Supplementary information

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A Practical Scoring System for Conversion Therapy Stratification in Intermediate-Stage Hepatocellular Carcinoma

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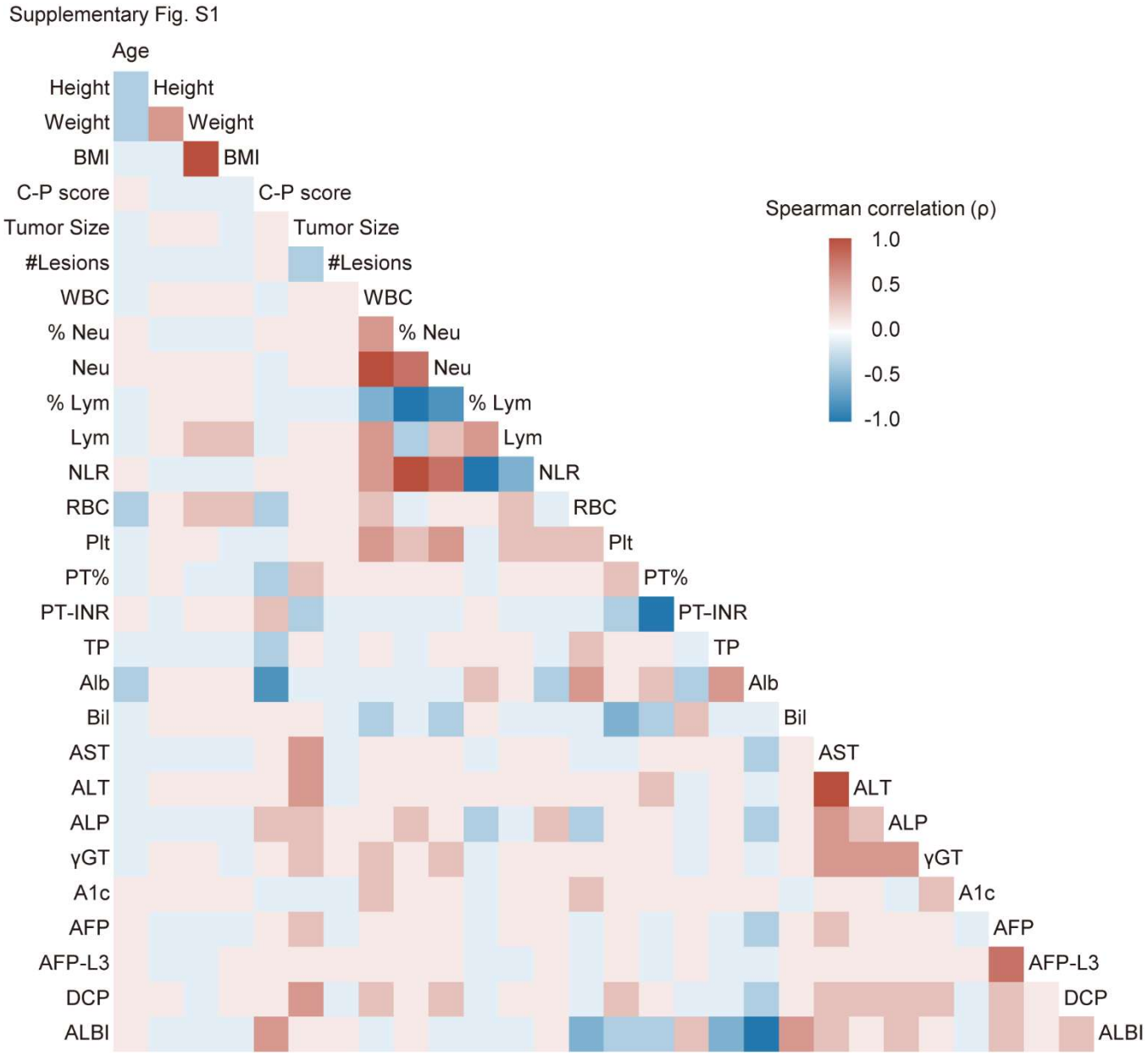
Supplementary Information Guide

Supplementary Table S3. Treatment responses and safety profiles in the derivation and validation cohorts.

Supplementary Table S4. Predictors identified by the bootstrap forest model and their relative contributions.

SUPPLEMENTARY FIGURES



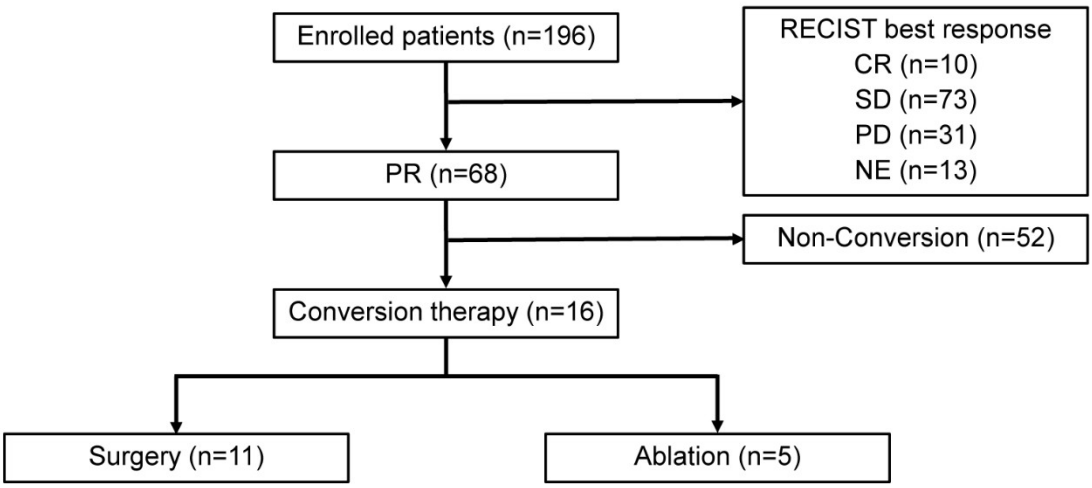
Supplementary Fig. S1. Correlation matrix of continuous variables.

Correlation matrix showing Spearman's correlation coefficients between continuous variables. Variables exhibiting high collinearity ($|r| > 0.3$) were reviewed, and one variable from each highly correlated pair was retained based on clinical relevance.

Abbreviations: BMI, body mass index; C-P score, Child–Pugh score; #Lesions, number of intrahepatic lesions; WBC, white blood cell count; %Neu, neutrophil percentage; Neu,

neutrophil count; %Lym, lymphocyte percentage; Lym, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell count; Plt, platelet count; PT%, prothrombin time activity percentage; PT-INR, prothrombin time international normalized ratio; TP, total protein; Alb, albumin; T-BIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γGT, γ-glutamyl transferase; A1c, glycated hemoglobin A1c; AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; DCP, des-γ-carboxyprothrombin; ALBI, albumin–bilirubin score.

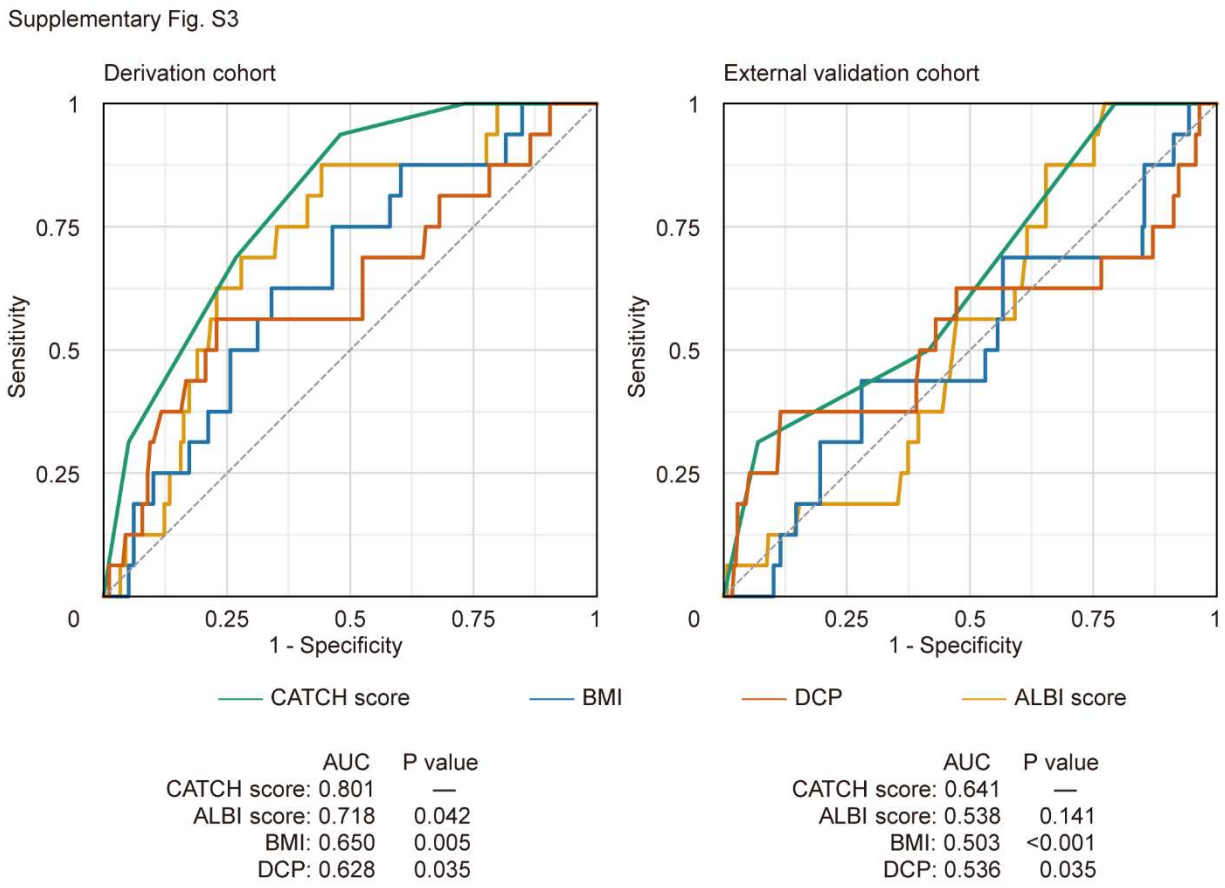
Supplementary Fig. S2



Supplementary Fig. S2. Treatment flowchart for the derivation cohort.

Flowchart illustrating treatment outcomes for 196 patients with Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC) who initiated atezolizumab plus bevacizumab (ATZ/BEV) therapy between 2020 and 2024. Of these, 68 achieved a partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and 16 subsequently underwent conversion therapy (11 surgical resections and 5 ablations).

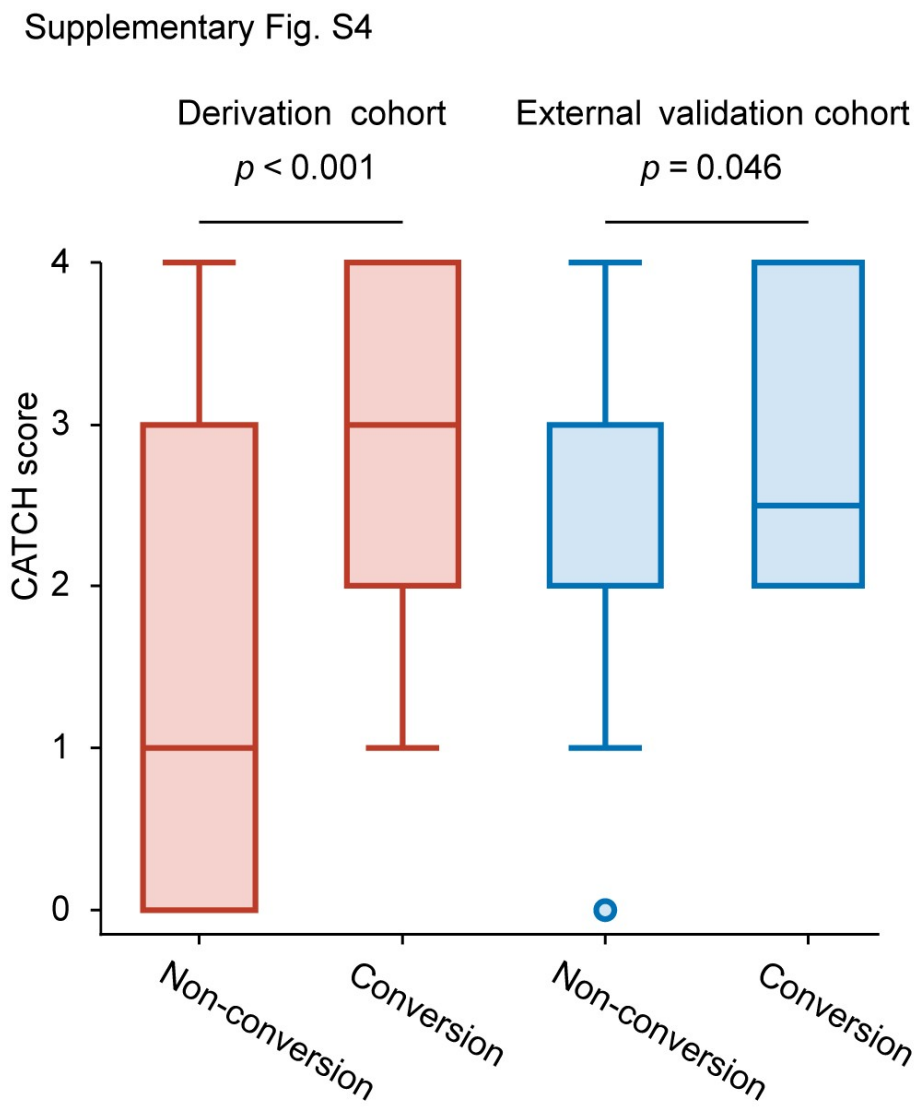
Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.



Supplementary Fig. S3. Receiver operating characteristic (ROC) curves comparing the predictive performance of the CATCH score with its individual components in the derivation and external validation cohorts.

ROC curves are shown for the derivation and external validation cohorts. The AUCs of the CATCH score were 0.801 in the derivation cohort and 0.641 in the external validation cohort. In the derivation cohort, the AUCs for the ALBI score, BMI, and DCP were 0.718, 0.650, and 0.628, respectively; in the external validation cohort, the corresponding AUCs were 0.538, 0.503, and 0.536. The AUC of the CATCH score was higher than those of its individual components in both cohorts. P values were calculated using DeLong's test versus the CATCH score.

Abbreviations: ALBI = albumin–bilirubin score; BMI = body mass index; DCP = des-γ-carboxyprothrombin.



Supplementary Fig. S4. Comparison of CATCH scores between the conversion and non-conversion groups in the derivation and external validation cohorts.

Box-and-whisker plots showing the distribution of CATCH scores in the conversion and non-conversion groups for the derivation cohort (left) and the external validation cohort (right). In the derivation cohort, the median CATCH score was significantly higher in the conversion group than in the non-conversion group (3.0 vs. 1.0, $p < 0.01$, Wilcoxon rank-sum test). Similarly, in the external validation cohort, the median CATCH score was higher in the conversion group than in the non-conversion group (2.5 vs. 2.0, $p < 0.05$). Circles indicate

outliers. Whiskers extend to the most extreme values within 1.5 times the interquartile range from the first and third quartiles.

SUPPLEMENTARY TABLES

Supplementary Table S1. All data collected prior to data preprocessing.

Data type	Collected data	Missing (%)
Demographics and medical history	Sex	0.0
	Age	0.0
	Height	0.0
	Weight	0.0
	Body mass index (BMI)	0.0
	Etiology (viral or non-viral)	0.0
	Diabetes	0.0
	Hypertension	0.0
	Dyslipidemia	0.0
	Current alcohol consumption (former drinkers classified as "no")	22.4
	Current smoking (former smokers classified as "no")	24.5
	Warfarin use	0.0
	History of transarterial chemoembolization (TACE) prior to ATZ/BEV	0.0
Tumor characteristics	Maximum intrahepatic tumor diameter (mm)	0.0
	Number of intrahepatic lesions	0.0
	Vascular invasion	0.0
	Portal vein invasion	0.0
	Macrovascular invasion (MVI)	0.0
	Venous invasion	0.0
	Bile duct infiltration	0.0
	Oncologic resectability criteria	0.0
	Up-to-seven criteria	0.0
	Clinical stage (Japan Liver Cancer Association)	0.0
Liver function and disease severity	Child–Pugh score	0.0
	Modified albumin–bilirubin (mALBI) grade	0.0
	Albumin–bilirubin (ALBI) score	0.0
	Ascites	0.0
	Hepatic encephalopathy	0.0
	Gastroesophageal varices	3.1

	Eastern Cooperative Oncology Group Performance Status (ECOG-PS)	0.0
Hematological and biochemical parameters and tumor markers	Red blood cell count	0.0
	White blood cell count	0.0
	Platelet count	0.0
	Neutrophil count	17.9
	Lymphocyte count	6.1
	Neutrophil-to-lymphocyte ratio (NLR)	24.0
	Prothrombin time (PT) activity, %	3.1
	Total protein	19.4
	Albumin	0.0
	Total bilirubin (T-BIL)	0.0
	Aspartate aminotransferase (AST)	0.0
	Alanine aminotransferase (ALT)	0.0
	Alkaline phosphatase (ALP)	20.4
	Gamma-glutamyl transferase (GGT)	18.4
	Glycated hemoglobin A1c (HbA1c)	7.7
	Alpha-fetoprotein (AFP)	0.0
	Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3)	16.3
	Des-γ-carboxyprothrombin (DCP)	0.5

Abbreviations: ATZ/BEV = atezolizumab plus bevacizumab.

Supplementary Table S2. Patient characteristics of the external validation cohort.

	Total (n=303)	Conversion (n=16)	Non-Conversion (n=287)	P value
Age, years	75 [69–81]	72 [69–78]	75 [69–82]	.20
Sex: Male	241 (79.5)	12 (75.0)	229 (79.8)	.75
Body mass index: kg/m^2	23.8 [21.1–26.0]	23.4 [19.9–26.6]	23.8 [21.2–26.0]	.97
Etiology: Non-B, non-C	175 (57.8)	9 (56.2)	166 (57.8)	1
Comorbidities				
Hypertension	200 (66.0)	9 (56.2)	191 (66.6)	.42
Hyperlipidemia	67 (22.1)	2 (12.5)	65 (22.6)	.54
Diabetes	144 (47.5)	8 (50.0)	136 (47.4)	1
ECOG-PS				
0	246 (81.2)	15 (93.8)	231 (80.5)	.32
1	48 (15.8)	1 (6.2)	47 (16.4)	.48
2	9 (3.0)	0 (0)	9 (3.1)	1
Maximum intrahepatic lesion size (mm)[a]	29.0 [20.0–50.0]	34.5 [27.8–79.8]	28.0 [19.8–50.0]	.11
Met Up-to-7 criteria [b]	63 (21.1)	3 (18.8)	60 (21.3)	1
Laboratory parameters				
Platelets, ×10^4/μL [c]	15.4 [10.5–21.2]	14.6 [12.2–22.1]	15.5 [10.5–20.6]	.93
AST, U/L	36.0 [26.0–50.0]	39.5 [31.0–61.5]	36.0 [26.0–48.0]	.24
HbA1c, %[d]	6.0 [5.5–6.7]	6.0 [5.7–7.0]	6.0 [5.5–6.7]	.39
AFP, ng/mL[e]	10.5 [4.0–77.8]	6.0 [3.8–28.2]	10.6 [4.0–81.8]	.36
DCP, mAU/mL[f]	151.0 [32.8–838.0]	79.0 [19.5–4902.5]	155.5 [35.0–735.5]	.63
ALBI score	−2.48 [−2.74–−2.26]	−2.50 [−2.64–−2.38]	−2.48 [−2.74–−2.25]	.61
Prior TACE	40 (13.2)	1 (6.2)	39 (13.6)	.70

Data are expressed as median [interquartile range] or n (%). Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; AST = aspartate aminotransferase; HbA1c = hemoglobin A1c; AFP = alpha-fetoprotein; DCP = des-γ-carboxyprothrombin; ALBI

= albumin–bilirubin; TACE = transarterial chemoembolization. Missing data were as follows: [a]maximum intrahepatic lesion size, n = 1; [b]Met Up-to-7 criteria, n = 5; [c]platelets, n = 1; [d]HbA1c, n = 9; [e]AFP, n = 1; and [f]DCP, n = 1.

Supplementary Table S3. Treatment responses and safety profiles in the derivation and validation cohorts.

	Derivation (n = 196)	Validation (n = 303)
Overall response*	78 (39.8)	85 (28.1)
Disease control†	151 (77.0)	248 (81.8)
Best overall response per RECIST v1.1		
CR	10 (5.1)	12 (4.0)
PR	68 (34.7)	73 (24.1)
SD	73 (37.2)	163 (53.8)
PD	31 (15.8)	42 (13.9)
NE	14 (7.1)	13 (4.3)
Adverse events		
Any Grade	116 (59.2)	250 (82.5)
Grade ≥3	53 (27.0)	111 (36.6)
irAEs	32 (16.3)	Not collected
Conversion therapy	16 (8.2)	16 (5.3)
Surgery	11 (5.6)	7 (2.3)
Ablation	5 (2.6)	9 (3.0)

Data are presented as n (%). irAEs were not collected in the validation cohort.

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; irAEs = immune-related adverse events.

*Overall response includes CR and PR.

†Disease control includes CR, PR, and SD.

Supplementary Table S4. Predictors identified by the bootstrap forest model and their relative contributions.

Factor	Contribution (%)
ALBI score	15.47
BMI	9.08
DCP	8.97
Platelet count	8.85
AST	8.23
Age	6.90
AFP	6.89
Maximum tumor diameter	5.70
HbA1c	4.76
Smoking	3.86
Alcohol consumption	3.76
Number of intrahepatic lesions	3.00
Etiology: Viral	2.59
Comorbidity: Hypertension	2.17
Comorbidity: Diabetes	1.97
History of TACE	1.90
ECOG-PS	1.21
Comorbidity: Hyperlipidemia	1.19
Sex	1.15
Gastroesophageal varices	1.15
Up-to-seven criteria	0.89
Ascites	0.30
Warfarin use	0.01
Encephalopathy	0.00

Abbreviations: ALBI = albumin–bilirubin; BMI = body mass index; DCP = des-γ-carboxyprothrombin; AST = aspartate aminotransferase; AFP = alpha-fetoprotein; HbA1c = glycated hemoglobin A1c; TACE = transarterial chemoembolization; ECOG-PS = Eastern Cooperative Oncology Group performance status.