Tumor burden with AFP improves survival prediction for TACE-treated patients with HCC: An international observational study

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Table of contents

Methods

Detailed primary investigators and number of eligible patients were summarized in **Table S1**, and **Fig. 1** showed the flow chart of this study.

Training dataset. This dataset comprised 1604 eligible cases after screening 3819 patients with HCC undergoing conventional TACE (cTACE) from 24 Chinese academic centres between January 2010 and May 2016. In contrast with the previous study, we used entire cohort to derive the model, not randomized splitting into training and validation cohort. The data of the training cohort have been published in Journal of Hepatology [1].

Internal validation dataset. A total of 3496 consecutive patients who underwent cTACE from another five centres (between January 2010 and December 2017, n=2386) and drug-eluting beads TACE (DEB-TACE) from seven centres (between January 2016 and June 2019, n=1110) were retrospectively screened. Parameters, including baseline demographics, tumor characteristics, laboratory testing and TACE procedures, were collected by two independent investigators using a previously reported method [1]. Finally, a total of 803 patients were enrolled to analysis. These data have never been published previously.

External validation dataset. Finally, as shown in Fig S1-C, European dataset consisted of 1,130 eligible and anonymous cases at 6 centers in two countries, the French cohort of 362 patients was consisted of three datasets from Marseille (252 patients), Nancy (72 patients), and Nice (38 patients); and the Germany cohort of 768 patients was consisted of three datasets from Mainz (113 patients), Hannover (242 patients) and Freiburg (413 patients). The Asian dataset was obtained from three centers with 840 eligible and anonymous cases (442 and 187 patients from SNUH and Yonsei, Korea; 211 patients from Songkla, Thailand). These datasets with the same parameters were collected by the primary investigators and their colleagues at each center, including age, sex, aetiology, previous treatment (yes/no), ECOG score, tumor characteristics (ts and tn), liver function (Child–Pugh score and albumin-bilirubin [ALBI] score), and laboratory tests (including AFP value; the international normalized ratio [INR]; levels of alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, total bilirubin, creatinine; white blood cell count (WBC), platelet count (PLT) level), and TACE procedures (DEB-TACE or cTACE, superselective or not, and total sessions of TACE). The French cohort of 362 patients from Marseille (252), Nancy (72), and Nice (38) have been published in the following journal: World journal of hepatology (World J Hepatol 2020 August 27; 12(8): 0-0)[2]; World Journal of Clinical Cases (World J Clin Cases 2021 June 26; 9(18): 4559-4572)[3]; European Journal of Gastroenterology and Hepatology (Eur J Gastroenterol Hepatol. 2019 Nov;31(11):1414-1423)[4]. Part

of Thailand cohort was published in Clinical Translational Gastroenterology (Clin Transl Gastroenterol. 2021 Feb 18;12(2): e00310) [5]. Part of Germany cohort was published in Fronters in Oncology (Front Oncol. 2022 Feb 23:12:850454.)[6].

Statistical analysis

Multiple imputation by chained equations (MICE) was used to impute missing outcome data after adjustment for all measured variables potentially associated with missing data. Our intention was to include all factors that could be associated with missingness. Pattern and percent of missing value were depicted in **Fig. S1**.

Table S2-S3 summarized correlation coefficient between these indicator variables with missing values, and correlation coefficient between variables with missing values and other observable variables, respectively. The correlation coefficient is not particularly large, indicating that the data is less likely to be pattern of Missing Completed at Random (MCAR) and more likely to be pattern of Missing at Random, which suggests a multiple imputation is needed. Then, we produced 5 datasets (C1-C5, Table S4) with imputed missing values and non-missing values consistent with the observed data using the MICE processes. Each of the 5 datasets were used to analyze the primary outcome. The estimated coefficients and standard errors from the 5 models were combined into a final estimated coefficient and standard error using robust methods. We used R to implement the multiple imputation with packages of "VIM", "survival", "ggplot2", "survminer", and "mice".

Table S1: Summarization of participated centers, primary investigator and number of eligible patients at each center.

Datasets	Participated centers	City	Country	Primary investigator	No.
Training (N=1604)	Xijing Hospital	Xi'an	China	Han GH	211
	First Affiliated Hospital of Fujian Medical University	Fuzhou	China	Lin ZY	36
	Hunan Provincial People's Hospital	Changsha	China	Zhang YJ	25
	The Affiliated Cancer Hospital of Zhengzhou University	Zhengzhou	China	Li HL	90
	The First Affiliated Hospital of Nanjing Medical University	Nanjing	China	Shi HB	29
	The Affiliated Cancer Hospital of Nanjing Medical University	Nanjing	China	Yin GW	117
	The First Affiliated Hospital of Lanzhou University	Lanzhou	China	Wang WH	14
	The Second Affiliated Hospital of Nanchang University	Nanchang	China	Wu JB	48
	Nanjing General Hospital of the Nanjing Military Command	Nanjing	China	Xu J	18
	The Affiliated Hospital of Nantong University	Nantong	China	Zhao H	69
	The Affiliated Hospital of Qingdao University	Qingdao	China	Li ZX	39
	The 910 Hospital of the Chinese People's Liberation Army Joint Logistic Support Force	Quanzhou	China	Xu T	35
	Shandong Province Hospital Affiliated to Shandong University	Jinan	China	Zhang CQ	47
	Shandong Tumor Hospital	Jinan	China	Song JL	31
	The First Affiliated Hospital of Soochow University	Suzhou	China	Zhu XL	49
	Tangdu Hospital, Fourth Military Medical University	Xi'an	China	Gong WD	41
	The Affiliated Tumor Hospital of Xinjiang Medical University	Urumqi	China	Yang SF	21
	Southwest Hospital, Third Military Medical University	Chongqing	China	Zhang H	164
	Xinqiao Hospital, Third Military Medical University	Chongqing	China	Li J	67
	The Third Affiliated Hospital of Kunming University	Kunming	China	Huang M	164
	Yantai Yuhuangding Hospital	Yantai	China	Zheng YB	20

	Hospital	City	Country	Author	N
	The First Affiliated Hospital of Zhejiang University	Hangzhou	China	Nie CH	197
	Zhejiang Cancer Hospital	Hangzhou	China	Shao GL	29
	The First Affiliated Hospital of Sun Yat-sen University	Guangzhou	China	Li JP	43
Internal validation (N=633, cTACE)	West China Hospital	Chengdu	China	Zeng Y	278
	Hubei Cancer Hospital	Wuhan	China	Yin T	33
	The Affiliated Tumor Hospital of Xinjiang Medical University	Urumqi	China	Ren WX	26
	General Hospital of Ningxia Medical University	Yinchuan	China	Ding XC	144
	The First Affiliated Hospital of Wenzhou Medical University	Wenzhou	China	Hu WH	152
Internal validation (N=170, DEB-TACE)	Peking University Cancer Hospital	Beijing	China	Zhu X	13
	The Affiliated Hospital of Qingdao University	Qingdao	China	Li ZX	11
	Southwest Hospital, Third Military Medical University	Chongqing	China	Zhang H	31
	The Third Affiliated Hospital of Kunming University	Kunming	China	Huang M	4
	The First Affiliated Hospital of Zhejiang University	Hangzhou	China	Nie CH	91
	The First Affiliated Hospital of Sun Yat-sen University	Guangzhou	China	Li JP	12
	The Second Affiliated Hospital of Nanchang University	Nanchang	China	Wu JB	8
European validation (N=1130)	Hôpital Saint-Joseph	Marseille	France	Adhoute	252
	Centre Hospitalo-Universitaire de Nancy	Nancy	France	Bronowicki	72
	Hôpital Universitaire de l'Archet Nice	Nice	France	Anty	38
	University Medical Center of the Johannes Gutenberg University Mainz	Mainz	Germany	Kloeckner	113
	Hannover Medical School	Hannover	Germany	Vogel	242
	University Medical Center Freiburg	Freiburg	Germany	Bettinger	413
Asian validation (N=840)	Seoul National University Hospital	Seoul	Korea	Chung JW	442
	Yonsei University College of Medicine	Seoul	Korea	Kim SU	187
	Faculty of Medicine, Prince of Songkla University	Songkhla	Thailand	Sripongpun	211

Table S2: Correlation coefficients (r) between these indicator variables with missing values.

Variables	AFP	WBC	PLT	INR	BUN	Cr
AFP	1	0.24	0.24	-0.01	-0.03	-0.02
WBC		1	0.98	-0.01	0.24	0.33
PLT			1	-0.01	0.28	0.39
INR				1	-0.01	-0.004
BUN					1	0.67
Cr						1

Abbreviations: AFP, alpha-fetoprotein; BUN, blood urea nitrogen; Cr, creatinine; INR, international normalized ratio; PLT, platelet; WBC, white blood cell.

Table S3. Correlation coefficient (r) between variables with missing values and

other observable variables.

Variables	AFP	WBC	PLT	INR	BUN	Cr
AFP	NA	0.031	0.028	-0.007	-0.003	-0.006
WBC	0.037	NA	0.058	-0.005	-0.008	0.078
PLT	0.023	NA	NA	-0.001	-0.022	0.023
INR	0.013	0.000	-0.002	NA	0.033	0.032
BUN	-0.020	0.099	0.099	0.030	NA	0.005
Cr	-0.048	-0.038	-0.038	0.018	-0.003	NA
ALT	0.029	0.007	0.006	-0.018	0.087	0.048
AST	0.000	0.009	0.006	0.01	0.062	0.037
ALB	-0.035	-0.048	-0.043	0.03	-0.072	-0.056
TBIL	0.038	0.021	0.025	0.047	0.015	0.059
Gender	-0.016	-0.018	-0.001	-0.014	-0.010	0.005
Age	0.012	-0.030	-0.035	0.032	0.015	-0.014
Aetiology	-0.003	-0.025	-0.027	-0.015	0.008	0.001
Tumor size	-0.008	0.038	0.044	-0.004	-0.007	0.018
Tumor number	0.026	-0.012	-0.014	0	0.030	0.017
ECOG	NA	NA	NA	NA	NA	NA
Child-Pugh score	0.044	0.010	0.006	-0.018	0.002	0.047

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; cm, centimeter; Cr, creatinine; INR, international normalized ratio; NA, not available; PLT, platelet; TBIL, total bilirubin; WBC, white blood cell.

Table S4. Predictors for OS by Cox multivariable regression in each imputed cohort and pooled all cohorts. (SE, standard error; AFP, alpha-fetoprotein).

	Tumor size, per 1cm increase			Tumor number, refer to single			$Log_{10}AFP$, per 1 increase		
	beta coefficient	SE	p value	beta coefficient	SE	p value	beta coefficient	SE	p value
C1	0.103	0.0093	<0.001	0.097	0.0172	<0.001	0.150	0.0280	<0.001
C2	0.102	0.0093	<0.001	0.096	0.0173	<0.001	0.152	0.0279	<0.001
C3	0.102	0.0093	<0.001	0.098	0.0173	<0.001	0.148	0.0279	<0.001
C4	0.101	0.0093	<0.001	0.097	0.0173	<0.001	0.148	0.0279	<0.001
C5	0.101	0.0093	<0.001	0.096	0.0172	<0.001	0.151	0.0278	<0.001
Pooled	0.102	0.0093	<0.001	0.096	0.0173	<0.001	0.150	0.0279	<0.001

*Age, gender, aetiology, ALT, AST, ALBI score, BUN, Cr, and INR were not identified as prognostic factors of overall survival in C1-C5 and pooled cohort.

Table S5. Baseline demographics and clinical characteristics in Chinese DEB-

TACE cohort.

Variables	DEB-TACE (n=170)
Sex	
male	149 (87.6%)
female	21 (12.4%)
Age, years	62 (53-69)
Aetiology	
HBV	159 (93.5%)
Others	11 (6.5%)
The largest tumor diameter, cm	4.6 (3.0-7.1)
$\leq$ 3 cm	44 (25.9%)
>3, $\leq$ 7 cm	83 (48.8%)
>7, $\leq$ 10 cm	24 (14.1%)
>10 cm	19 (11.2%)
Tumor number	
1	86 (50.6%)
2	47 (27.6%)
$\geqq$ 3	37 (21.8%)
Current BCLC staging	
A	107 (62.9%)
B	63 (37.1%)
Child-Pugh score	
5	141 (82.9%)
6	26 (15.3%)
7	3 (1.8%)

ALBI grade	
1	106 (62.4%)
2	64 (37.6%)
AFP, ng/ml	30.8 (5.4-296.5)
ALT, U/L	30.5 (20-49)
AST, U/L	37 (26-54)
ALB, g/L	41.3 (37.7-43.9)
TBIL, μmol /L	14.4 (10.9-20.8)
INR	1.1 (1.0-1.1)
WBC, $*10^9$/L	5.3 (4.0-6.5)
PLT, $*10^9$/L	127 (88-185)
Cr umol/L	74 (66-82)
Sessions of TACE	2 (2–3)
Follow-up time, months	30.6 (23.1-38.1)

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cm, centimeter; Cr, creatinine; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; HBV, hepatic B virus; HCV, hepatic C virus; INR, international normalized ratio; PLT, platelet; TACE, transarterial chemoembolization; TBIL, total bilirubin; WBC, white blood cell.

Table S6. Comparation of the performance and discrimination among current available prognostic metrics in different subgroups of

gender and age.

Prognostic metrics	Male				Female				Age≤60 years				Age>60 years			
	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC
6-and-12 model 2.0	0.673	0.011	8965.11	8978.76	0.675	0.027	1010.05	1018.20	0.672	0.013	5939.51	5952.09	0.673	0.015	3597.17	3608.49
6-and-12 model	0.666	0.010	8984.12	8993.22	0.649	0.026	1020.09	1025.53	0.661	0.013	5964.45	5972.84	0.668	0.015	3601.71	3609.26
Up to seven criteria	0.613	0.009	9039.55	9044.10	0.605	0.024	1031.01	1033.73	0.612	0.011	5999.38	6003.57	0.61	0.013	3634.03	3637.80
Four and seven criteria	0.616	0.010	9045.40	9049.95	0.579	0.026	1036.11	1038.83	0.605	0.012	6014.46	6018.65	0.619	0.014	3627.99	3631.76
Seven and eleven criteria	0.646	0.010	8997.04	9001.59	0.634	0.026	1022.64	1025.36	0.639	0.012	5979.62	5983.81	0.652	0.015	3598.68	3602.46
BCLC subclassification	0.586	0.088	9067.83	9072.38	0.592	0.023	1029.30	1032.01	0.599	0.01	6002.03	6006.23	0.567	0.013	3659.14	3662.92
HAP score	0.607	0.011	9074.50	9079.05	0.587	0.029	1037.57	1040.29	0.599	0.013	6025.34	6029.53	0.615	0.016	3646.61	3650.39
mHAP III score	0.656	0.011	9014.25	9018.80	0.640	0.027	1020.20	1022.92	0.661	0.013	5966.33	5970.52	0.64	0.016	3632.80	3636.58
mHAP II score	0.617	0.011	9056.38	9060.93	0.601	0.03	1033.62	1036.34	0.615	0.013	6008.0	6012.19	0.614	0.016	3643.96	3647.53
mHAP score	0.615	0.011	9062.24	9066.79	0.613	0.027	1029.63	1032.35	0.612	0.013	5979.62	5983.81	0.62	0.016	3641.45	3645.24
ALBI score	0.532	0.012	9134.41	9138.06	0.530	0.029	1041.25	1043.97	0.510	0.014	6060.15	6064.35	0.564	0.017	3673.15	3676.94

Abbreviations: AIC, Akaike Information Criterion; ALBI, albumin-bilirubin; BIC, Bayesian Information Criterion; BCLC, Barcelona

Clinic Liver Cancer; C-index, concordance index; HAP, Hepatoma arterial-embolization prognostic; SD, standard deviation;

Table S7. Comparation of the performance and discrimination among current available prognostic metrics in different subgroups of

ALBI grade and aetiology.

Prognostic metrics	ALBI grade 1				ALBI grade 2				HBV				Other aetiology			
	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC	C-index	SD	AIC	BIC
6-and-12 model 2.0	0.676	0.015	4460.37	4472.18	0.674	0.013	4846.94	4859.04	0.669	0.011	8834.25	8847.82	0.694	0.024	1117.41	1125.75
6-and-12 model	0.656	0.015	4485.71	4493.58	0.672	0.013	4852.87	4860.94	0.658	0.011	8860.21	8869.29	0.692	0.023	1118.93	1128.49
Up to seven criteria	0.609	0.012	4510.96	4514.90	0.614	0.012	4894.0	4898.03	0.611	0.009	8910.85	8915.39	0.616	0.019	1134.97	1137.75
Four and seven criteria	0.616	0.013	4508.70	4512.64	0.605	0.013	4910.32	4914.36	0.603	0.010	8931.07	8935.61	0.654	0.02	1122.79	1129.57
Seven and eleven criteria	0.635	0.014	4496.31	4500.25	0.654	0.013	4855.08	4859.11	0.64	0.01	8873.87	8878.41	0.671	0.022	1119.20	1121.97
BCLC subclassification	0.580	0.011	4520.76	4524.68	0.589	0.011	4916.83	4920.86	0.588	0.008	8929.30	8933.84	0.578	0.019	1143.07	1145.85
HAP score	0.617	0.015	4515.66	4519.60	0.585	0.014	4937.9	4941.94	0.606	0.011	8942.74	8947.28	0.600	0.027	1143.90	1146.68
mHAP III score	0.660	0.015	4492.53	4496.47	0.671	0.013	4949.95	4853.99	0.648	0.011	8887.16	8891.70	0.683	0.024	1124.52	1127.30
mHAP II score	0.623	0.015	4510.48	4514.42	0.60	0.014	4921.58	4925.61	0.617	0.011	8922.03	8926.57	0.602	0.026	1142.06	1144.84
mHAP score	0.633	0.015	4500.13	4504.07	0.592	0.014	4930.04	4934.07	0.617	0.011	8922.83	8927.36	0.603	0.026	1143.50	1146.28
ALBI score	0.489	0.016	4555.00	4558.94	0.496	0.015	4958.10	4962.14	0.536	0.012	8996.49	9001.03	0.502	0.029	1153.66	1156.44

Abbreviations: AIC, Akaike Information Criterion; ALBI, albumin-bilirubin; BIC, Bayesian Information Criterion; BCLC, Barcelona

Clinic Liver Cancer; C-index, concordance index; HAP, Hepatoma arterial-embolization prognostic; HBV, Hepatic B virus; SD, standard deviation;

Table S8. Comparation of the performance and discrimination among current available prognostic metrics in Chinese DEB-TACE cohort.

Prognostic metrics	C-index	SD	AIC	BIC
6-and-12 model 2.0	0.639	0.033	664.1	666.4
6-and-12 model	0.607	0.037	669.6	674.1
Up to seven criteria	0.584	0.031	670.2	672.4
Four and seven criteria	0.606	0.029	667.3	669.6
Seven and eleven criteria	0.592	0.033	670.4	672.7
BCLC subclassification	0.583	0.031	659.8	662.1
HAP score	0.585	0.034	671.0	673.3
mHAP III score	0.632	0.033	664.4	666.6
mHAP II score	0.592	0.033	669.1	671.4
mHAP score	0.591	0.031	669.8	672.1
ALBI score	0.507	0.037	678.2	680.5

Abbreviations: AIC, Akaike Information Criterion; ALBI, albumin-bilirubin; BIC, Bayesian Information Criterion; BCLC, Barcelona Clinic Liver Cancer; C-index, concordance index; HAP, Hepatoma arterial-embolization prognostic; HBV, Hepatic B virus; SD, standard deviation;

Table S9. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in internal validation cohort.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	18.3% (7.10%-27.1%)	0.002	0.7% (-0.1%-1.7%)	0.092	11.5% (4.0%-18.5%)	0.004	1.3% (0.2%-2.7%)	0.004
Up to seven criteria	30.0% (16.1%-39.6%)	<0.001	4.0% (2.1%-6.6%)	<0.001	15.5% (4.9%-24.5%)	0.012	4.5% (2.0%-7.0%)	0.002
Four and seven criteria	22.5% (10.1%-35.3%)	0.002	3.4% (1.5%-5.7%)	<0.001	10.9% (-0.1%-21.1%)	0.052	3.4% (0.8%-5.7%)	0.022
Seven and eleven criteria	20.5% (9.80%-32.2%)	0.002	2.5% (1.0%-4.6%)	0.002	16.6% (6.3%-25.3%)	0.004	3.4% (1.3%-5.5%)	0.002
BCLC subclassification	23.5% (6.70%-32.8%)	0.012	2.6% (1.2%-3.9%)	<0.001	15.8% (4.2%-28.4%)	0.002	2.9% (0.8%-5.2%)	0.016
HAP score	13.1% (0.30%-25.2%)	0.044	2.9% (1.0%-5.5%)	<0.001	8.7% (-1.3%-20.0%)	0.098	4.5% (1.6%-7.5%)	0.002
mHAP III score	22.0% (10.4%-36.0%)	<0.001	1.9% (0.5%-4.2%)	0.004	16.5% (5.9%-24.8%)	0.008	1.6% (0.3%-3.6%)	0.02
mHAP II score	14.6% (-0.1%-29.3%)	0.056	2.5% (0.3%-5.1%)	0.026	6.9% (-6.2%-18.1%)	0.304	3.0% (0.0%-6%)	0.05
mHAP score	9.30% (-2.0%-21%)	0.100	2.1% (0.2%-4.6%)	0.026	10.2% (0.0%-19%)	0.044	3.7% (1%-6.3%)	0.002
ALBI score	28.7% (13.6%-36.3%)	<0.001	5.3% (3.0%-8.4%)	<0.001	26.9% (15.2%-33.8%)	<0.001	8.7% (5.5%-12.2%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S10. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in European validation cohort.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	23.1% (15.1% - 32.0%)	<0.001	1.6% (0.7% - 2.5%)	<0.001	17.9% (9.9% - 24.1%)	<0.001	1.6% (0.5% - 2.6%)	<0.001
Up to seven criteria	20.7% (8.80% - 31.0%)	<0.001	3.5% (2.0% - 5.5%)	<0.001	18% (6.4% - 23.8%)	<0.001	3.0% (1.1% - 4.5%)	<0.001
Four and seven criteria	21.2% (11.7% - 27.8%)	<0.001	3.8% (2.0% - 5.7%)	<0.001	14.9% (7.1% - 23.7%)	<0.001	3.5% (1.45 - 5.5%)	0.004
Seven and eleven criteria	21.2% (9.5% - 31%)	<0.001	2.9% (1.4% - 4.4%)	<0.001	15.6% (5.1% - 23.2%)	0.004	2.3% (0.8% - 3.7%)	<0.001
BCLC subclassification	21.4% (9.6% - 31.3%)	<0.001	3.3% (1.5% - 5.5%)	<0.001	18.5% (7.4% - 25.3%)	0.004	2.9% (1.1% - 4.7%)	0.004
HAP score	2.4% (-9.6% - 12.7%)	0.758	1.5% (-0.6% - 3.7%)	0.172	-1.5% (-12.7% - 8.9%)	0.802	0.9% (-1.9% - 3.1%)	0.527
mHAP III score	16.7% (3.2% - 28.3%)	0.012	1.3% (0.1% - 2.5%)	0.044	6.3% (-8.4% - 15.2%)	0.427	0.7% (-0.6% - 2.0%)	0.315
mHAP II score	9.3% (-3.9% - 20.5%)	0.168	2.3% (0.3% - 4.6%)	0.028	1.4% (-11.7% - 8.4%	0.958	0.4% (-2.6% - 2.8%)	0.798
mHAP score	5.1% (-7.6% - 16%)	0.431	1.6% (-0.4% - 3.5%)	0.120	6.7% (-5.6% - 15.1%)	0.319	0.2% (-0.2% - 4.0%)	0.064
ALBI score	17% (6.5% - 26.2%)	<0.001	3.3% (1.5% - 5.5%)	<0.001	7.1% (0.3% - 18.1%)	0.06	3.7% (0.8%-6.2%)	0.028

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S11. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard model) at 1-year and 3-year timepoint in Asian validation cohort.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	19.3% (0.61% - 29.0%)	<0.001	1.3% (-2.0% - 2.7%)	0.088	17.1% (8.8% - 24.5%)	<0.001	2.2% (0.7% - 4.1%)	0.004
Up to seven criteria	22.9% (9.9% - 34.9%)	<0.001	4.8% (1.7% - 8.4%)	<0.001	18.5% (4.3% - 26.8%)	0.020	4.8% (1.9% - 7.7%)	0.008
Four and seven criteria	24.7% (9.5% - 35.3%)	0.004	4.6% (1.7% - 8.7%)	0.004	17.7% (4.9% - 26.6%)	0.004	4.1% (0.8% - 7.7%)	0.024
Seven and eleven criteria	30.2% (17.4% - 40.5%)	<0.001	3.6% (1.2% - 6.4%)	0.008	28.4% (19.8% - 35.1%)	<0.001	6.4% (4.2% - 9.1%)	<0.001
BCLC subclassification	20.9% (3.3% - 32.8%)	0.02	3.1% (-0.7% - 10%)	0.100	18.2% (2.7% - 26.8%)	0.016	3.1% (-0.4% - 6.8%)	0.072
HAP score	12.6% (-3.8% - 27.2%)	0.136	4.2% (0.8% - 8%)	0.016	10.2% (-2.0% - 23%)	0.100	5.9% (2% - 9.4%)	<0.001
mHAP III score	24.4% (8.3% - 35.4%)	0.020	2.8% (0.8% - 6%)	0.008	13.4% (2.2% - 21.6%)	0.032	2.4% (0.05% - 4.7%)	0.012
mHAP II score	11.3% (-3.4% - 24.5%)	0.144	4.5% (0.8% - 8.4%)	0.008	6.8% (-4.1% - 19.0%)	0.208	5% (1% - 8.1%)	0.012
mHAP score	7.7% (-10.0% - 24.6%)	0.383	2.3% (-0.8% - 5.9%)	0.128	5.7% (-6.3% - 19.3%)	0.319	3.1% (-0.3% - 6.6%)	0.068
ALBI score	16.9% (2.5% - 31.4%)	0.02	6.2% (2.0% - 11.1%)	0.004	16.2% (3% -26.8%)	0.020	7.8% (3.3% - 12.6%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S12. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in patients with age> 60years.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	8.7% (0.2% - 20.9%)	0.048	0.9% (0.1% - 2.7%)	0.028	5.5% (-3.6% - 15.6%)	0.236	-0.5% (-0.2% - 2.1%)	0.251
Up to seven criteria	9.3% (-11.4% - 24%)	0.439	3.5% (0.2% - 7.4%)	0.024	10.4% (-7.9% - 27.0%)	0.323	4.2% (0.0% - 8.1%)	0.048
Four and seven criteria	8.1% (-7.5% - 27.4%)	0.303	2.9% (0.2% - 6.5%)	0.028	14.9% (-5.7% - 30.3%)	0.132	3.6% (0.5% - 7.5%)	0.046
Seven and eleven criteria	-2.2% (-17.4% - 18.6%)	0.886	0.4% (-1.8% - 3.5%)	0.651	-10.9% (-24.1% - 9.1%)	0.315	-0.9% (-4.2% - 2.3%)	0.659
BCLC subclassification	27.9% (17.7% - 42.9%)	0.004	6.2% (3.5% - 10.3%)	<0.001	21.2% (7.1% - 33.2%)	0.004	8.4% (4.3% - 12.5%)	0.004
HAP score	15.9% (0.5% - 31.9%)	0.046	3.6% (0.6% - 7.8%)	0.012	19.1% (3.7% - 31.9%)	0.008	6.8% (2.0% - 10.9%)	0.004
mHAP III score	20.9% (10.2% - 33.3%)	<0.001	3.1% (1.0% - 6.4%)	<0.001	22.6% (12% - 32.8%)	<0.001	5% (2.6% - 7.8%)	<0.001
mHAP II score	22.2% (5.4% - 34.3%)	0.008	3.6% (0.4% - 7.3%)	0.032	15.4% (4.2% - 29.7%)	0.016	6.3% (1.9% - 10.7%)	0.004
mHAP score	19.9% (2.6% - 33.8%)	0.024	3.3% (0.5% - 7.0%)	0.024	15% (-2.5% - 29.1%)	0.096	5.6% (1.4% - 9.8%)	0.008
ALBI score	32.8% (19.5% - 44.2%)	0.004	6.9% (3.7% - 11.3%)	0.004	21.3% (6.5% -31.9%)	0.004	9.3% (4.9% - 14.2%)	0.004

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S13. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in patients with age≤ 60years.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	24.9% (5.8% - 37.7%)	0.012	4.1% (0.7% - 8.7%)	0.008	11.6% (4.1% - 33.7%)	0.012	4.1% (0.8% - 10.0%)	0.008
Up to seven criteria	29.5% (5.9% - 47.4%)	0.012	7.3% (2.5% - 14.3%)	<0.001	17.6% (3.1% - 41.3%)	0.016	8.4% (3.4% - 15.3%)	<0.001
Four and seven criteria	35.1% (16.6% - 51.0%)	<0.001	9.7% (4.7% - 16.8%)	<0.001	20.1% (0.2% - 46.9%)	0.046	9.6% (3.4% - 18.1%)	0.008
Seven and eleven criteria	24.8% (0.8% - 41.8%)	0.046	4.3% (0.5% - 10.1%)	0.048	17.6% (-4.4% - 35.6%)	0.144	4.6% (0.0% -11.6%)	0.050
BCLC subclassification	25.1% (1.4% - 45.7%)	0.032	7.5% (1.4% - 14.5%)	0.012	4.2% (-10.7% - 32.8%)	0.383	7.6% (0.1% - 16.0%)	0.024
HAP score	34.1% (14.0% - 49.4%)	0.004	9.4% (3.9% - 17.2%)	<0.001	28.5% (0.2% - 42.6%)	0.048	10.4% (3.4% - 18.1%)	0.008
mHAP III score	29.8% (9.0% - 49.0%)	0.004	5.1% (2.2% - 10.3%)	<0.001	27.9% (0.4% - 43.2%)	0.048	5.1% (1.7% - 10.6%)	0.004
mHAP II score	27.1% (7.6% - 46.2%)	0.024	7.9% (2.1% - 15.3%)	0.020	27.1% (7.6% - 46.2%)	0.024	7.9% (2.1% - 15.3%)	0.020
mHAP score	22.3% (1.4% - 41.0%)	0.048	6.5% (0.3% - 13.7%)	0.036	17.4% (-6.3% - 38.3%)	0.116	6.3% (0.5% - 13.7%)	0.048
ALBI score	33.9% (15.7% - 50.4%)	<0.001	11.1% (5% - 19.3%)	<0.001	29.1% (0.6% - 47.2%)	0.044	12.2% (3.9% - 21.1%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S14. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in male patients.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	13.6% (2.8% - 24.5%)	0.004	1.4% (0.4%-2.4%)	0.012	9.3% (0.1% - 18.4%)	0.044	1.1% (-0.2% - 2.3%)	0.092
Up to seven criteria	18.1% (4.5% - 25.3%)	0.004	4.3% (2.1% - 6.4%)	<0.001	13.5% (2.9% - 22.2%)	0.016	3.9% (1.2% - 6.4%)	0.008
Four and seven criteria	16.8% (3.7% - 28.3%)	0.016	3.9% (1.8% - 5.9%)	<0.001	17.7% (6.7% - 27.4%)	<0.001	4.5% (1.9% - 7.0%)	<0.001
Seven and eleven criteria	11.4% (1.2% - 21.1%)	0.046	2.3% (0.6% - 4.0%)	0.004	3.9% (0.6% - 15.1%)	0.047	1.2% (0.1% -3.1%)	0.024
BCLC subclassification	28.4% (18% - 36.1%)	<0.001	5.9% (3.8% - 8.4%)	<0.001	16.3% (6.8% - 24.1%)	<0.001	5.4% (2.8% - 8.3%)	<0.001
HAP score	25.2% (14.7% - 34.0%)	<0.001	5.6% (3.5% - 7.9%)	<0.001	23.8% (16.7% - 30.7%)	<0.001	7.7% (4.8% - 10.2%)	<0.001
mHAP III score	23.6% (13.1% - 34.0%)	<0.001	2.2% (0.6% - 3.6%)	0.012	16.6% (6.4% - 24.5%)	<0.001	3.4% (1.5% - 50%)	<0.001
mHAP II score	26.2% (14.3% - 33.9%)	<0.001	5.0% (2.9% - 7.3%)	<0.001	24.0% (14.6% - 29.7%)	<0.001	6.7% (3.8% - 9.1%)	<0.001
mHAP score	21.2% (13.5% - 32.4%)	<0.001	4.5% (2.5% - 6.5%)	<0.001	21.2% (10.8% - 29.2%)	<0.001	1.2% (0.1% - 3.1%)	0.024
ALBI score	38.0% (28.6% - 44.4%)	<0.001	8.1% (5.5% - 10.7%)	<0.001	25.7% (18.5% - 32.5%)	<0.001	10.2% (6.6% - 13.1%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S15. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard model) at 1-year and 3-year timepoint in female patients.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	20.3% (0.6% - 46.1%)	0.048	3.9% (0.6% - 7%)	0.012	12.6% (4.7% - 31.8%)	0.002	3.9% (0.2% - 7.5%)	0.032
Up to seven criteria	27.3% (3.5% - 47.2%)	0.012	7.1% (2.3% - 12.9%)	<0.001	21.4% (4.6% - 42.6%)	0.020	8.2% (2.9% - 13.4%)	<0.001
Four and seven criteria	33.3% (17.5% - 50.7%)	<0.001	9.5% (4.3% - 15.7%)	<0.001	32.9% (5.7% - 47.8%)	0.020	9.4% (3.1% -15.7%)	<0.001
Seven and eleven criteria	24.6% (1.9% - 45.4%)	0.036	4.2% (-0.4% - 8.6%)	0.080	21.7% (-3.7% - 39.1%)	0.100	4.4% (-0.1% - 8.7%)	0.068
BCLC subclassification	24.7% (1.5% - 48.0%)	0.036	7.4% (1.1% - 14.0%)	0.012	15.7% (-9.5% -35.4%)	0.271	7.5% (0.3% - 14.1%)	0.044
HAP score	32.5% (11.6% - 47.2%)	0.004	9.2% (3.5%-16.3%)	<0.001	31.7% (1.4% - 45.3%)	0.036	10.2% (2.2% - 17.6%)	0.012
mHAP III score	25.1% (-1.5% - 46.2%)	0.076	5.0% (1.1% - 9.7%)	0.008	26.5% (1.1% - 40.2%)	0.032	4.9% (0.1% - 9.8%)	0.046
mHAP II score	20.1% (5.8% - 41.1%)	0.016	7.7% (1.3% - 14.9%)	0.020	17.1% (3.4% - 39.7%)	0.014	8.5% (0.5% - 16.0%)	0.032
mHAP score	20.4% (3.9% - 38.9%)	0.048	6.4% (0.5% - 12.5%)	0.012	19.9% (6.0% - 36.1%)	0.012	6.1% (2.4% - 13.3%)	0.028
ALBI score	32.3% (16.1% - 50.3%)	<0.001	11% (4.8% - 18.3%)	<0.001	32.3% (2.1% - 47.9%)	0.005	12% (2.9% - 20.6%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S16. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard model) at 1-year and 3-year timepoint in patients with ALBI grade 1.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	18.3% (6.7% - 31.4%)	<0.001	2.3% (1.1% - 4.0%)	<0.001	14.2% (3.2% - 23.6%)	<0.001	2.2% (0.6% - 3.7%)	0.008
Up to seven criteria	21.9% (2.0% - 31.3%)	0.040	4.9% (1.8% - 8.2%)	<0.001	15.2% (0.4% - 26.0%)	0.048	4.4% (1.4% - 8.0%)	0.012
Four and seven criteria	19.2% (2.7% - 32.7%)	0.024	4.3% (1.4% - 7.7%)	<0.001	15.7% (2.0% - 27.5%)	0.032	4.1% (0.9% - 7.5%)	0.008
Seven and eleven criteria	20.2% (5.4% - 30.9%)	0.020	3.3% (0.9% - 6.1%)	0.008	11.4% (-2.1% - 23.2%)	0.092	2.8% (0.2% - 5.5%)	0.036
BCLC subclassification	25.8% (10.3% - 37.1%)	<0.001	6.1% (2.8% - 9.8%)	<0.001	18.7% (4.0% - 28.4%)	0.004	5.8% (2.2% - 9.3%)	0.004
HAP score	16.6% (0.5% - 33.4%)	0.048	3.9% (1.0% -7.3%)	0.008	24.0% (8.5% - 34.7%)	<0.001	6.8% (3.5% - 10.2%)	<0.001
mHAP III score	31.5% (20.5% - 41.8%)	<0.001	3.2% (1.3% -5.7%)	0.004	23.4% (14.2% - 32.2%)	<0.001	3.6% (1.7% -5.8%)	<0.001
mHAP II score	16.8% (3.8% - 28.9%)	0.024	3.8% (1.0% -7.0%)	0.012	23.4% (14.2% - 32.2%)	<0.001	6.0% (2.7% - 9.5%)	<0.001
mHAP score	16.3% (0.5% - 29.2%)	0.048	3.1% (0.3% - 5.9%)	0.016	17.5% (2.0% - 30.3%)	0.024	4.3% (1.3% - 7.3%)	0.008
ALBI score	38.3% (27.5% - 47.0%)	<0.001	8.1% (4.4% - 12.1%)	<0.001	24.4% (15.6% - 33.7%)	<0.001	9.7% (5.5% - 13.9%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S17. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard model) at 1-year and 3-year timepoint in patients with ALBI grade 2.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	13.1% (-0.1% - 25.9%)	0.052	1.0% (-0.5% - 2.6%)	0.156	4.1% (-6.7% - 17.8%)	0.431	0.5% (-1.3% - 2.3%)	0.635
Up to seven criteria	16.3% (2.3% - 29.8%)	0.024	4.3% (1.8% - 7.2%)	<0.001	14.8% (0.0% - 25.9%)	0.050	4.3% (0.6% - 7.3%)	0.012
Four and seven criteria	26.6% (8.4% - 36.2%)	0.004	5.0% (2.3% - 29.8%)	0.024	23.6% (7.3% - 32.8%)	<0.001	6.1% (2.5% - 9.3%)	<0.001
Seven and eleven criteria	5.6% (-6.5% - 18.6%)	0.311	1.3% (-0.6% - 3.7%)	0.168	2.3% (-10% - 13.9%)	0.731	0.0% (-2.7% - 2.3%)	1.034
BCLC subclassification	29.1% (16.6% - 40.5%)	<0.001	6.3% (3.5% - 9.6%)	<0.001	14.0% (1.4% - 24.3%)	0.028	5.8% (2.0% - 9.0%)	0.004
HAP score	35.4% (22.4% - 43.0%)	<0.001	6.8% (4.2% - 10.1%)	<0.001	25.6% (17.3% - 34.3%)	<0.001	9.1% (5.7% - 12.6%)	<0.001
mHAP III score	10.8% (-1.7% - 26.3%)	0.124	0.1% (-1.7% - 2.0%)	0.850	10.2% (-1.0% - 23.1%)	0.080	0.9% (-0.6% - 2.7%)	0.259
mHAP II score	27.4% (14.0% - 37.9%)	<0.001	5.7% (3.1% - 9.0%)	<0.001	22.2% (9.3% - 30.3%)	<0.001	7.0% (3.5% - 10.4%)	<0.001
mHAP score	27.9% (16.7% - 39.5%)	<0.001	6.0% (3.4% - 8.8%)	<0.001	25.0% (11.3% - 34.2%)	<0.001	8.1% (4.9% - 11.2%)	<0.001
ALBI score	37.9% (29.0% - 46.2%)	<0.001	8.8% (5.7% - 12.6%)	<0.001	28.9% (20.7% - 38.5%)	<0.001	11.5% (7.3% - 15.7%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S18. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard

model) at 1-year and 3-year timepoint in patients with HBV.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	16.7% (4.7% - 27.7%)	0.004	1.6% (0.5% - 2.6%)	0.004	13.2% (4.4% - 23.1%)	0.004	1.6% (0.3% - 2.9%)	0.004
Up to seven criteria	17.7% (6.3% - 26.9%)	0.004	4.4% (2.3% - 6.9%)	<0.001	14.5% (1.7% - 22.6%)	0.016	4.2% (1.3% - 6.6%)	0.008
Four and seven criteria	23.8% (11.1% - 33.1%)	<0.001	4.7% (2.7% - 7.5%)	<0.001	23.2% (12.1% - 31.1%)	<0.001	5.6% (3.1% - 8.1%)	<0.001
Seven and eleven criteria	16.3% (3.9% - 23.4%)	0.024	2.6% (0.9% - 4.4%)	0.004	7.0% (-5.0% - 17.6%)	0.359	1.7% (-0.3% - 3.5%)	0.124
BCLC subclassification	26.0% (14.8% - 34.1%)	<0.001	5.7% (3.2% - 8.4%)	<0.001	14.0% (3.3% - 23.5%)	0.004	5.2% (1.9% - 7.8%)	<0.001
HAP score	24.7% (13.3% - 31.3%)	<0.001	5.0% (2.7% - 7.3%)	<0.001	24.5% (13.1% - 32.9%)	<0.001	6.8% (4.0% - 9.3%)	<0.001
mHAP III score	23.0% (13.4% - 34.0%)	<0.001	2.3% (0.9% -3.8%)	0.004	18.0% (8.5% - 25.9%)	<0.001	3.7% (2.2% - 5.4%)	<0.001
mHAP II score	21.8% (7.5% - 31.5%)	<0.001	4.2% (2.1% - 6.8%)	<0.001	19.0% (9.2% - 27.0%)	<0.001	5.2% (2.4% - 8.0%)	<0.001
mHAP score	16.8% (8.5% - 28.8%)	<0.001	4.1% (2.1% - 6.4%)	0.004	18.2% (5.3% - 27.6%)	0.008	5.1% (2.3% -7.7%)	0.004
ALBI score	34.7% (26.3% - 41.5%)	<0.001	8.0% (5.4% - 10.9%)	<0.001	26.4% (20.7% - 33.9%)	<0.001	9.8% (6.5% - 13.1%)	<0.001

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-

embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S19. Comparation of NRI and IDI between 6-and-12 model 2.0 and other current available prognostic metrics (standard model) at 1-year and 3-year timepoint in Chinese DEB-TACE cohort.

	1-year survival timepoint				3-year survival timepoint			
	NRI (95% CI)	p value	IDI (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
6-and-12 model	9.90% (-19.1%-37.4%)	0.527	0.0% (-2.2%-1.4%)	0.951	13.7% (-8.50%-37.4%)	0.242	2.5% (-0.6%-6.1%)	0.148
Up to seven criteria	31.5% (-12.5%-48.8%)	0.206	1.2% (-0.3%-4.5%)	0.126	6.4% (-23.8%-31.4%)	0.703	3.5% (-3.1%-9.9%)	0.298
Four and seven criteria	1.5% (-31.8%-34.9%)	0.683	0.1% (-2.8%-2.6%)	0.929	-0.8% (-28.6%-29.5%)	0.987	1.7% (-5.4%-8.1%)	0.613
Seven and eleven criteria	9.9% (-22%-38.5%)	0.625	0.6% (-1.3%-3%)	0.523	12% (-16.8%-38.6%)	0.322	4.1% (-0.7%-9.5%)	0.098
BCLC subclassification	29.3% (-12.4%-50%)	0.18	1.3% (-0.3%-4.4%)	0.098	3.5% (-24.7%-28.6%)	0.755	2.8% (-3.8%-8.9%)	0.354
HAP score	-1.3% (-26.7%-35.7%)	1.137	1.1% (-1.4%-4.8%)	0.408	6.5% (-25.5%-33.4%)	0.713	3.1% (-4.2%-11.2%)	0.478
mHAP III score	5.9% (-29.2%-33.2%)	0.799	0.5% (-1.3%-2.7%)	0.505	5.1% (-24.3%-38.2%)	0.821	0.3% (-3.9%-4.7%)	0.901
mHAP II score	17.5% (-19.5%-44%)	0.354	1.8% (-0.2%-0.54%)	0.078	-5.8% (-30.4%-34%)	0.877	1.4% (-6.4%-9.5%)	0.727
mHAP score	29.3% (-12%-46.8%)	0.200	1.5% (-0.1%-5%)	0.076	4.8% (-19.9%-33.2%)	0.659	2.8% (-4.4%-9.9%)	0.440
ALBI score	20.2% (-10.6%-42.7%)	0.244	1.7% (-0.7%-5.8%)	0.210	28.5% (-10.4%-49.3%)	0.140	7.8% (-0.8%-16.9%)	0.09

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, Hepatoma arterial-embolization prognostic; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Table S20. Subgroup analyses of OS according to the current risk stratification and its' hazard ratio by COX multivariable analysis.

Subgroups	Low-risk strata	Intermediate-risk strata	High-risk strata	p value	HR, 95% CI	p value	Adjuested variables
Age≤60 years	45.0 (40.2-49.8) months	30.9 (25.5-36.3) months	15.1 (11.9-18.3) months	<0.001	1.78 (1.58-2.01)	<0.001	WBC, AST
Age>60 years	46.8 (37.8-55.8) months	28.6 (23.4-33.9) months	16.1 (14.5-17.7) months	<0.001	2.02 (1.73-2.36)	<0.001	ALT, AST, ALB, TBIL
Male	45.0 (37.3-52.3) months	30.1 (26.0-34.2) months	15.8 (13.7-17.9) months	<0.001	1.91 (1.72-2.12)	<0.001	WBC, PLT, ALT, AST, TBIL
Female	46.3 (40.4-52.2) months	29.4 (17.2-41.6) months	13.6 (9.30-17.9) months	<0.001	1.92 (1.49-2.47)	<0.001	None
ALBI grade 1	48.9 (40.7-57.1) months	30.9 (25.0-36.8) months	17.5 (12.9-22.1) months	<0.001	1.84 (1.61-2.11)	<0.001	Age, WBC, Cr
ALBI grade 2	42.6 (36.4-48.8) months	28.4 (23.2-33.6) months	14.8 (13.0-16.6) months	<0.001	1.90 (1.65-2.18)	<0.001	PLT, AST
HBV	44.4 (39.8-49.0) months	30.8 (27.1-34.5) months	15.5 (13.4-17.6) months	<0.001	1.83 (1.66-2.03)	<0.001	WBC, AST, ALB
Other etiologies	56.0 (NE-NE) months	26.6 (19.5-33.7) months	14.9 (9.40-20.4) months	<0.001	2.02 (1.59-2.57)	<0.001	TBIL

Abbreviations: ALBI, albumin-bilirubin; CI, confidence interval; HBV, hepatic B virus; HR, hazard ratio; NE, not estimated.

Table S21. Subgroup analyses of overall survival according to the current risk stratification in patients with BCLC-A and BCLC-B

HCC among these four cohorts.

Datasets	BCLC stage	Low-risk strata	Intermediate-risk strata	High-risk strata	p value
Training	A	44.3 (40.0-50.1) months	31.2 (28.2-38.2) months	17.3 (13.2-24.8) months	<0.001
	B	48.0 (39.6 - NR) months	21.6 (18.2-25.4) months	13.8 (12.2-16.0) months	<0.001
Internal validation	A	51.1 (43.2-57.5) months	32.0 (27.7-37.4) months	17.6 (9.90-33.3) months	<0.001
	B	38.3 (35.5-59.6) months	30.4 (28.9-34.4) months	21.0 (17.2-25.5) months	<0.001
European validation	A	34.5 (31.5-37.6) months	23.3 (18.2-32.9) months	14.8 (12.4-32.7) months	<0.001
	B	26.1 (24.2-30.8) months	19.2 (17.2-22.3) months	13.6 (10.2-17.8) months	<0.001
Asian validation	A	96.3 (81.7-108) months	33.9 (21.7 - NR) months	19.5 (7.87 - NR) months	<0.001
	B	55.4 (47.3-91.5) months	34.7 (27.0-43.7) months	20.7 (13.6-26.7) months	<0.001

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; NR, not reached.

Table S22. Summarization of the pivotal randomized controlled trials related to TACE.

Publication (year)	Trial	Country	Treatment	Primary endpoint	Outcomes	P
Okusaka et al[7]. 2009	NA	Japan	TAI (n = 82) cTACE (n = 79)	OS	22.3 21.2	0.383
Kudo et al[8]. 2011	POST-TACE	Japan, Korea	cTACE (responders) plus sorafenib (n = 229) cTACE plus placebo (n = 229)	TTP	5.4 3.7	0.252
Yu et al[9]. 2014	NA	China	TEA (n = 49) cTACE (n = 49)	OS	24.3 20.1	0.513
Golfieri et al[10]. 2014	PRECISION ITALIA	Italy	DEB- TACE (n = 89) cTACE (n = 88)	OS (2 years)	56.80% 55.40%	0.949
Kudo et al[11]. 2014	BRISK- TA	Global	cTACE or DEB- TACE plus brivanib (n = 249) cTACE plus placebo (n = 253)	OS	26.4 26.1	0.53
Lencioni et al[12]. 2016	SPACE	Global	DEB- TACE plus sorafenib (n = 154) DEB- TACE plus placebo (n = 153)	TTP	5.6 5.5	0.072
Meyer et al[13]. 2017	TACE-2	UK	DEB- TACE plus sorafenib (n = 157) DEB- TACE plus placebo (n = 156)	PFS	7.8 7.7	0.85
Kudo et al[14]. 2018	ORIENTAL	Japan, Korea, Taiwan	cTACE plus orantinib (n = 445) cTACE plus placebo (n = 444)	OS	31.1 32.3	0.435
Ikeda et al[15]. 2018	NA	Japan	cTACE with miriplatin (n = 129) cTACE with epirubicin (n = 128)	OS	36.5 37.1	0.946
Kudo et al[16]. 2022	TACTICS	Japan	cTACE plus sorafenib (n = 80) cTACE (n = 76)	OS	36.2 30.8	0.40

Abbreviations: cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; OS, overall survival; PFS, progression-free survival; TAI, transarterial infusion; TEA, transarterial ethanol ablation; TTP, time to progression;
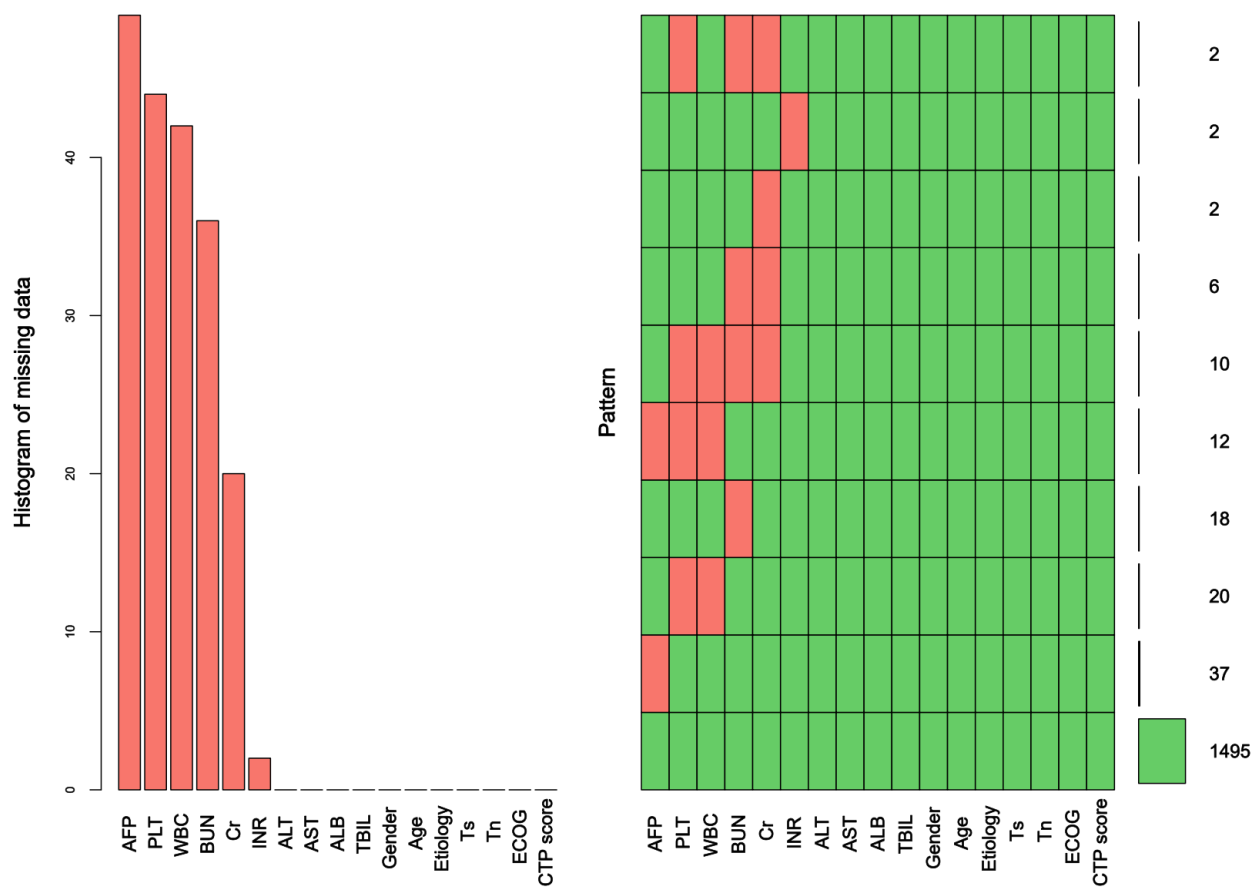
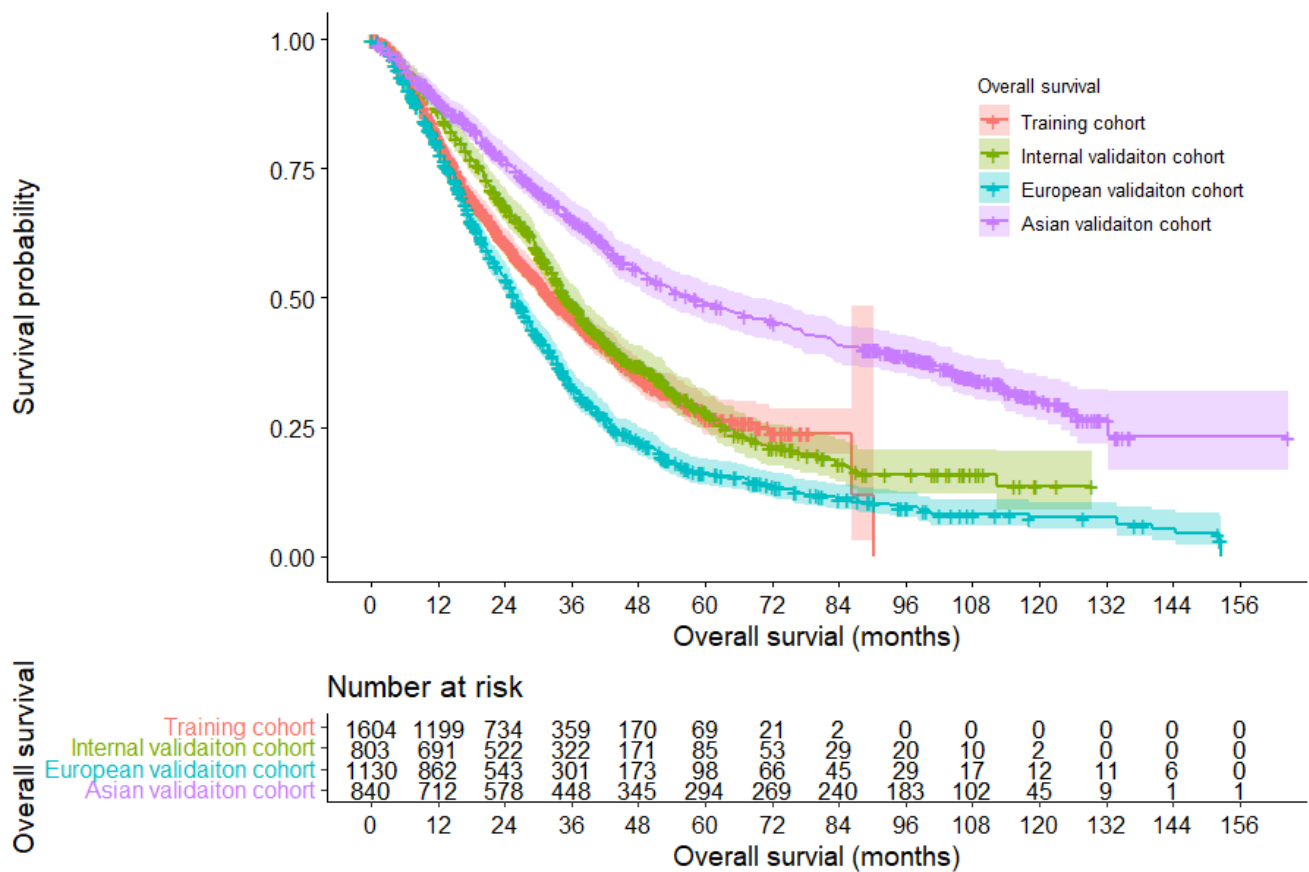**Fig. S1. Patterns of missing value in the training cohort.**

Fig. S2. Overall survival analysis by Kaplan-Meier method in training, internal, European and Asian validation cohorts. (median overall survival time was 32.9 (95% CI, 30.4–35.4) in the training cohort, 35.1 (95% CI, 32.9–37.3) in the internal validation cohort, 24.9 (95% CI, 22.0–27.9) in the European validation cohort, and 57.9 (95% CI, 48.7–67.1) months in the Asian validation cohort, p<0.001 for overall comparison by log-rank test)
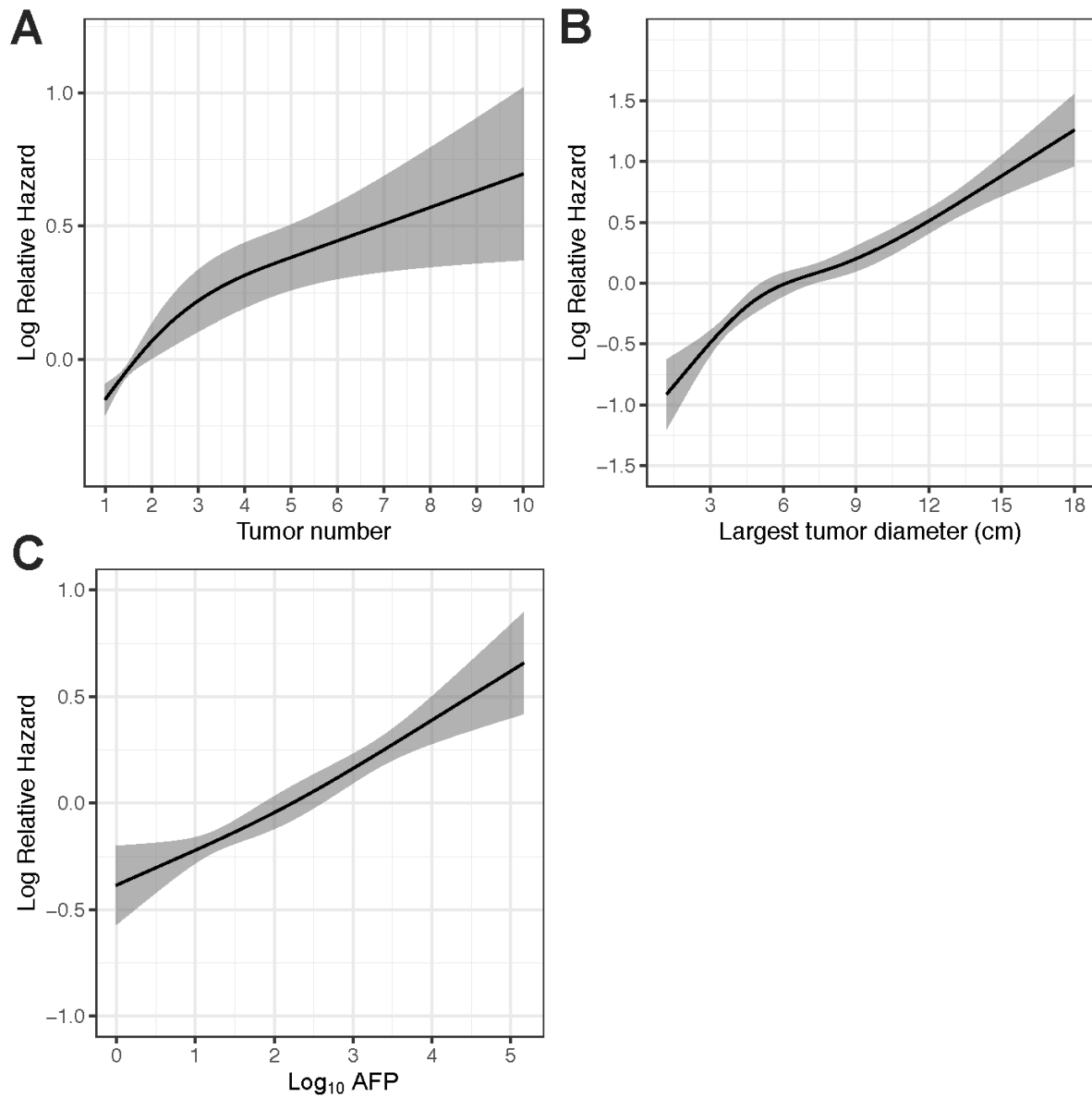
Fig S3. Relation between tumor number, largest tumor diameter, log₁₀AFP and relative hazard. (**A**, Restricted cubic spline of tumor number in training cohort (non-linear $p = 0.05$); **B**, Restricted cubic spline of largest tumor diameter in training cohort (non-linear $p = 0.11$); **C**, Restricted cubic spline of log₁₀AFP in training cohort (non-linear $p = 0.40$).
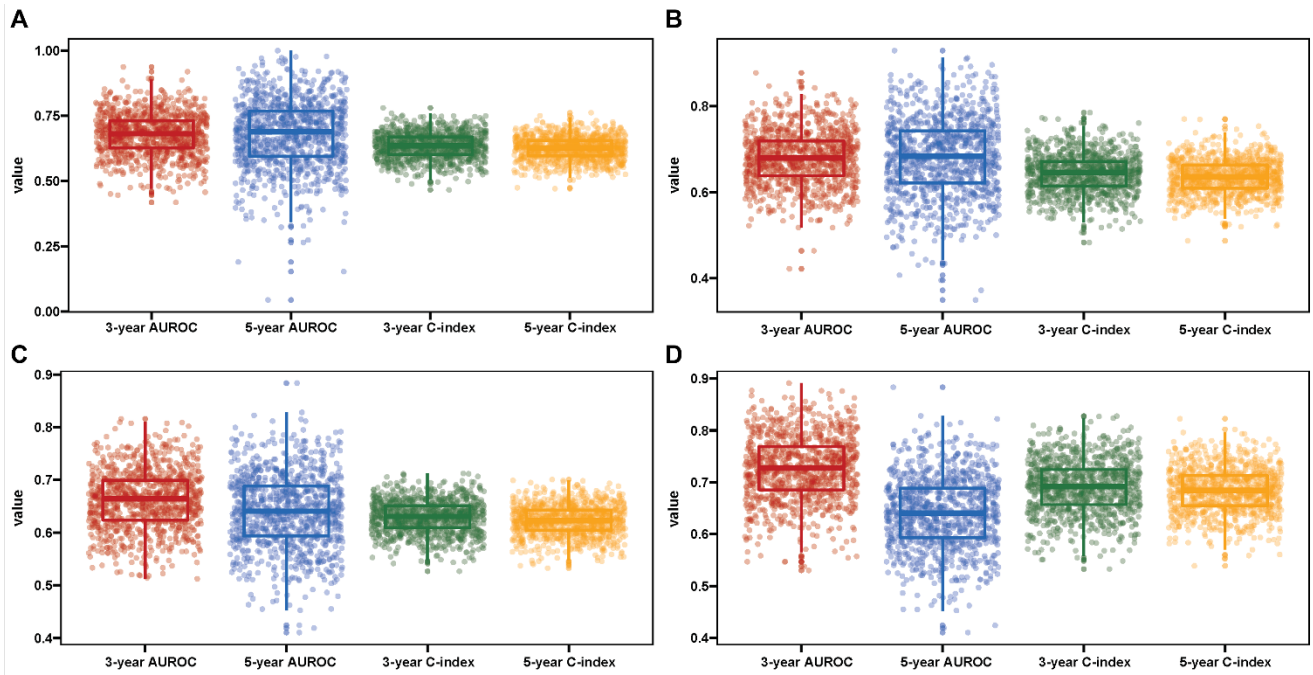
Fig. S4. Discrimination analyses of 6-and-12 model 2.0 using the concordance index (C-index) and the area under the receiver operating characteristics curve (AUROC) with a 10-fold-100-times cross validation approach in ideal TACE candidates. (Each scatter represents each cross-validation result, bars represent interquartile range and bold lines inside the box plot median levels. **A**, training cohort; **B**, internal validation cohort; **C**, European validation cohort; **D**, Asian validation cohort)
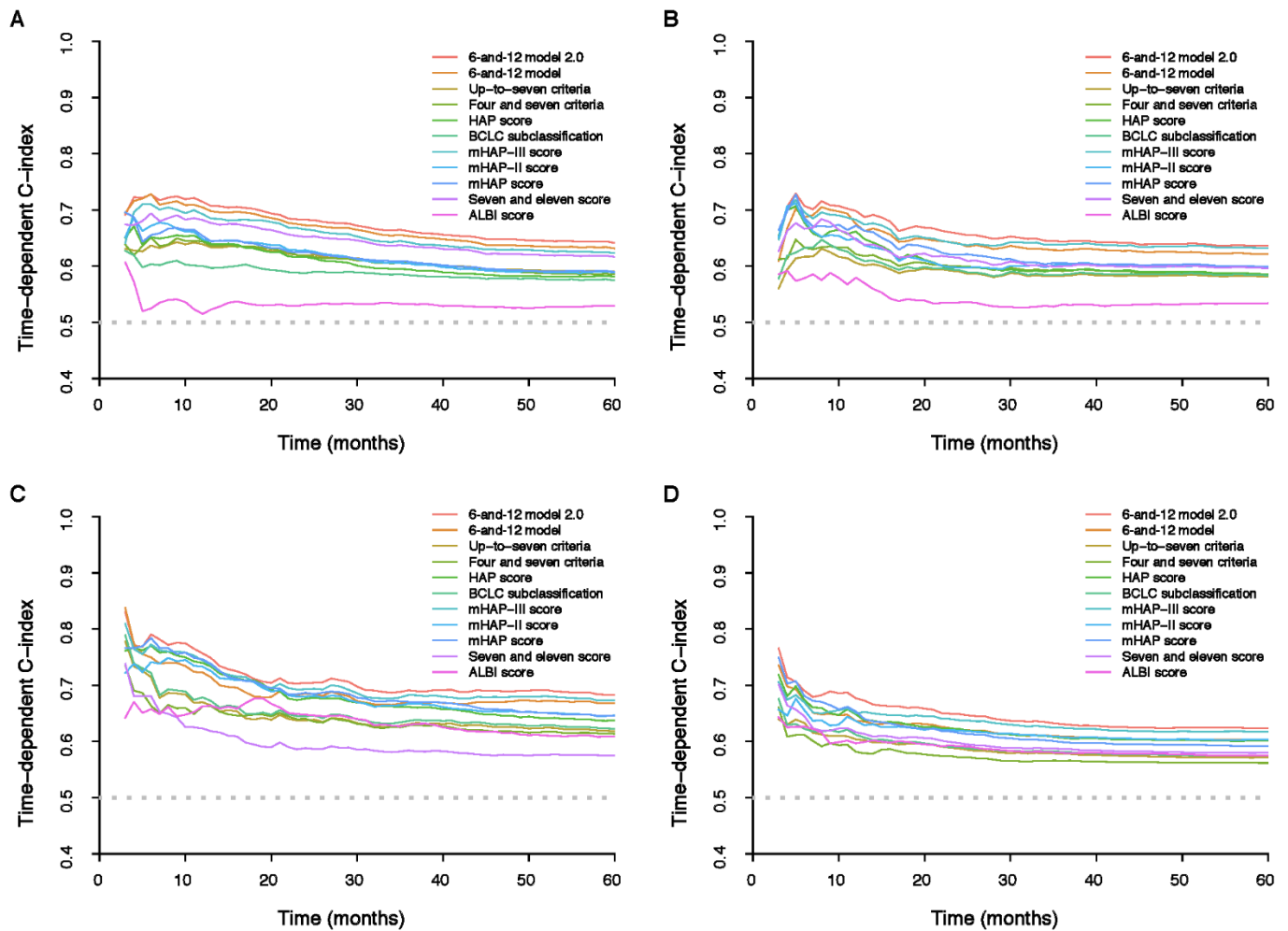
Fig. S5. Time-dependent C-index values of 6-and-12 model 2.0 and other available models. (**A**) training cohort; (**B**) internal validation cohort; (**C**)Asian validation cohort; (**D**) European validation cohort. Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; C-index, concordance index; HAP, hepatoma arterial-embolization prognostication.
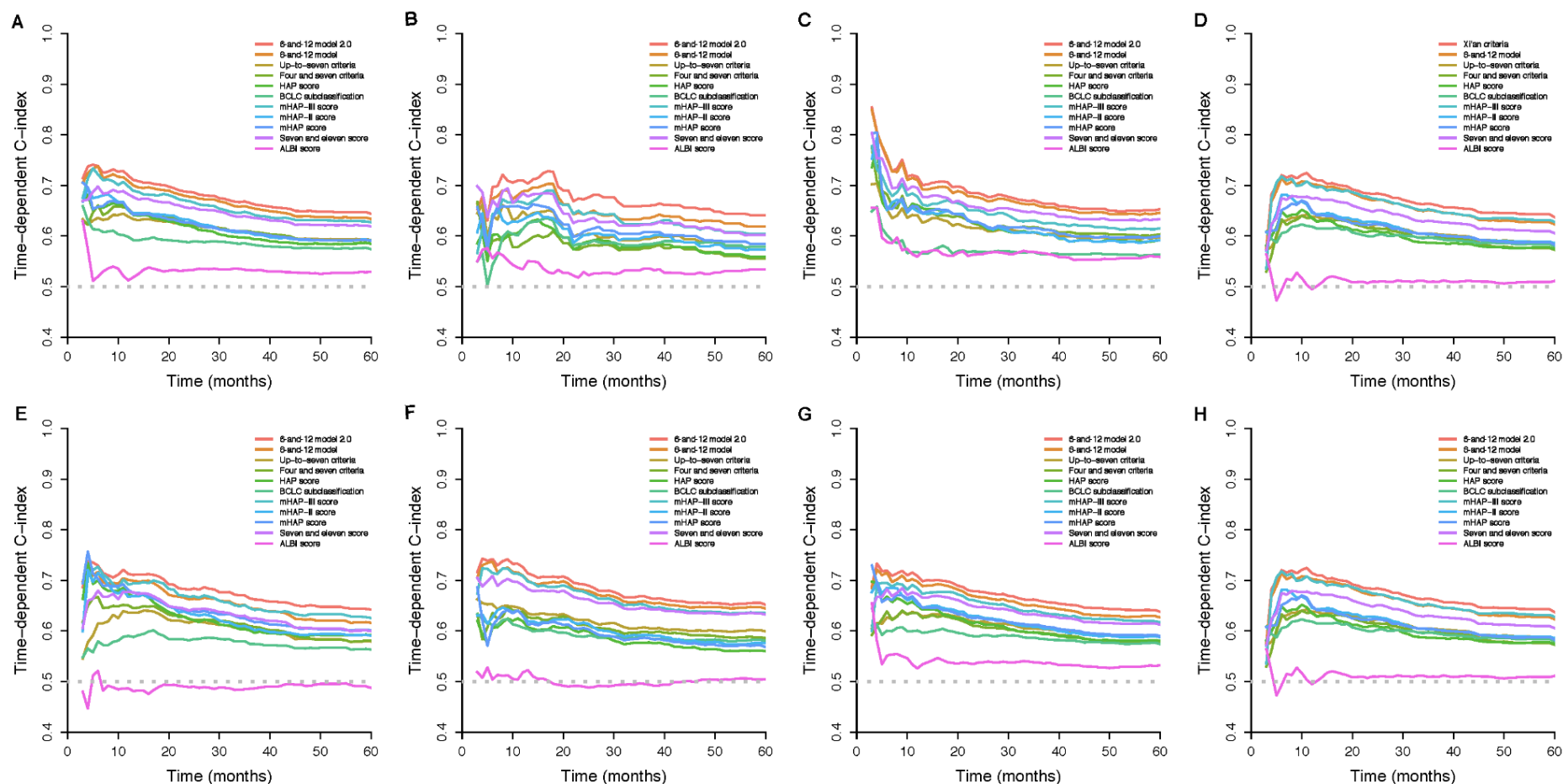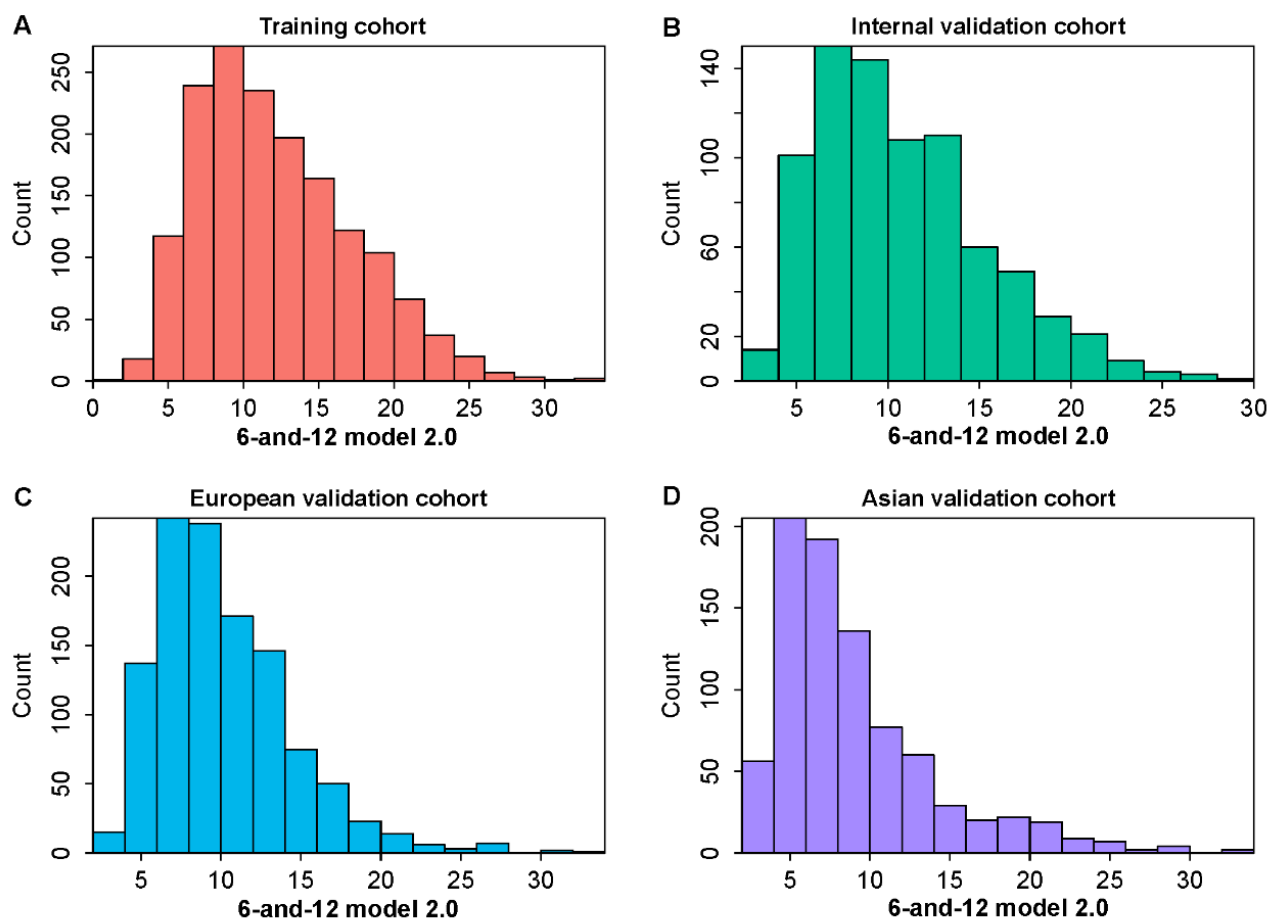
Fig S6. Time-dependent C-index values of 6-and-12 model 2.0 and other available models in different subgroups. (**A**) male; (**B**) female; (**C**) Age>60 years; (**D**) Age≤60 years; (**E**) ALBI grade 1; (**F**) ALBI grade 2; (**G**) HBV; (**H**) Other aetiology. Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; C-index, concordance index; HAP, hepatoma arterial-embolization

prognostication.

Fig. S7. Overall distribution of cases according to 6-and-12 model 2.0 in training cohort (**A**), internal validation cohort (**B**), European validation cohort (**C**), and Asian validation cohort (**D**).

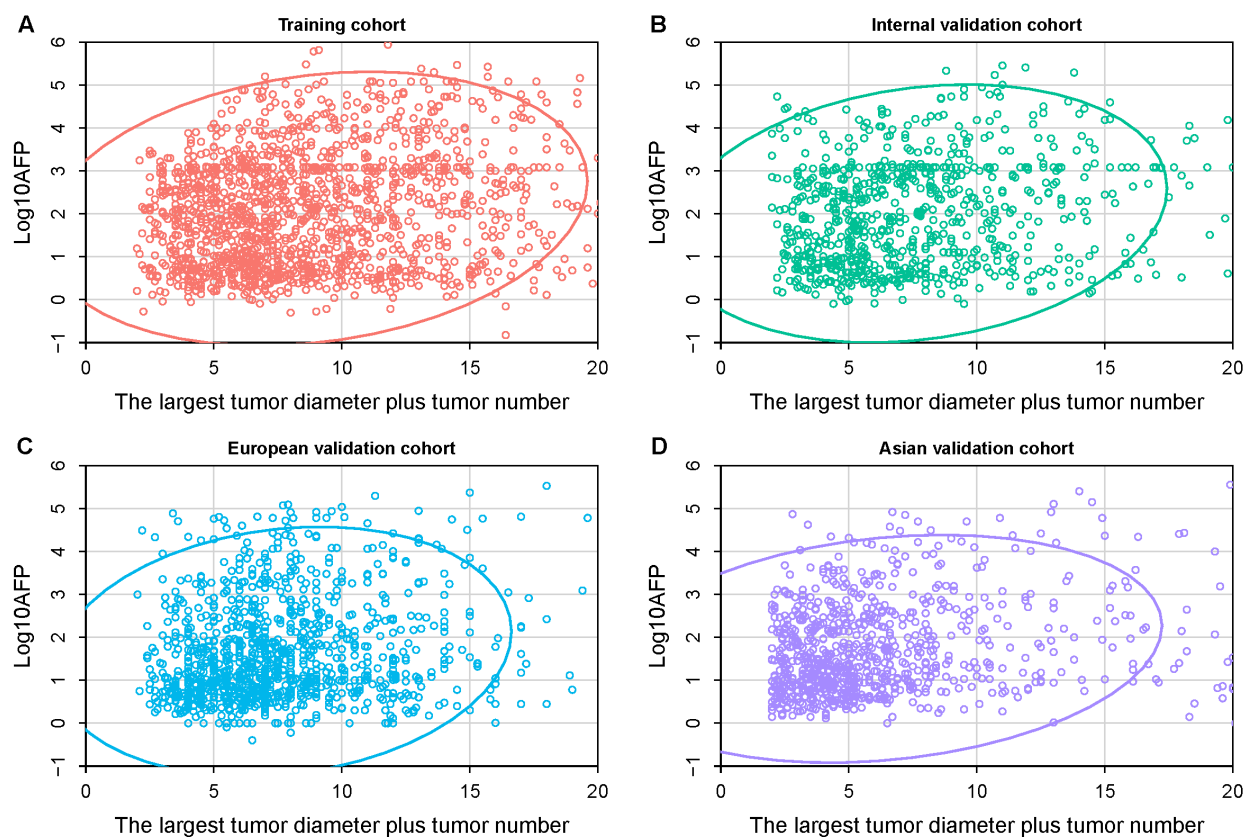**Fig S8. Overall distribution of cases according to baseline log₁₀AFP and tumor burden** in training cohort (**A**), internal validation cohort (**B**), European validation cohort (**C**), and Asian validation cohort (**D**).
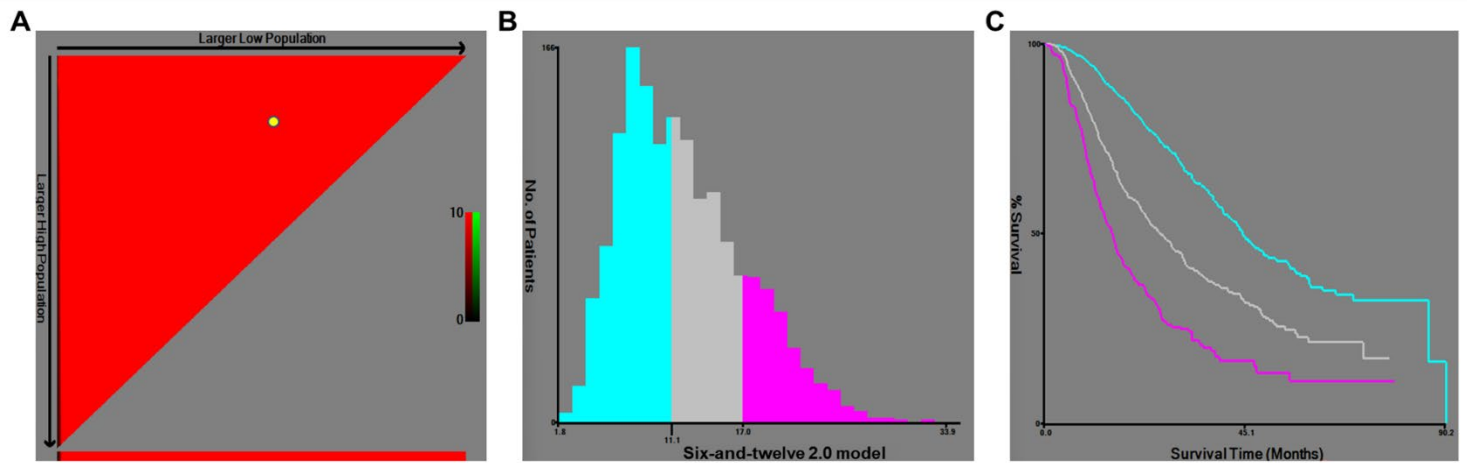
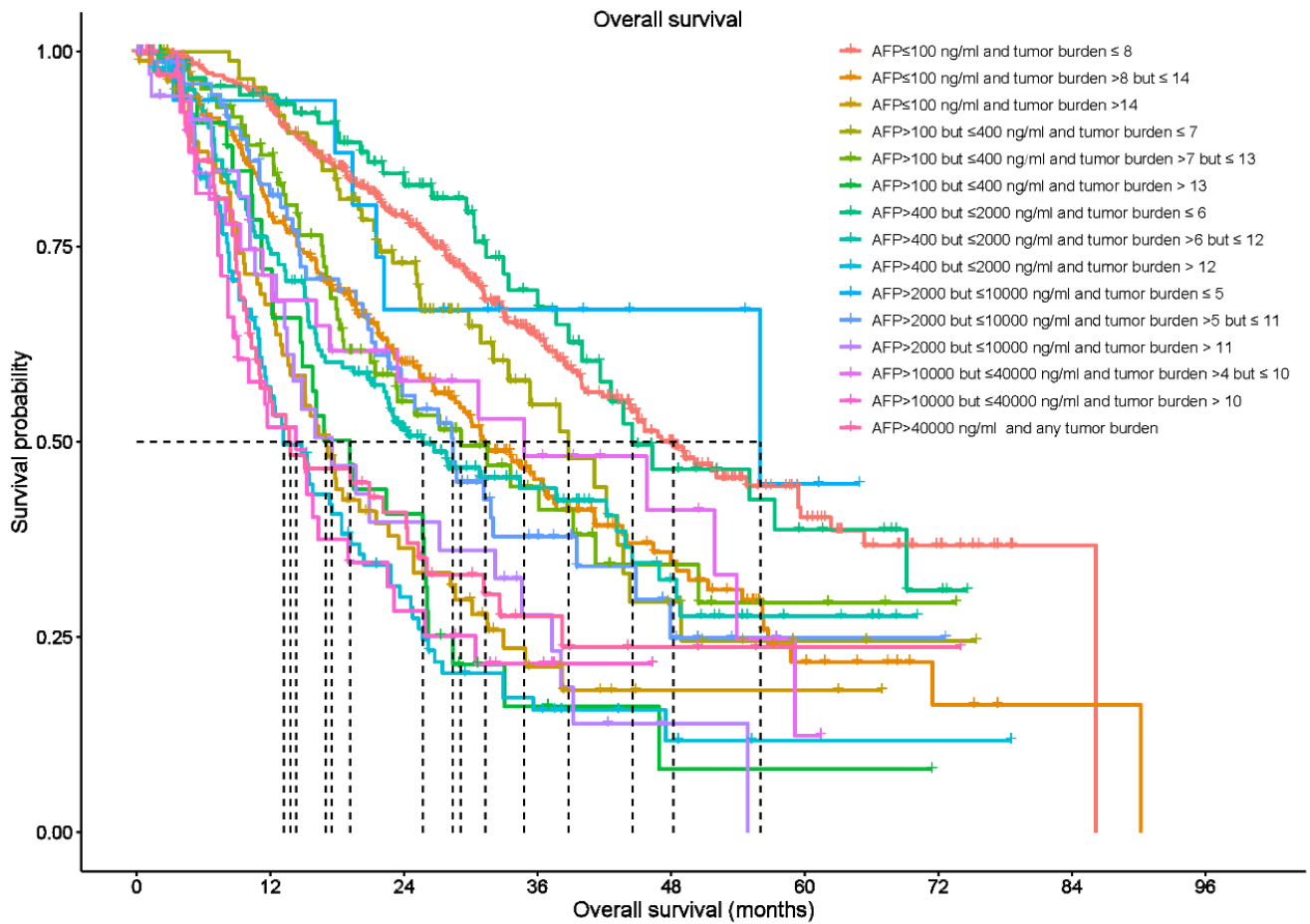**Fig. S9. Determination of the cut-offs of 6-and-12 model 2.0 by X-tile software.**

Fig. S10. Overall survival by Kaplan-Meier curve according to the risk stratification in different level of AFP value in training cohort.
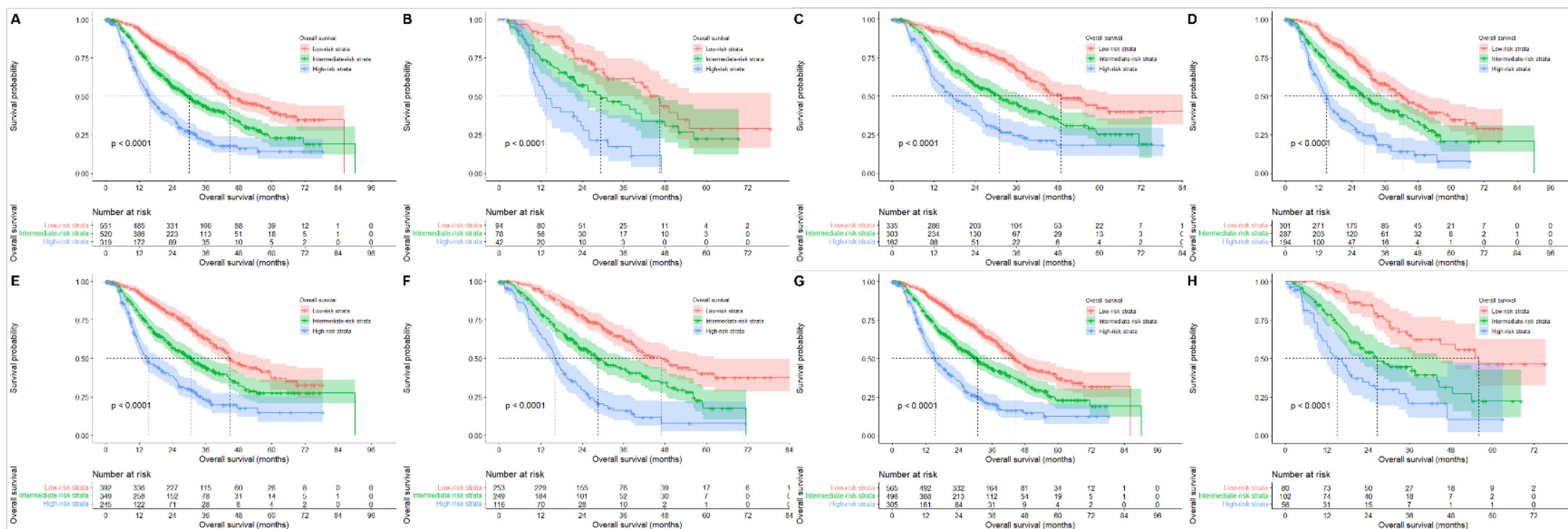
Fig. S11. Survival analyses by Kaplan-Meier method according to the risk stratification of 6-and-12 model 2.0 in different subgroups. (**A**, male; **B**, female; **C**, ALBI grade 1; **D**, ALBI grade 2; **E**, age ≤ 60 years; **F**, age > 60 years; **G**, HBV; **H**, other aetiologies, all p < 0.001 by log-rank test).
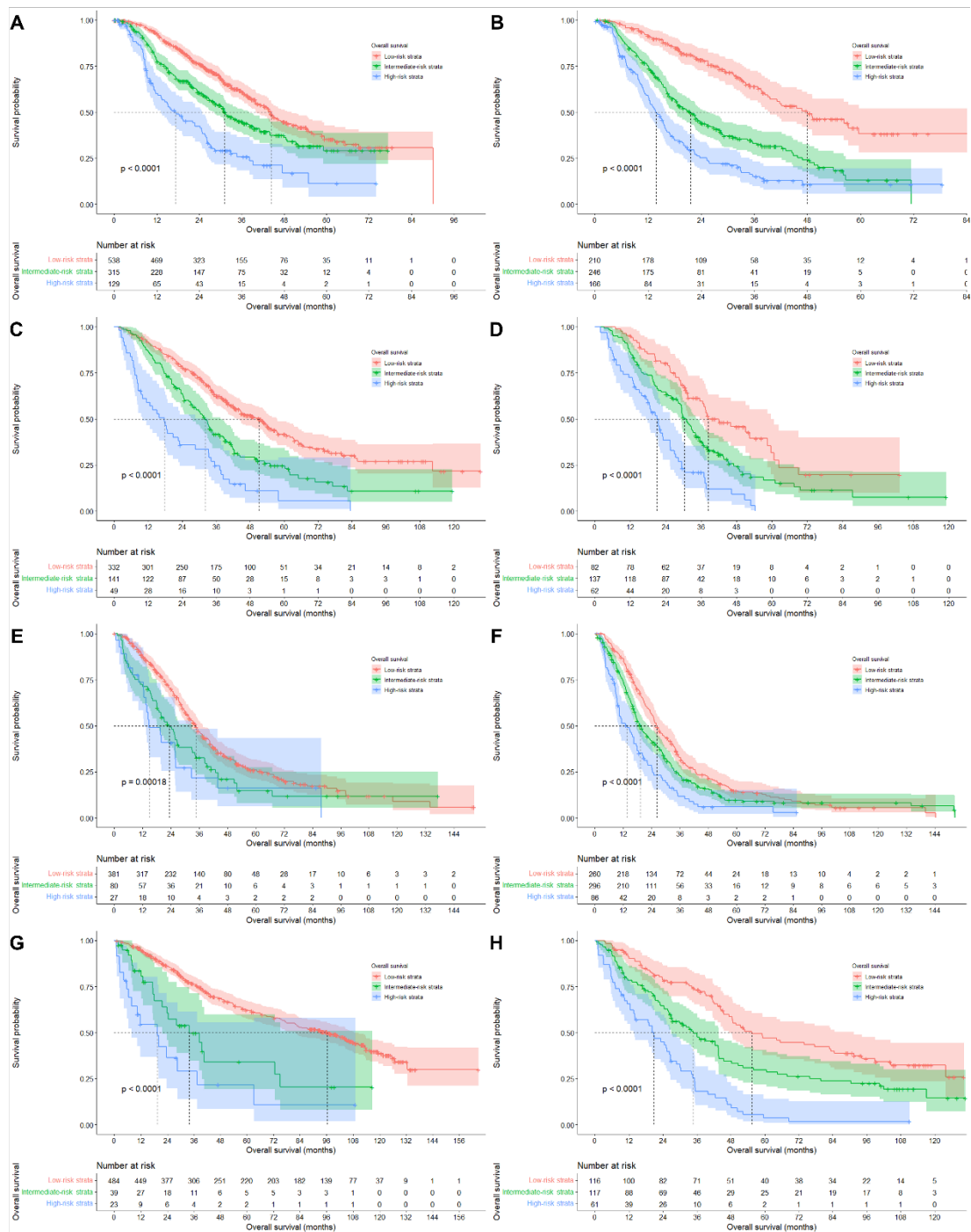
Fig. S12. Survival analyses by Kaplan-Meier method according to the risk stratification of 6-and-12 model 2.0 in BCLC-A and BCLC-B HCC among these four cohorts. (**A**, BCLC-A in training cohort; **B**, BCLC-B in training cohort; **C**, BCLC-A in internal validation cohort; **D**, BCLC-B in internal validation cohort; **E**, BCLC-A in European validation cohort; **F**, BCLC-B in European validation

cohort; **G**, BCLC-A in Asian validation cohort; **H**, BCLC-B in Asian validation
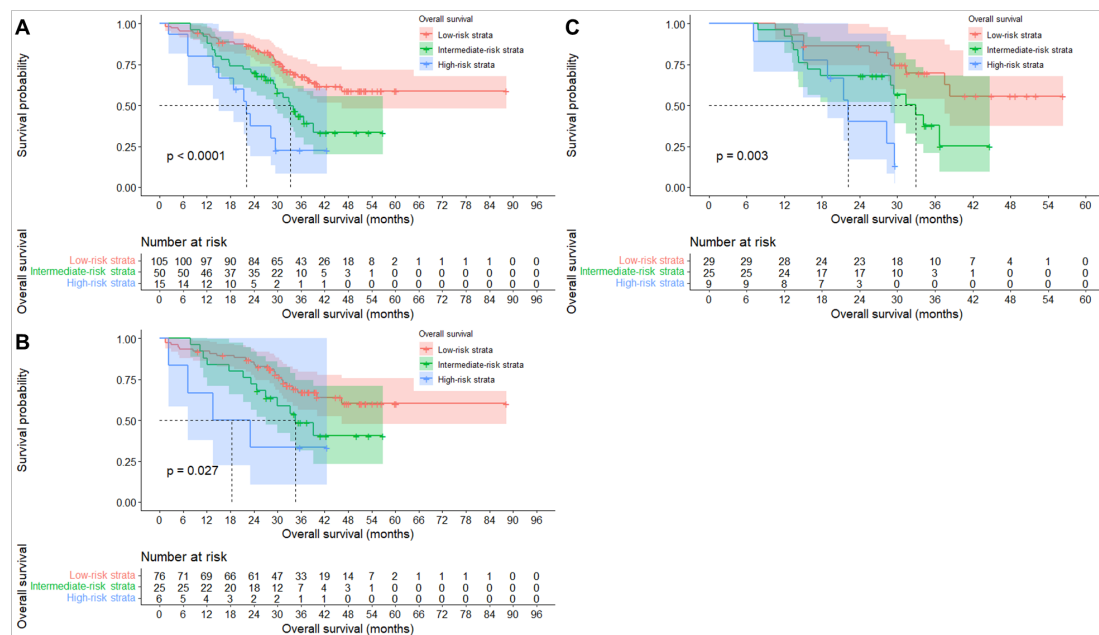
cohort, all p < 0.001 by log-rank test).

Fig.S13. Survival analyses by Kaplan-Meier method according to the risk stratification of 6-and-12 model 2.0 in Chinese DEB-TACE cohort. (A, whole cohort, p<0.001 by log-rank test; **B**, BCLC stage A, p=0.027 by log-rank test; **C**, BCLC stage B, p=0.003 by log-rank test).
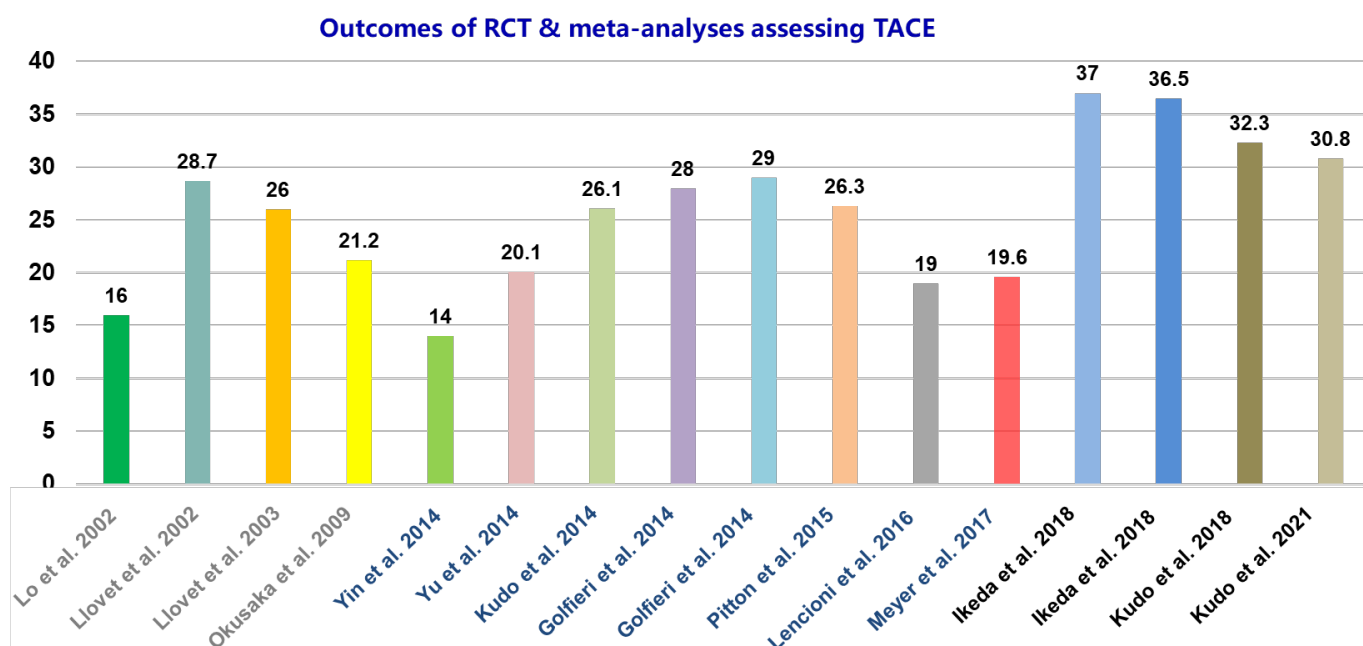
Fig. S14. The main outcomes of OS of TACE in pivotal randomized controlled

trials and meta-analysis

References

[1] **Wang Q, Xia D, Bai W**, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: A multicentre observational study. J Hepatol 2019;70:893-903.

[2] Adhoute X, Penaranda G, Raoul JL, et al. "Six-and-twelve" score for outcome prediction of hepatocellular carcinoma following transarterial chemoembolization. In-depth analysis from a multicenter French cohort. World J Hepatol 2020;12:525-532.

[3] Adhoute X, Larrey E, Anty R, et al. Expected outcomes and patients' selection before chemoembolization-"Six-and-Twelve or Pre-TACE-Predict" scores may help clinicians: Real-life French cohorts results. World J Clin Cases 2021;9:4559-4572.

[4] Adhoute X, Penaranda G, Raoul JL, et al. Hepatocellular carcinoma macroscopic gross appearance on imaging: predictor of outcome after transarterial chemoembolization in a real-life multicenter French cohort. Eur J Gastroenterol Hepatol 2019;31:1414-1423.

[5] Kaewdech A, Sripongpun P, Cheewasereechon N, et al. Validation of the "Six-and-Twelve" Prognostic Score in Transarterial Chemoembolization-Treated Hepatocellular Carcinoma Patients. Clin Transl Gastroenterol 2021;12:e00310.

[6] Muller L, Hahn F, Auer TA, et al. Tumor Burden in Patients With Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization: Head-to-Head Comparison of Current Scoring Systems. Front Oncol 2022;12:850454.

[7] Okusaka T, Kasugai H, Shioyama Y, et al. Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: a randomized phase III trial. J Hepatol 2009;51:1030-1036.

[8] Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117-2127.

[9] Yu SC, Hui JW, Hui EP, et al. Unresectable hepatocellular carcinoma: randomized controlled trial of transarterial ethanol ablation versus transcatheter arterial chemoembolization. Radiology 2014;270:607-620.

[10] Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255-264.

[11] Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology 2014;60:1697-1707.

[12] Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64:1090-1098.

[13] Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017;2:565-575.

[14] Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma

(ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol 2018;3:37-46.

[15] Ikeda M, Kudo M, Aikata H, et al. Transarterial chemoembolization with miriplatin vs. epirubicin for unresectable hepatocellular carcinoma: a phase III randomized trial. J Gastroenterol 2018;53:281-290.

[16] Kudo M, Ueshima K, Ikeda M, et al. Final Results of TACTICS: A Randomized, Prospective Trial Comparing Transarterial Chemoembolization Plus Sorafenib to Transarterial Chemoembolization Alone in Patients with Unresectable Hepatocellular Carcinoma. Liver Cancer 2022;11:354-367.