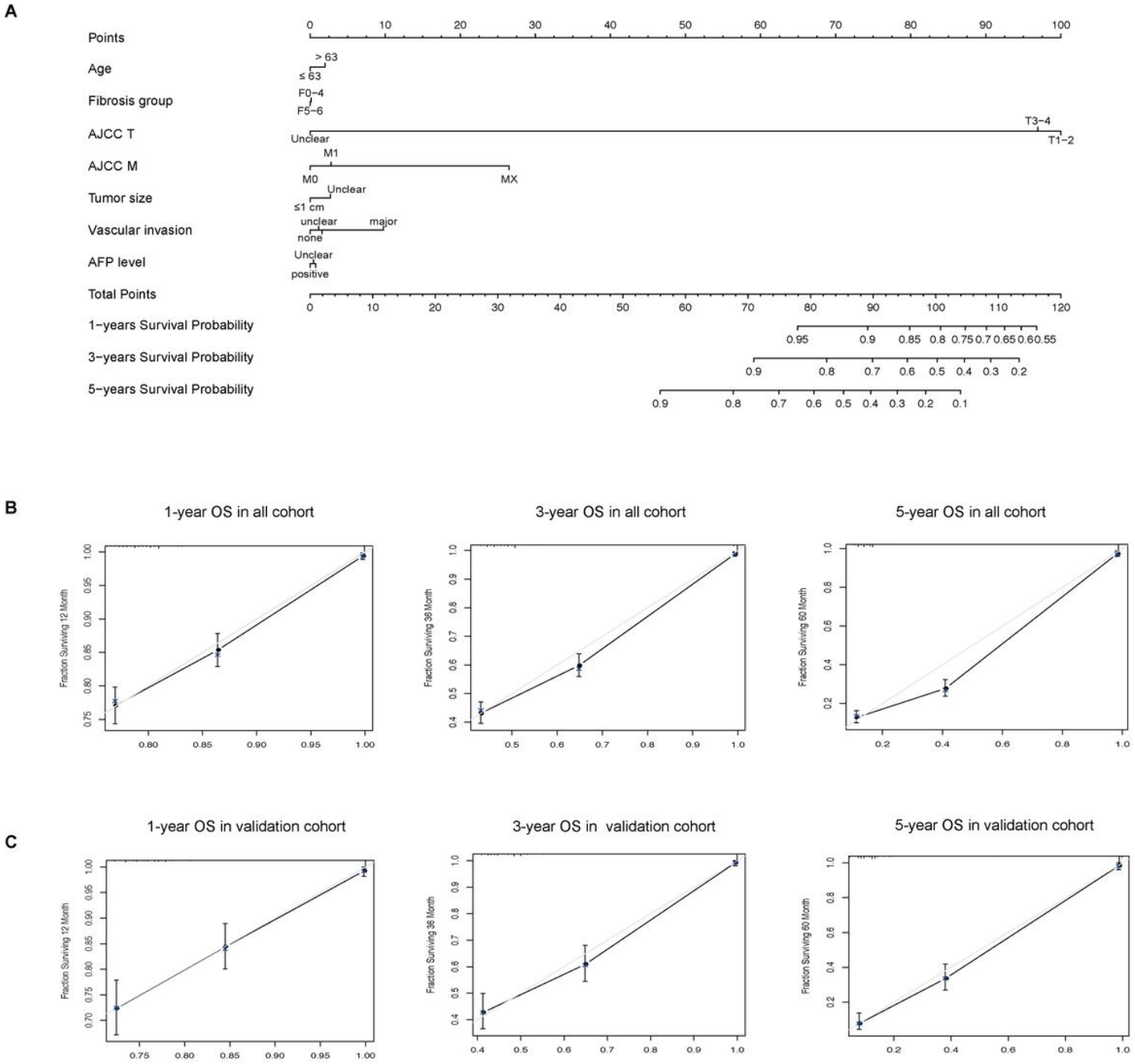
A
Points
Age
Fibrosis group
AJCC T
AJCC M
Tumor size
Vascular invasion
AFP level
Total Points
1−years Survival Probability
3−years Survival Probability
5−years Survival Probability
> 63
≤ 63
F0−4
F5−6
Unclear
T3−4
T1−2
M1
M0
MX
Unclear
≤1 cm
unclear
major
none
Unclear
positive
B
1-year OS in all cohort
3-year OS in all cohort
5-year OS in all cohort
C
1-year OS in validation cohort
3-year OS in validation cohort
5-year OS in validation cohort

Figure 3