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ORIGINAL RESEARCH

Prediction Model of Survival in Unresectable HCC with Central Bile Duct Invasion Receiving TACE After Biliary Drainage: TEMP Score

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Purpose: Central bile duct invasion (BDI) by hepatocellular carcinoma (HCC) is rare and associated with poor prognosis, lacking treatment guidelines. While transarterial chemoembolization (TACE) is often used for unresectable cases, determining optimal candidates post-biliary drainage is controversial. We aim to develop a prognostic prediction model for unresectable HCC (uHCC) patients with central BDI receiving sequential TACE after successful biliary drainage.

Patients and Methods: We retrospectively analyzed 267 uHCC patients with central BDI receiving successful biliary drainage and sequential TACE from seven tertiary centers (2015–2021), divided into training (n=187) and validation (n=80) sets. Using Cox proportional-hazards regression model, we identified key prognostic indicators for overall survival (OS) and constructed a prediction model.

Results: Pre-TACE total bilirubin (TBil) values, extrahepatic spread (EHS), multiple intrahepatic tumors (MIT), and portal vein tumor thrombus (PVTT) were identified as the significant clinical indicators for OS. These four parameters were included in a novel prediction model, named TEMP score, which could successfully categorize patients in the training set into three distinct risk grades with median OS of 26.9, 9.4, and 5.8 months, respectively. The TEMP score predicted the time-dependent areas under the receiver operating characteristic curves for OS at 6 months, 1 year, and 2 years of 0.813/0.907, 0.833/0.782, and 0.838/0.811 in the training and validation sets, with corresponding C-indices of 0.812/0.929, 0.829/0.761, and 0.818/0.791, respectively, outperforming other currently available models in both cohorts. The calibration curve of the model for predicting OS presented good consistency between observations and predictions in both the training set and validation set.

Conclusion: The TEMP score effectively stratifies the prognosis of uHCC patients with central BDI who have undergone successful bile drainage and sequential TACE, helping to identify those who may benefit from TACE treatment.

Keywords: bile duct invasion, hepatocellular carcinoma, transarterial chemoembolization, prognosis, risk stratification

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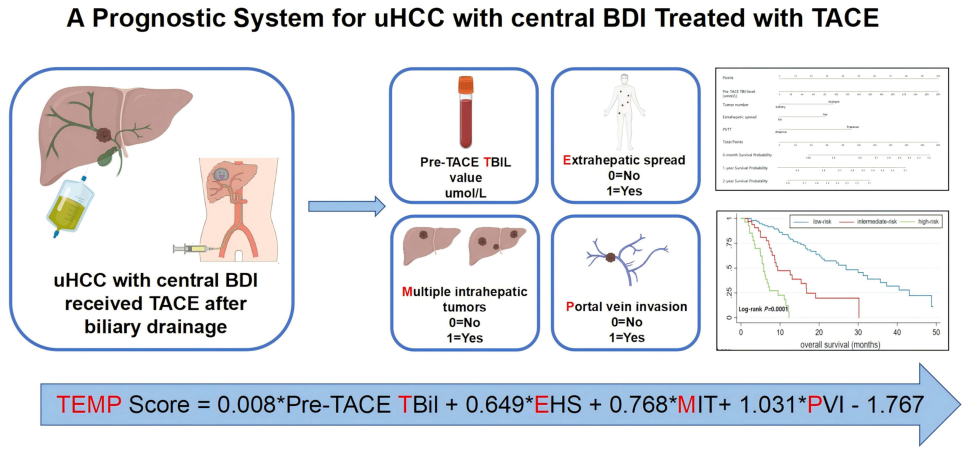
Graphical Abstract



Introduction

Central bile duct invasion (BDI) by hepatocellular carcinoma (HCC) is an uncommon condition with a poor prognosis,[1] occurring in 0.5% to 13% of cases.[2] Unlike usual HCC, it often presents with obstructive jaundice. This occurs due to tumor infiltration, compression, or thrombosis in the central bile ducts, including the common hepatic duct or first-order bile duct branches.[3,4] Its dismal prognosis is mainly due to the advanced stage at diagnosis,[5,6] limited therapeutic options for fragile liver function reserve, high recurrence risk post-resection,[7] and the lack of guideline-recommended treatments for unresectable cases.[8,9]

For central BDI unresectable HCC (uHCC) patients with obstructive jaundice, biliary drainage can alleviate the condition and enable subsequent anti-tumor treatment.[2,10] Transarterial chemoembolization (TACE) following successful drainage has been shown to be an effective approach, with a median survival of 13.7 months (IQR: 8.2–40.0), significantly longer than that of conservative treatment (2.6 months, IQR: 1.8–4.9, $P< 0.001$).[11] However, the prognosis of uHCC patients with BDI after TACE remains inconsistent, with reported outcomes varying widely. Previous research has revealed the clinical diversity among HCC patients with BDI, characterized by a higher prevalence of poorly differentiated tumors, lymphovascular invasion, and macrovascular invasion due to the infiltrative nature of the disease.[12] These factors have been linked to heterogeneous and often unfavorable clinical outcomes with TACE.[13] Therefore, a comprehensive assessment of individual patient characteristics and the implementation of a patient stratification system are crucial when contemplating TACE as a treatment option.

There are several assessment tools used to predict the prognosis of HCC patients treated with TACE, such as the Hepatoma arterial-embolisation prognostic (HAP) score,[14] modified HAP-II score.[15] In addition, the rating system for liver function in patients with HCC, which helps determine the suitability for TACE treatment, includes the Child-Pugh score and the albumin-bilirubin (ALBI) score.[16] (Supplemental Table 1, However, these tools are not specifically applicable to uHCC patients with central BDI. They fail to comprehensively assess the patient's condition or the complexities introduced by BDI. Decision-making for TACE in HCC with central BDI is often challenging due to difficulties in selecting appropriate candidates. This challenge is compounded by overestimated liver function scores resulting from obstructive jaundice,[17] the complexity of the disease,[12] and the timing of subsequent treatments following biliary drainage.[10] Currently, nomograms are well-developed tools that can provide personalized, evidence-based, and accurate risk estimations.[18] The purpose of this study was to create and validate a novel nomogram using baseline independent variables to predict individualized survival outcomes for uHCC patients with central BDI after biliary drainage and subsequent TACE and help to identify the ideal candidates.

Materials and Methods

Study Design and Patient Eligibility

For this retrospective study, data were collected from January 1, 2015, to December 31, 2021, from seven tertiary medical centers. Approval was obtained from the institutional review board of Sun Yat-Sen University First Affiliated Hospital (Approval ID 2023[898]), and informed consent was waived because of the study's retrospective design without involving any direct patient contact or intervention. All patient data were anonymized before analysis to ensure confidentiality and comply with Declaration of Helsinki and current ethical guidelines. This analysis was reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[19]

The eligibility criteria were as follows: (a) age, 18–75 years; (b) unresectable HCC diagnosed according to the American Association for Liver Disease and European/American Association for Liver Disease guidelines;[8,20] (c) at least one typical enhanced measurable intrahepatic target lesion based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST);[21] (d) central BDI diagnosis based on elevated total bilirubin (TBil) level and the typical appearance of cholangiectasis (common duct diameter > 6 mm and intrahepatic duct diameter > 3 mm) caused by a tumor infiltrating the common hepatic duct or the first-order branch of the bile ducts, as observed in CT or MRI;[4] (e) successful biliary drainage was achieved by percutaneous transhepatic cholangial drainage (PTCD) or stent implantation through PTCD or endoscopic retrograde cholangiopancreatography (ERCP) before TACE; and (f) TACE was performed as the first-line local treatment for HCC after successful biliary drainage.

We excluded patients who met the following criteria: (a) portal vein tumor thrombus (PVTT), also known as portal vein invasion (PVI), in the main portal vein; (b) elevated TBil levels due to other etiologies; (c) prior treatment with TACE or systemic therapy; (d) presence of other accompanying cancers; (e) loss to follow-up; (f) incomplete medical records.

Patients from seven tertiary medical centers between January 1, 2015, and December 31, 2018, were assigned to the training set, while patients from three of the seven centers between January 1, 2019, to December 31, 2021, were enrolled in the validation set.

Biliary Drainage and Subsequent TACE Procedures

After diagnosing uHCC with central BDI and obstructive jaundice, biliary drainage was performed either by percutaneous transhepatic cholangial drainage (PTCD) or biliary stenting through PTC/ERCP. Cholangitis was prevented or managed by antibiotics before TACE. Successful biliary drainage is defined as a reduction in the serum TBil concentration to > 50% of the pre-procedural value or a decrease to < 3 mg/dL (51 umol/L) within four weeks and the absence of cholangitis.[22]

In our study, TACE was performed after confirming successful biliary drainage and was administered on an on-demand basis. Pre-TACE TBil was defined as the total bilirubin level measured before TACE after successful drainage. TACE, including cTACE or DEB-TACE after successful biliary drainage, was performed by interventional radiologists with at least 5 years of experience under digital subtraction angiography. Local anesthesia was administered by injecting 5 mL of lidocaine into the subcutaneous tissue of the groin. Before chemoembolization, diagnostic angiography was first performed to assess portal vein patency and the arterial supply to the liver. Details of DEB-TACE and cTACE are shown in supplemental method. The embolization endpoint was reached when contrast agent in the tumor-feeding artery cleared within 2–5 heartbeats. If the endpoint was not achieved, the same embolic agents and particles were used for further embolization. Angiography was repeated 5 minutes later to confirm whether stasis was achieved in the segmental or subsegmental vessels.

Data Collection and Outcomes Assessment

Patients' data were extracted from electronic medical records, including demographic characteristics, clinical features, laboratory indexes of blood routine and liver function within 72 hours before TACE, serum α-fetoprotein (AFP) level, and the details of the biliary drainage and TACE procedure. The overall survival (OS) was measured from the first TACE after successful biliary drainage to death or the last follow-up. Time to progression (TTP) was defined as the number of

days from the first TACE until the detection of progressive disease. Triphasic contrast-enhanced CT or MRI was performed at baseline and at regular follow-ups post-TACE, typically at 4–6 weeks, as per the mRECIST criteria, to assess tumor response.[21] Overall response rate (ORR) was defined as the sum of complete response and partial response. The best overall response during treatment was considered the final response. The last follow-up date was in June 2023.

Statistical Analysis

Comparisons between groups were performed using Student's *t*-test for continuous variables, expressed as mean ± standard deviation, and Pearson's chi-squared (χ^2) test for categorical data, presented as frequency values. Survival curves were estimated using the Kaplan-Meier analyses and compared by Log rank test. Univariate and multivariate analyses used a Cox proportional-hazards regression model on the training set to identify clinical indicators that were significantly associated with OS of TACE-treated patients. Then, a predictive nomogram was established based on these clinical indicators, resulting in the development of a new prognostic scoring system named the TEMP score, which incorporates Pre-TACE TBil, extrahepatic spread (EHS), multiple intrahepatic tumors (MIT; defined as ≥2 tumors in the liver), and PVTT from the above-mentioned analyses. Discrimination and performance of the nomogram were measured by Harrell's C concordance index (C-index), and area under the time-dependent receiving operator characteristic curve (AUROC), respectively. The effectiveness and calibration of the nomogram were shown using the calibration plot. The net benefits at different threshold probabilities in the both datasets were measured, and Decision curve analysis (DCA) was used to establish the nomogram's clinical relevance. The TEMP score was calculated for every patient and cutoff value of different risk grade for OS was determined by X-tile 3.6.1 (Robert L Camp, M.D., Ph.D., Yale University, USA),[23,24] and ultimately validated through Kaplan-Meier survival analysis. The novel nomogram was compared with some current models, including the ALBI score,[16] Barcelona Clinic Liver Cancer (BCLC) stage,[25] Child-Pugh score, HAP score,[14] mHAP-II score[15] in both training and validation datasets. All statistical analyses were achieved using R version 4.0.2 (Packages: ggplot2, glmnet, rms, pROC, survival, survminer, timeROC) and STATA version 15.0 (StataCorp Lp). All statistical tests were two-sided, and a P value < 0.05 indicated statistical significance.

Results

Characteristics of uHCC Patients with Central BDI and Treatment Outcome

After exclusion, a total of 267 uHCC patients with central BDI who underwent TACE after successful drainage were enrolled in this retrospective study and sorted into the training (n = 187) and validation (n = 80) datasets (shown in Figure 1). The baseline characteristics of the patients are shown in Table 1. There were no differences in baseline demographics between datasets (all $P > 0.05$). The median interval between biliary drainage and TACE was 9.6 (range: 1–30) days. The baseline characteristics of patients from each institute are shown in Supplemental Table 2.

The median survival of the entire cohort was 16.7 (95% CI:15.2–21.6) months, with 6-month, 1-year, and 2-year survival rates being 84.5%, 65.2%, and 41.5%, respectively (shown in Supplemental Figure 1a). There was no difference in the median survival between the training (16.8 [95% CI: 13.1–21.4] months) and validation datasets ((16.7 [95% CI: 13.3–25.0] months); $P = 0.759$; shown in Supplemental Figure 1b). ORR according to mRECIST criteria of the entire cohort, the training, and validation datasets are 65.2%, 61.5%, and 73.8%, respectively (Supplemental Table 3).

Univariate and Multivariate Analysis

The results of univariate and multivariate analyses are presented in Table 2. Univariate analysis showed AFP, Pre-TACE TBil, intrahepatic tumors number, PVTT, extrahepatic spread (EHS), and treatment allocation were significantly correlated with OS. Multivariate Cox proportional hazards analysis showed that high Pre-TACE TBil (HR = 1.01, $P < 0.001$), EHS (HR = 1.89, $P = 0.001$), MIT (HR = 2.33, $P < 0.001$), and the presence of PVTT (HR = 2.20, $P < 0.001$) were independent factors for OS.

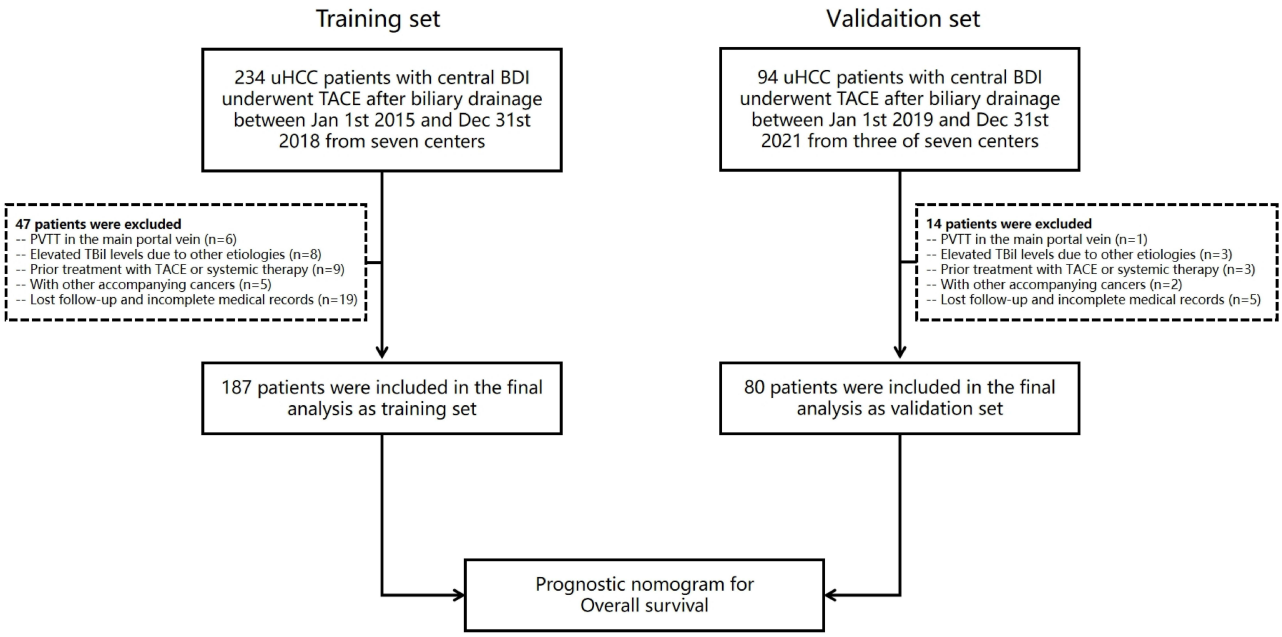


Figure 1 Patient inclusion flowchart.

Development of the Prognostic Model

The final prognostic model was developed using the four aforementioned variables, with β-coefficients detailed in Table 3. Using the regression coefficients of the multivariable model, the linear predictor was calculated as follows: the TEMP score = 0.008*Pre-TACE TBil (umol/L) + 0.649*EHS (0 = no, 1 = yes) + 0.768*MIT (0 = no, 1 = yes) + 1.031*PVTT (0 = no, 1 = yes) - 1.767. This calculated linear predictor represents the new prognostic model for uHCC patients with central BDI after successful biliary drainage and sequential TACE. A nomogram based on the model was created to visualize for individual patient risk stratification and predict the 6-month, 1-year, and 2-year survival probabilities (shown in Figure 2).

Table 1 Characteristics of the Study Population

Characteristics	Number (%)/Median (IQR) [a]		
	Training Set (n = 187)	Validation Set (n = 80)	*P* value
Age (y)	54.5±10.9	54.1±10.8	0.660
< 50	66 (35.3%)	26 (32.5%)	
≥ 50	121 (64.7%)	54 (67.5%)	
Sex			0.839
Male	163 (87.2%)	69 (86.3%)	
Female	24 (12.8%)	11 (13.7%)	
Treatment allocation			0.799
DEB-TACE	92 (49.2%)	38 (47.5%)	
cTACE	95 (50.8%)	42 (52.5%)	
HBV			0.407
No	36 (19.3%)	12 (15.0%)	
Yes	151 (80.7%)	68 (85.0%)	
AFP (ng/mL)			0.168
< 400	80 (42.8%)	27 (33.7%)	
≥ 400	107 (57.2%)	53 (66.3%)	

(*Continued*)

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Table 1 (Continued).

Characteristics	Number (%)/Median (IQR) [a]		
	Training Set (n = 187)	**Validation Set (n = 80)**	***P* value**
WBC (× 10^9)	8.1 (5.1–10.1)	6.9 (6.2–7.7)	0.528
RBC (× 10^{12})	4.1 (3.9–4.2)	4.0 (3.8–4.2)	0.629
Platelet count (× 10^9)	182 (168–195)	190 (162–218)	0.573
ALB (g/L)	34.5 (33.7–35.2)	34.6 (33.3–35.8)	0.838
ALT (U/L)	74.2 (62.6–85.8)	79.9 (60.8–99.0)	0.600
PT (s)	13.3 (12.9–13.8)	13.3 (12.9–13.7)	0.974
TBil on admission [b](umol/L)	191.7 (175.2–208.3)	213.3 (184.6–242.1)	0.175
Pre-TACE TBil [c] (umol/L)	84.5 (77.0–92.0)	93.6 (82.0–105.2)	0.191
Multiple intrahepatic tumors			0.053
No	100 (53.5%)	53 (66.3%)	
Yes	87 (46.5%)	27 (33.7%)	
Tumor size [d](cm)			0.718
< 7 cm	82 (43.8%)	37 (46.3%)	
≥ 7 cm	105 (56.2%)	43 (53.7%)	
PVTT			0.969
No	86 (46.0%)	37 (46.3%)	
Yes	101 (54.0%)	43 (53.7%)	
Extrahepatic spread			0.388
No	136 (72.7%)	54 (67.5%)	
Yes	51 (27.3%)	26 (32.5%)	
BCLC stage			0.733
A	17 (9.1%)	5 (6.3%)	
B	51 (27.3%)	20 (25.0%)	
C	119 (63.6%)	55 (68.7%)	
Child-Pugh score	8 (7–8)	8 (7–8)	0.842
ALBI score	−1.70[(−1.78)-(−1.63)]	−1.68[(−1.80)-(−1.56)]	0.751
HAP score	2 (1–3)	2 (1–3)	0.417
mHAP-II score	3 (2–4)	3 (2–4)	0.572
Biliary stent			0.607
No	163 (87.2%)	71 (88.8%)	
Yes	24 (12.8%)	9 (11.2%)	

Notes: [a] Median with interquartile range are shown for quantitative variables, whereas counts with proportions are shown for categorical variables. [b] TBil on admission, TBil measured at the time of the first diagnosis. [c] Pre-TACE TBil, TBil measured after successful drainage before performing TACE. [d] Tumor size, size of the largest tumor.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads TACE; HAP, Hepatoma arterial-embolisation prognostic; mHAP-II, modified HAP-II; PVTT, portal vein tumor thrombus; RBC, red blood cells; TBil, total bilirubin; WBC, white blood cells.

Table 2 Univariate and Multivariate Cox Analyses of Predictors of Overall Survival After Treatment

	Overall Survival					
	Univariate			**Multivariate**		
Factor	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.99	0.98–1.02	0.877			
Sex, Male vs Female	0.66	0.39–1.12	0.124			

(*Continued*)

Table 2 (Continued).

	Overall Survival					
	Univariate			Multivariate		
HBV, No vs Yes	0.86	0.52–1.43	0.566			
AFP, < 400 vs ≥ 400 ng/mL	1.71	1.03–2.83	0.007	1.38	0.97–1.96	0.072
WBC (× 10^9)	0.99	0.98–1.01	0.535			
RBC (× 10^{12})	0.99	0.78–1.24	0.904			
Platelet count (× 10^9)	0.99	0.99–1.01	0.330			
Pre-TACE TBil [a] (per 1 umol/L increase)	1.01	1.00–1.01	<0.001	1.01	1.00–1.01	<0.001
ALB (g/L)	0.97	0.93–1.01	0.091			
ALT (U/L)	0.99	0.99–1.01	0.614			
PT (s)	0.96	0.88–1.05	0.354			
Multiple intrahepatic tumors, No vs Yes	2.24	1.47–3.41	<0.001	2.33	1.63–3.34	<0.001
Tumor size [b] (cm), < 7 vs ≥ 7 cm	0.92	0.61–1.39	0.689			
PVTT, No vs Yes	2.81	1.81–4.36	<0.001	2.20	1.51–3.22	<0.001
Extrahepatic spread, No vs Yes	1.96	1.27–3.03	0.003	1.89	1.32–2.72	0.001
Treatment allocation [c], DEB-TACE vs cTACE	1.98	1.27–3.09	0.003	1.30	0.89–1.89	0.173
Biliary stent, No vs Yes	1.06	0.59–1.92	0.833			

Notes: [a] Pre-TACE TBil, TBil measured after successful drainage before performing TACE. [b] Tumor size, size of the largest tumor. [c] Treatment allocation, conventional transarterial chemoembolization or drug-eluting beads transarterial chemoembolization.
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; HBV, hepatitis B virus; PVTT, portal vein tumor thrombus; RBC, red blood cells; TBil, total bilirubin; WBC, white blood cells.

Table 3 Prognostic Factors and Estimated Scores in the Training Set

Variable	β	HR	95% *CI*	*P* value
Pre-TACE TBil [a] (per 1 umol/L increase)	0.0081	1.01	1.00–1.01	<0.001
Extrahepatic spread				
No		Ref		
Yes	0.6485	1.86	1.29–2.67	0.001
Multiple intrahepatic tumors				
No		Ref		
Yes	0.7681	2.28	1.60–3.25	<0.001
PVTT				
No		Ref		
Yes	1.0308	2.36	1.63–3.41	<0.001

Notes: [a] Pre-TACE TBil, TBil measured after successful drainage before performing TACE.
Abbreviations: PVTT, portal vein tumor thrombus; TBil, total bilirubin.

The Novel Model Predicts Overall Survival and Tumor Response

According to the above formula developed in our research, the TEMP score was calculated for all patients. To generate different risk grades for OS, the following cutoffs of the TEMP score were applied (determined using X-tile software in the training set): ≤ 0.34 for low-risk, > 0.34 and ≤ 0.95 for intermediate-risk, and > 0.95 for high-risk. The median OS for patients in each of the three grades was analyzed by Kaplan-Meier survival curve. In the training set, the median OS for patients in the low-risk, intermediate-risk, and high-risk grades were 26.9 (95% CI, 20.5–35.7), 9.4 (95% CI, 7.7–16.7), and 5.8 (95% CI, 3.6–7.0) months, respectively (Figure 3a). In the validation set, the median OS for patients in the low-risk, intermediate-risk, and high-risk grades were 24.4 (95% CI, 16.3–40.4), 13.0 (95% CI, 8.3–18.7), and 3.0 (95% CI, 1.2–11.8) months, respectively (Figure 3b). The 6-month, 1-year, and 2-year survival rates of all grades in the training and validation datasets are shown in Supplemental Table 4. The ORR of the three grades were 77.6%, 51.3%, and 15.6%

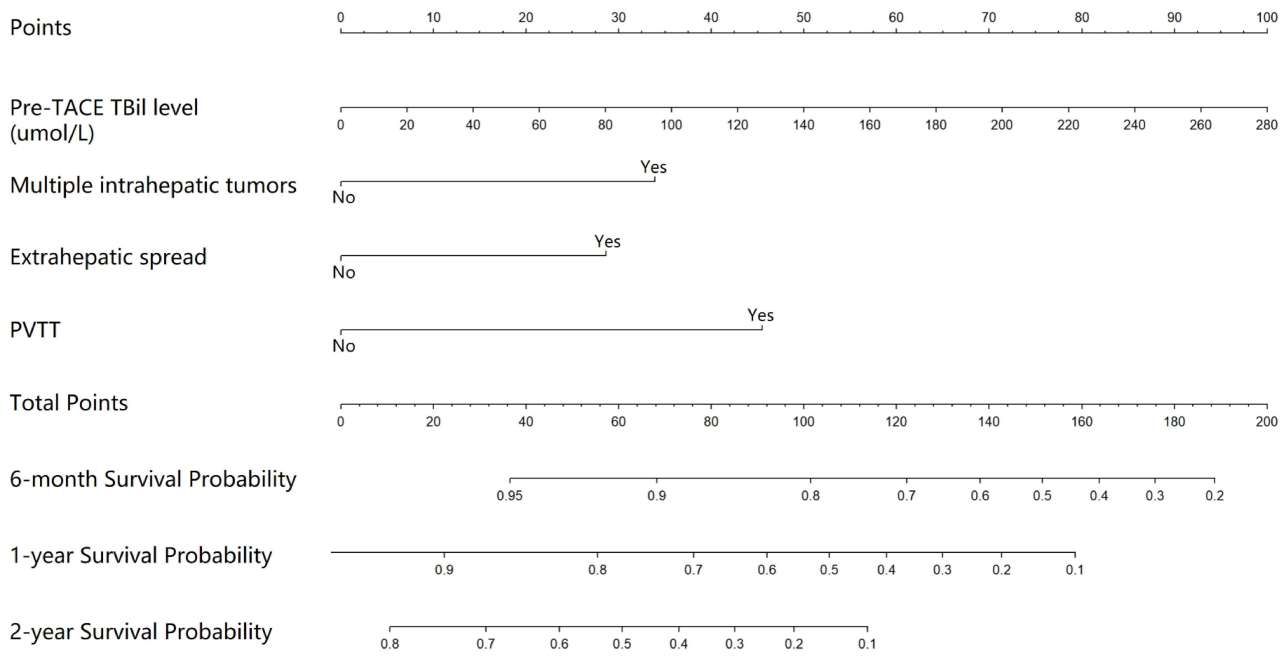

Figure 2 Nomogram of the TEMP score for individual survival prediction.
Abbreviations: PVTT, portal vein tumor thrombus; TBil, total bilirubin.

in the training set, and 84.0%, 66.7%, and 41.7% in the validation set (Supplemental Table 5). Survival curves and tumor response were significantly different among the three risk grades in the training and validation datasets.

Discrimination and Calibration of the Model and Comparison with Other Models

The calibration plot for the probabilities of 6-month, 1-year, 2-year OS fitted well between the actual observation and the prediction of the TEMP score using a nomogram in the training and validation datasets (Figure 4).

The performance of the TEMP score and the other models (BCLC stage, Child-Pugh score, ALBI score, HAP score, and mHAP-II score) was compared using the AUROC, C-index and DCA. As presented in Figure 5 and Table 4, The AUROC at 6-month, 1- year, and 2-year of the novel model for OS was consistently greater than 0.7, indicating robust discriminatory capability. Additionally, the C-index of our model was superior to those of other models, suggesting favorable performance and accuracy in predicting OS outcomes. The DCA in the training and validation datasets showed a superior net clinical benefit of our model over other models (Supplemental Figure 2). The 6-month, 1- year, and 2-year AUROC values and C-index of the novel model for TTP were shown in Supplemental Figure 3.

Discussion

Although most HCC staging systems overlook the impact of BDI on HCC patient staging and survival, the importance of BDI is increasingly being recognized. Liver Cancer Study Group of Japan (LCSGJ) staging system[26] asserts that the presence of BDI has as much impact on patient survival as vascular invasion. Huang et al[17] and Lu et al[27] proposed re-staging for HCC patients with BDI. This study, based on a multicenter cohort with a sample size of 267 central BDI uHCC patients receiving successful drainage and subsequent TACE, attempted to establish a model that could predict survival probabilities on the basis of routine clinical features. The predictive model of our study is the first model to stratify patient survival outcomes with a favorable performance and discrimination compared with the most frequently used current TACE prognostic models and liver function rating system, may be helping to select the ideal post-biliary drainage TACE candidates.

Tumor burden and liver function reserves were well-known predictors of survival in HCC patients undergoing TACE. Nevertheless, there was no consensus for the best surrogate markers for assessing these factors.[28] In cases of HCC with

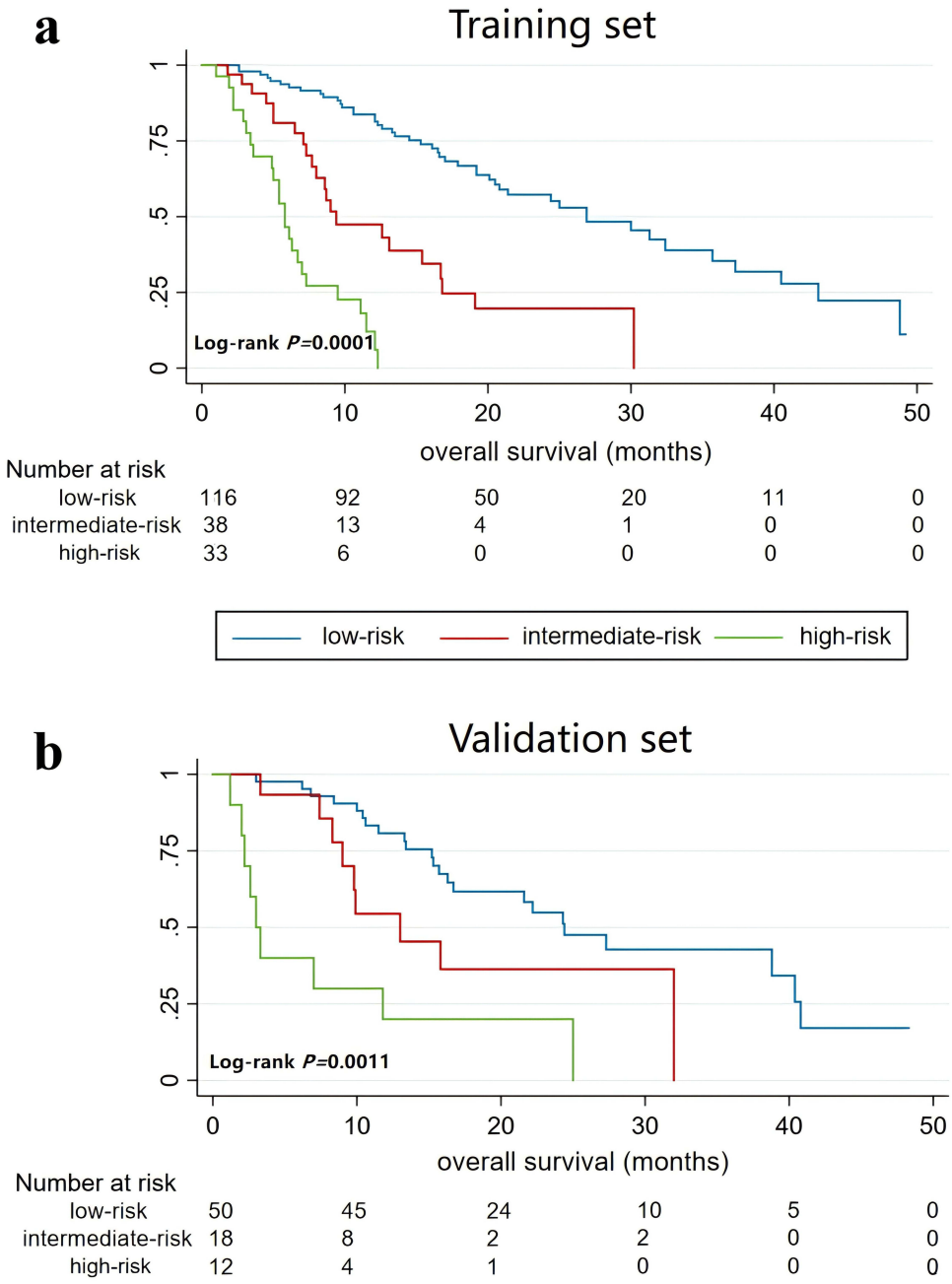

Figure 3 Overall survival according to risk grades as defined by the TEMP score in the three cohorts. Kaplan–Meier survival curves in the (**a**) Training, and (**b**) Validation sets.

BDI, patients often experience obstructive jaundice, making it challenging to evaluate their hepatic functional reserve prior to treatment.[7] These patients tend to exhibit elevated Child-Pugh and ALBI scores due to hyperbilirubinemia, implying compromised liver function.[2] Consequently, this can limit their eligibility for adequate treatment,[28] as many anticancer therapies necessitate a high level of liver function (typically classified as Child-Pugh class A).[29] Nonetheless, it's important to note that some of these patients may still have preserved hepatic function, allowing them to pursue more aggressive treatment strategies.[7,10] Park et al[30] found that biliary drainage to normalize the TBil level before chemoembolization may not be necessary for HCC patients with BDI. In their cases, the elevated bilirubin levels are primarily a result of bile duct obstruction rather than liver insufficiency or tumor progression.[2,30] Although current clinical practice guidelines, such as the BCLC staging system, and TACE-specific predictive tools like the HAP score and mHAP-II score,

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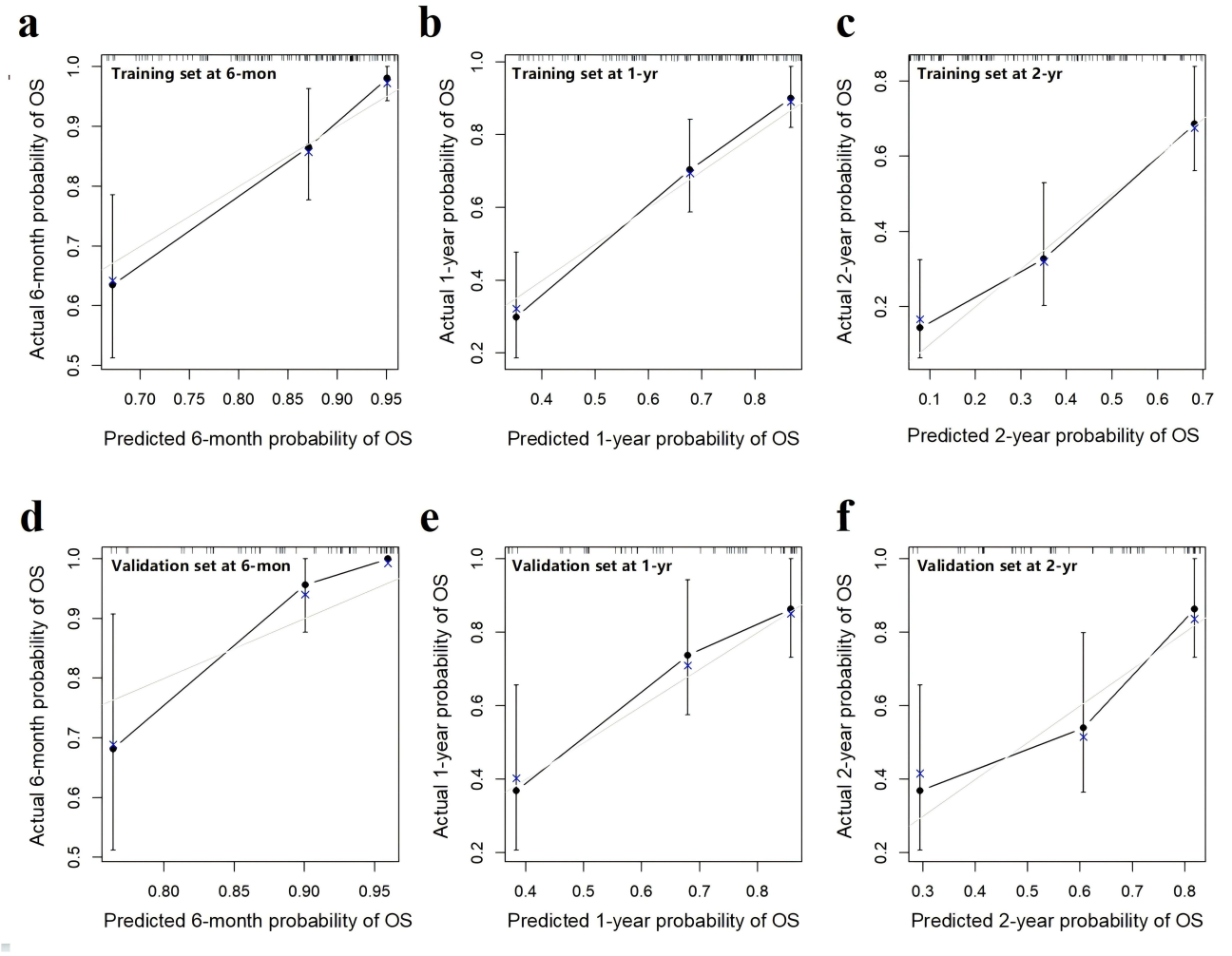

Figure 4 Calibration curve of the TEMP score for predicting 6-month, 1-year, and 2-year probability of OS in training set (**a–c**) and validation set (**d-f**), respectively, with the x-axes are actual survival estimated by the nomogram, the y-axes are observed survival calculated by the Kaplan-Meier method.

do include assessments of tumor burden and liver function to some extent, they did not take into account the context of BDI. Importantly, BDI in HCC is recognized as a negative prognostic factor,[26] and always accompanies with heavy tumor burden due to infiltrative nature.[7,31] Additionally, the Child-Pugh score is designed primarily for cirrhotic patients whereas a certain proportion of HCC arises from the noncirrhotic liver.[32] As a result, the predictive accuracy of those systems in BDI HCC patients remain uncertain. Therefore, the development of a comprehensive tool that accounts for pertinent factors and offers guidance for treatment decisions is imperative.

In this study, we conducted a comprehensive analysis of various parameters related to tumor burden and liver function. Through multivariate analysis, we identified MIT, Pre-TACE TBil, PVTT and EHS as risk factors of OS. Serum bilirubin has previously been recognized as a prognostic predictor associated with liver function and incorporated in certain TACE-specific models. Our study further corroborated that Pre-TACE TBil could independently predict OS and emphasized the essential role of biliary drainage. However, it should be acknowledged that the arbitrary selection of cutoff values for serum bilirubin in currently existing models may impose limitations on their accuracy and practical utility, a drawback also reported in the Child-Pugh score.[33] Thus, to overcome this shortcoming, we adopted a continuous variable approach for bilirubin in our model rather than relying on a fixed cutoff value, which could enhance the precision of prediction models and offers guidance for determining the optimal timing for TACE treatment following biliary drainage based on bilirubin values.

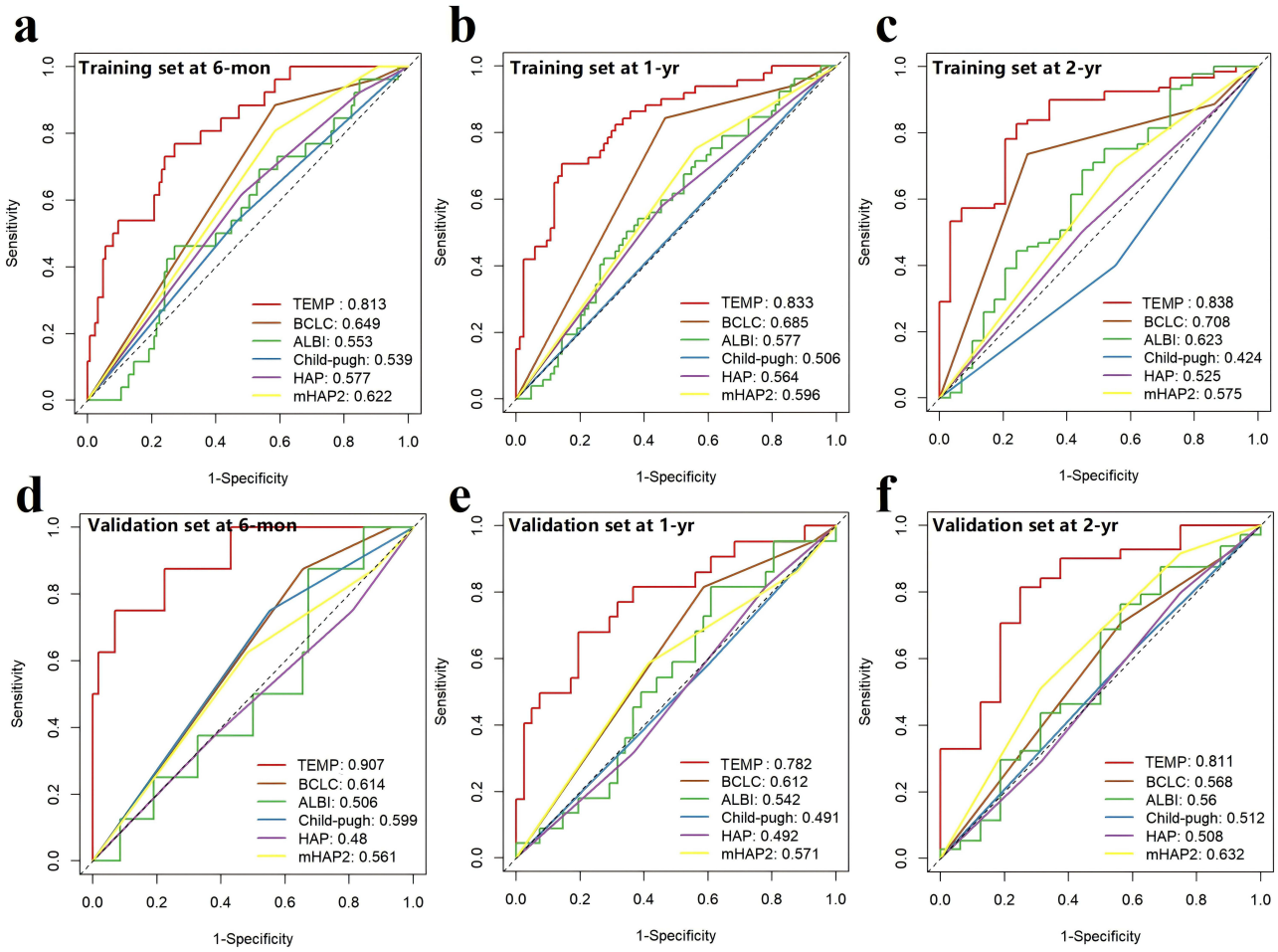

Figure 5 The time-dependent ROC curves of the TEMP score for overall survival. The time-dependent ROC curves of the TEMP score compared with those of other models for 6-month 1-, and 2-year overall survival in the training set (**a–c**) and the validation set (**d–f**), respectively. The area under the ROC curve for each model is depicted on the graph.

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; HAP, Hepatoma arterial-embolisation prognostic; mHAP-II, modified HAP-II; ROC, receiver operating characteristic curve.

The number of tumor nodules has been incorporated into the mHAP-II score and HCC staging system, and linked to the OS of HCC patients.[34,35] Meanwhile, vascular involvement and distant metastasis have been identified as reliable indicators for HCC patient survival,[36] their presence deteriorating patients' BCLC staging, and as risk factors for the prognosis of HCC patients with central BDI receiving TACE (HR of 3.484 and 6.145, respectively; both $P < 0.05$) in Choi's study.[2] PVTT and the number of tumors are key factors in determining liver function, as sufficient non-tumor-bearing liver and unobstructed portal vein flow can ensure adequate liver function for treatment.[37] Although TACE as a local therapy can alleviate hepatic lesions in patients with EHS or MIT,[38] embolize the PVTT feeding vessels, and ultimately improve prognosis in those with EHS, MIT, or PVTT,[39] our study shows that these three factors (EHS, MIT, PVTT) are associated with a poorer prognosis of TACE treatment in patients with BDI. Notably, HCC patients with BDI had a higher rate (28.8%-76.5%) of PVTT compared to those without BDI.[40] In our study, 53.9% of patients had accompanying PVTT, which is consistent with findings from previous studies. The high incidence of PVTT may be attributed to the close proximity of the portal vein and bile duct within the Glisson sheath, allowing tumors with infiltrative characteristics to simultaneously invade both structures.[40] Therefore, when diagnosing BDI, it is necessary to be vigilant that PVTT may accompany it.

The four above-mentioned predictors included in the TEMP score can be easily obtained by routine serum biochemical tests and imaging examinations. Accordingly, the TEMP score has the potential to fill the gap as an optimal tool for survival

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Table 4 Comparison of the Discriminative Ability Among the TEMP Score and Other Models

		6-month Overall Survival		1-year Overall Survival		2-year Overall Survival	
Cohort	Models	C-index	95% CI	C-index	95% CI	C-index	95% CI
Training set	TEMP	0.812	0.727–0.897	0.829	0.758–0.900	0.818	0.736–0.901
	BCLC stage	0.648	0.570–0.725	0.677	0.602–0.752	0.684	0.585–0.783
	Child-Pugh	0.461	0.356–0.566	0.494	0.408–0.581	0.579	0.479–0.679
	ALBI	0.552	0.437–0.667	0.571	0.475–0.667	0.587	0.475–0.697
	HAP	0.578	0.474–0.681	0.565	0.475–0.654	0.530	0.425–0.635
	mHAP-II	0.623	0.541–0.705	0.602	0.521–0.684	0.607	0.503–0.711
Validation set	TEMP	0.929	0.809–0.998	0.761	0.632–0.890	0.791	0.662–0.921
	BCLC stage	0.614	0.489–0.738	0.610	0.496–0.724	0.552	0.416–0.687
	Child-Pugh	0.601	0.437–0.765	0.496	0.368–0.625	0.564	0.423–0.705
	ALBI	0.504	0.309–0.698	0.531	0.386–0.676	0.467	0.303–0.632
	HAP	0.479	0.270–0.687	0.489	0.352–0.626	0.479	0.322–0.637
	mHAP-II	0.561	0.365–0.757	0.569	0.430–0.708	0.604	0.452–0.756

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; HAP, Hepatoma arterial-embolisation prognostic; mHAP-II, modified HAP-II.

prediction among central BDI uHCC patients receiving TACE treatment after biliary drainage. Our research established an easy-to-use prognostic model which demonstrated superior accuracy in predicting survival, and showed better discriminatory power at half-, 1-, and 2- year compared to commonly used predictive systems. Significantly higher C-index values and AUROC of it were achieved in both the training and validation datasets. This TEMP score offers consistent and reliable data for predicting outcomes across a wide range of scenarios in TACE treatment for central BDI uHCC patients post-drainage, effectively categorizing them into three risk grades. Firstly, patients classified in the low-risk grade in our study exhibited a median OS of 26.9 months, which was higher than the OS (ranging from 8 to 16.7 months) reported for patients treated with TACE.[10,41] This implies that patients in the low-risk group are strong candidates for TACE after biliary drainage. On the other hand, patients in the high-risk grade achieved a median OS of 5.8 months, which is similar to the OS (5 months) of patients treated solely with conservative management.[42] Consequently, systemic therapy or palliative care is recommended for this category. For patients in the intermediate-risk group, systemic therapy is recommended, with TACE administered as needed based on individual circumstances. DCA showed the TEMP score had a higher overall net benefit, thus highlighting its value as a better tool for informing clinical decision-making. However, further validation is essential to reinforce these findings.

This study had several limitations. First, its retrospective nature may have led to selection bias. And a significant proportion (82%) of the patients in our study had hepatitis B, and further validation is needed to ascertain the applicability of the TEMP score to patients with other etiologies. Second, this study had relatively modest sample size due to the rarity of BDI, the statistical power of our results might be mitigated; therefore, further external validation is needed to confirm the reliability of our predictive model through an independent and larger dataset. Thirdly, the impact of post-TACE treatment, such as local ablation therapy, repeated TACE, radioembolization or systemic therapy, were not assessed in this study. Although the post-TACE treatment could be impactful on OS, the subsequent treatment for residual or progressive HCC varied widely among the patients. Therefore, it is hard to analyze the effect of post-TACE treatment strategy on survival.

Conclusion

The TEMP score represents a novel prognostic model for stratifying suitable TACE candidates among patients with central BDI uHCC after biliary drainage. This convenient tool, incorporating routinely available clinical parameters, has demonstrated good performance in providing individualized survival predictions and effectively categorizing patients into three distinct risk groups with differing survival outcomes.

Ethical Approval and Informed Consent Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Sun Yat-Sen University First Affiliated Hospital (Approval ID 2023[898]). The informed consents were waived because

of the retrospective nature of this study without involving any direct patient contact or intervention. Patient records/information was anonymized and de-identified prior to analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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