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Original Article

Clinical predictors for liver function impairment and post-embolization syndrome following transcatheter arterial chemoembolization in primary hepatic carcinoma patients: a retrospective study

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Abstract: Objective: To identify clinical predictors of liver function impairment and post-embolization syndrome (PES) following transcatheter arterial chemoembolization (TACE) in patients with primary hepatic carcinoma (PHC), to facilitate risk stratification and improve clinical outcomes. Methods: A retrospective study was conducted on 549 PHC patients who underwent TACE at Eastern Hepatobiliary Surgery Hospital, Naval Military Medical University from June 2020 to January 2024. Data on demographics, liver function, imaging findings, and TACE regimens were collected. Multivariate Logistic regression analysis was employed to identify the independent risk factors for liver function impairment and PES. The predictive performance of these factors was evaluated using receiver operating characteristic (ROC) curve analysis. Results: Among the 549 PHC, 61.93% (340/549) developed liver function impairment and 26.96% (148/549) experienced PES after TACE. ROC analysis indicated that alcohol consumption, cirrhosis, liver function grade, and TACE frequency demonstrated predicted value for liver impairment (AUCs: 0.565-0.619) and PES (AUCs: 0.581-0.656). Multivariate logistic regression identified neutrophils (OR=2.349, P=0.001), prealbumin (PA) (OR=1.674, P=0.028), liver function grade (OR=3.135, P<0.001), alcohol consumption (OR=0.296, P<0.001), cirrhosis (OR=0.528, P=0.005), and TACE frequency (OR=0.482, P=0.001) as independent predictors for liver impairment; For PES, alcohol consumption (OR=1.959, P=0.003), body mass index (BMI) (OR=0.288, P<0.001), albumin (ALB) (OR=0.384, P=0.005), PA (OR=0.288, P<0.001), and ECOG score (OR=0.527, P=0.006) were identified as the independent predictors, whereas liver function grade (P=0.287) and TACE frequency (P=0.634) were not. Nomograms based on these predictors demonstrated good discriminative ability (AUC=0.854 for liver impairment; AUC=0.826 for PES) and satisfactory calibration (P>0.05), with consistent performance in both training and validation cohorts (AUC: 0.852-0.854 for liver impairment; 0.820-0.843 for PES). Conclusion: Key clinical variables, including alcohol consumption, cirrhosis, and specific biochemical markers, are significantly associated with liver function impairment and PES following TACE in PHC patients. These findings support the development of individualized treatment strategies to improve patient outcomes.

Keywords: Primary hepatic carcinoma, TACE, liver function impairment, post-embolization syndrome, clinical predictors, retrospective study

Introduction

Hepatocellular carcinoma (HCC) is a malignancy with relatively high mortality rate worldwide [1]. According to the World Health Organization (WHO), HCC ranks third among cancer-related fatalities globally, following lung and gastric cancers [2]. In Asia, particularly in China, both the incidence and mortality of HCC are notably high [3, 4]. The development of HCC is closely linked to multiple etiological factors, including chronic hepatitis B virus (HBV) or hepatitis C

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virus (HCV) infection, alcoholic liver disease, and non-alcoholic fatty liver disease, all of which can lead to cirrhosis and eventually HCC [5].

Transcatheter arterial chemoembolization (TACE) is a widely employed local therapy for HCC and has been shown to improve survival and alleviate clinical symptoms [6, 7]. Despite its extensive clinical application, TACE is associated with complications that may compromise treatment outcomes. Among these, liver function impairment and post-embolization syndrome (PES) are particularly common and challenging [8-10]. These complications not only affect therapeutic outcomes but also substantially degrade their quality of life. Consequently, accurate assessment and management of post-TACE complications remain critical clinical concerns.

Although certain investigations have explored the pathogenesis of liver function impairment and PES, the specific high-risk factors across diverse patient populations remain elusive. Factors such as liver cirrhosis, alcohol consumption, viral hepatitis, and embolic agent selection may potentially influence the risk of liver function impairment [11], while tumor characteristics, embolization agent, and baseline liver function are intimately correlated with PES [12]. Accurately identifying high-risk patients and minimizing adverse events during TACE remain clinical challenges.

Current research on TACE-associated clinical complications focuses on elucidating underlying mechanisms, identifying influencing factors, and developing effective intervention strategies. Studies have shown that patients with cirrhosis, especially those with lower liver function grades, are at significantly higher risk of post-TACE liver function impairment due to increased susceptibility to embolization-induced liver damage [13]. Additionally, a history of alcohol consumption, viral hepatitis, and the selection of embolic agents are potential contributors to liver function impairment [14]. PES is a systemic reaction due to tumor embolization, typically presenting with fever, nausea, and abdominal pain, and may progress to multiple organ failure in severe cases. PES occurrence is strongly linked to tumor size and location, embolic agent, and the patient's baseline liver function [15].

Despite progress in understanding TACE-associated complications, high-risk factors remain poorly defined due to the heterogeneity and complexity of clinical presentations. Accurately identifying high-risk patients prior to treatment and tailoring individualized treatment regimens to prevent complications remain ongoing clinical and research challenges. This study aims to conduct an in-depth analysis to identify independent risk factors for the occurrence of liver function impairment and PES following TACE, with an expectation to provide references for clinical practice.

Methods and materials

Research design

This retrospective study included 549 patients with primary hepatic carcinoma (PHC) who underwent TACE at Eastern Hepatobiliary Surgery Hospital, Naval Military Medical University from June 2020 to January 2024. This study was approved by the institutional ethics committee OF Eastern Hepatobiliary Surgery Hospital, Naval Military Medical University.

Research subjects

Inclusion criteria: 1) Patients were diagnosed with PHC according to the *Primary Liver Cancer Diagnosis and Treatment Guidelines* (2022 Edition) [16]; 2) Diagnosis was confirmed by imaging modalities such as ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]; 3) Patients had focal hepatic lesions amenable to TACE; 4) Patients received TACE during the time frame from June 2020 to January 2024; 5) Patients with complete follow-up data, including relevant data of liver function and PES.

Exclusion criteria: 1) Patients with other severe comorbidities (e.g., cardio-cerebrovascular disorders, advanced diabetes); 2) Patients who did not adhere to the treatment protocol or had missing data; 3) Patients with other malignancies or extrahepatic metastases.

Data collection

Comprehensive clinical data were collected as follows for all these patients.

Demographic data: age, sex, and body mass index (BMI), and history of smoking and alcohol consumption.

Medical history: hypertension, diabetes, hepatitis B virus (HBV) infection, cirrhosis, and portal hypertension.

Tumor characteristics: tumor stage and size, location, number, portal vein tumor thrombus (PVTT), pathological subtype (massive, nodular, or diffuse) and presence of distant metastasis.

Imaging: pre- and post-treatment assessments of tumor size, location, and blood supply using CT, MRI, or ultrasound.

Liver function indices: pre- and post-treatment levels of albumin (ALB), total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IDB), prealbumin (PA), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), as well as cirrhosis status and liver function classification (Grade A or Grade B).

Laboratory parameters: tumor markers (alpha-fetoprotein (AFP), CA125, CA153, CA199), hematological indices (white blood cell count (WBC), red blood cell count (RBC), platelet count, and hemoglobin), and other liver function-related indices (alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and creatinine).

Treatment-related information: TACE protocol, type of embolic agent (e.g., microspheres, lipiodol, or combined), and the number of TACE sessions. All data were collected prior to treatment initiation.

TACE treatment protocol

Prior to TACE, all patients underwent comprehensive preoperative evaluations, including hematological tests, liver and renal function panels, coagulation profiles, electrocardiograms, CT scans, and B-mode ultrasonography. Allergy testing for iodine and antibiotics was conducted, and patients fasted for 6-8 hours before the procedure. During treatment, patients were placed in a supine position on a digital subtraction angiography (DSA) table. After femoral artery puncture, embolization was executed under DSA guidance. Chemotherapeutic agents mixed with embolic materials, including iodinated oil emulsions, gelatin sponges, and polyvinyl alcohol (PVA) microspheres, were infused into tumor-feeding arteries. Upon completion of the treatment, angiography was repeated to assess the efficacy of treatment. Hemostasis at the puncture site was achieved, and patient remained recumbent for 8 to 12 hours. Postoperative care included bed rest, vital sign monitoring, limb perfusion assessment, and increased fluid intake to prevent nephrotoxicity. Supportive care measures, including symptoms management for fever and nausea as well as psychological counseling were administered. Embolic agent selection was based on tumor characteristics and patient-specific factors.

Definition of liver function impairment

According to the American College of Gastroenterology (ACG) guidelines for hepatic biochemical abnormalities, serum ALT <40 U/L is considered normal, ALT levels of 40-80 U/L, 80-200 U/L, and >200 U/L correspond to mild, moderate, and severe hepatic injury, respectively [17]. In this study, liver function impairment was defined as ALT elevation post-TACE compared to baseline level, such as the transition from normal liver function to mild hepatic injury, from mild hepatic injury to moderate hepatic injury, or from moderate hepatic injury to severe hepatic injury.

Definition of PES

PES is to a common systemic reaction following TACE, characterized by symptoms as fever, nausea, vomiting, abdominal pain, anorexia, and fatigue. In severe cases, PES may progress to multi-organ failure or death. Diagnosis of PES is based on clinical presentation and imaging findings. Specifically, PES was diagnosed if patients developed persistent fever, abdominal pain, or other related symptoms within 48 hours after TACE, in the absence of other etiologies, and accompanied by hematological or biochemical abnormalities [18]. Severe PES was further categorized based on clinical monitoring and imaging evidence.

Statistical analysis

All data were processed with SPSS 26.0 and R 4.3.3. The normality of data distribution was examined using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) and compared using independent sample t-tests or one-way analy-

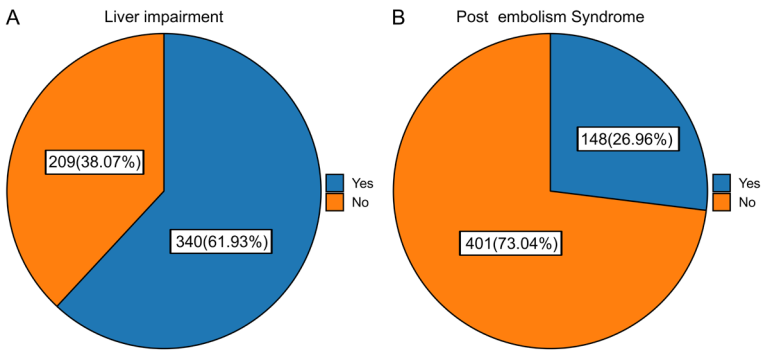


Figure 1. Incidence of liver function impairment and post-embolism syndrome (PES) following transcatheter arterial chemoembolization (TACE) treatment. A: The incidence of liver function impairment was 61.93% (340/549); B: The incidence of PES was 26.96% (148/549).

sis of variance (ANOVA). on-normally distributed data were expressed as median and interquartile range (IQR), with inter-group comparisons compared using rank-sum tests. Categorical variables were presented as counts and percentages, and group comparisons were performed using the chi-square test.

Multivariate Logistic regression analysis was utilized to identify the independent risk factors associated with liver function impairment and PES. Receiver operating characteristic (ROC) curve analysis, calibration curve plotting, forest plot analysis, and Nomogram construction were conducted using R 4.3.3 software, with relevant packages including pROC, ggplot2, forestplot, and rms. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Incidence of liver function impairment and PES after TACE

Among the 549 PHC patients who underwent TACE, 340 patients (61.93%) developed liver function impairment, while 209 (38.07%) maintained normal liver function after TACE. PES occurred in 148 patients (26.96%), manifested by postoperative fever, abdominal pain, and nausea, whereas 401 (73.04%) did not exhibit PES symptoms (**Figure 1**).

Comparison of clinical and laboratory features between patients with and without liver function impairment

Significant differences were observed between the patients with and without liver function impairment in terms of alcohol consumption (P< 0.001), cirrhosis (P<0.001), ascites (P<0.001), tumor pathological stage (P<0.001), liver function classification (P<0.001), ECOG performance status (P=0.043), neutrophils (P=0.011), DB (P<0.001), ALB (P<0.001), ALP (P<0.001), PA (P<0.001), prognostic nutritional index (PNI, P=0.003), and the number of TACE sessions (P<0.001). No significant differences were found in sex, smoking status, comorbidities (diabetes, hypertension), HBV infection, portal hypertension, multiple tumor foci, PVTT, distant metastasis, splenomegaly, collateral circulation, and most laboratory parameters (e.g., AFP, WBC) (P> 0.05). The choice of embolic agent did not significantly affect liver function (P>0.05) (**Table 1**).

Comparison of clinical and laboratory features between patients with and without PES

Significant differences were identified between patients with and without PES in terms of sex (P=0.027), alcohol consumption (P<0.001), cirrhosis (P=0.041), collateral circulation (P= 0.050), liver function classification (P<0.001), ECOG score (P=0.002), embolic agent type (P<0.001), BMI (P<0.001), ALB (P<0.001), PA (P<0.001), PNI (P<0.001), and number of TACE sessions (P=0.001). Specifically, patients with PES were more frequently had a history of alcohol consumption, cirrhosis, collateral circulation, poorer liver function (notably grade B), higher ECOG scores, lower BMI, ALB, PA, and PNI, and were more likely to receive microsphere-based embolization. Other variables, including smoking, diabetes, hypertension, HBV status, portal hypertension, tumor burden, and most laboratory indices, showed no significant differences (P>0.05) (**Table 2**).

ROC curve analysis and dichotomization of variables

To facilitate logistic regression, ROC curves were generated for continuous variables significantly associated with liver impairment and PES. Optimal cutoff values were determined

Table 1. Comparison of clinical characteristics and laboratory indicators between patients with and without liver function impairment following TACE treatment

Variable	Total	Impairment group (n=340)	Non-impairment group (n=209)	Statistic	P
Sex					
Male	468	292	176	0.288	0.592
Female	81	48	33		
Smoking history					
With	107	61	46	1.365	0.243
Without	442	279	163		
Alcohol consumption history					
With	246	190	56	44.284	<0.001
Without	303	150	153		
Gallstones					
With	70	41	29	0.384	0.535
Without	479	299	180		
Diabetes					
With	32	17	15	1.118	0.290
Without	517	323	194		
Hypertension					
With	43	24	19	0.740	0.390
Without	506	316	190		
HBV infection					
With	415	252	163	1.052	0.305
Without	134	88	46		
Cirrhosis					
With	302	214	88	22.705	<0.001
Without	247	126	121		
Portal vein hypertension					
With	94	61	33	0.422	0.516
Without	455	279	176		
Multiple tumor foci					
With	324	207	117	1.286	0.257
Without	225	133	92		
Portal vein tumor thrombus					
With	201	119	82	1.000	0.317
Without	348	221	127		
Distant metastasis					
With	75	44	31	0.393	0.531
Without	474	296	178		
Splenomegaly					
With	132	78	54	0.594	0.441
Without	417	262	155		
Ascites					
With	216	153	63	11.971	<0.001
Without	333	187	146		
Collateral circulation					
With	74	51	23	1.772	0.183
Without	475	289	186		
Tumor pathological staging					
Massive	411	300	111	84.873	<0.001
Nodular	68	20	48		
Diffuse	70	20	50		
Liver function classification					
A	133	54	79	33.869	<0.001
B	416	286	130		

ECOG score					
0	347	226	121	4.093	0.043
1	202	114	88		
Type of embolic agent					
Microspheres	59	41	18	2.777	0.250
Iodinated oil	173	100	73		
Mixed	317	199	118		
Age (years)	55.00 [48.00, 63.00]	55.00 [48.00, 63.00]	54.00 [47.00, 62.00]	0.955	0.339
BMI (kg/m^2)	21.61 [19.86, 23.43]	21.38 [19.86, 23.15]	22.05 [19.85, 23.93]	1.901	0.057
AFP (ng/mL)	705.60 [404.52, 1043.04]	680.42 [396.38, 1015.59]	726.19 [433.47, 1130.43]	1.378	0.168
CA125 (U/mL)	106.56 [51.97, 172.68]	102.85 [52.11, 162.33]	114.13 [51.73, 187.96]	1.320	0.187
CA153 (U/mL)	30.54 [15.90, 51.35]	29.88 [15.05, 49.45]	31.13 [16.59, 54.94]	1.089	0.276
CA199 (U/mL)	89.89 [44.19, 152.25]	89.21 [45.58, 145.81]	90.59 [37.82, 163.20]	0.610	0.542
White blood cells (×10^9/L)	6.72 [4.82, 8.94]	6.56 [4.97, 8.29]	7.24 [4.47, 9.93]	1.901	0.057
Neutrophils (×10^9/L)	4.63 [2.80, 6.16]	4.44 [2.84, 5.84]	5.08 [2.74, 7.14]	2.552	0.011
Lymphocytes (×10^9/L)	1.436±0.588	1.452±0.615	1.409±0.541	-0.831	0.406
Monocytes (×10^9/L)	0.66 [0.46, 0.86]	0.64 [0.43, 0.84]	0.69 [0.49, 0.89]	1.771	0.077
Red blood cells (×10^12/L)	4.44 [3.79, 5.06]	4.36 [3.79, 4.97]	4.54 [3.79, 5.16]	1.466	0.143
Hemoglobin (%)	124.00 [110.00, 138.00]	122.00 [107.00, 137.00]	125.00 [114.00, 142.00]	1.646	0.100
Platelets (×10^9/L)	217.00 [148.00, 281.00]	222.00 [150.25, 282.00]	212.00 [140.00, 276.00]	1.351	0.177
TB (μmol/L)	32.661±9.491	33.275±10.106	31.663±8.322	-1.938	0.053
DB (μmol/L)	22.988±7.533	23.861±8.391	21.569±5.612	-3.496	<0.001
IDB (μmol/L)	9.39 [5.21, 13.72]	9.23 [5.12, 13.20]	9.84 [5.52, 14.60]	1.234	0.217
ALB (g/L)	34.427±4.979	33.773±4.924	35.491±4.895	3.979	<0.001
ALP (U/L)	180.678±81.667	191.401±80.814	163.234±80.211	-3.977	<0.001
GGT (U/L)	250.65 [129.87, 404.28]	239.63 [130.78, 372.10]	271.94 [124.62, 440.51]	1.605	0.109
Creatinine (μmol/L)	78.471±20.175	78.038±20.724	79.176±19.275	0.641	0.522
PA (mg/L)	87.40 [59.20, 112.80]	82.35 [55.00, 108.30]	96.00 [69.00, 120.50]	3.748	<0.001
SIRI	1.89 [1.01, 3.60]	1.80 [0.95, 3.28]	2.15 [1.03, 4.26]	1.901	0.057
LMR	2.24 [1.43, 3.35]	2.32 [1.44, 3.62]	2.10 [1.42, 3.10]	1.540	0.124
PLR	155.56 [94.24, 231.68]	159.17 [96.34, 235.55]	149.14 [93.45, 216.33]	0.748	0.454
PNI	41.604±5.858	41.032±5.974	42.536±5.552	2.941	0.003
Number of TACE sessions (times)	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	2.00 [2.00, 3.00]	5.182	<0.001

Note: TACE, transcatheter arterial chemoembolization; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; AFP, alpha-fetoprotein; CA125/153/199, cancer antigen 125/153/199; TB, total bilirubin; DB, direct bilirubin; IDB, indirect bilirubin; ALB, albumin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; PA, prealbumin; SIRI, Systemic Inflammatory Response Index; LMR; lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; PNI, Prognostic Nutritional Index.

Table 2. Comparison of clinical characteristics and laboratory indices between patients with and without PES following TACE

Variable	Total	PES group (n=148)	Non-PES group (n=401)	Statistic	P
Sex					
Male	468	118	350	4.902	0.027
Female	81	30	51		
Smoking history					
With	107	33	74	1.018	0.313
Without	442	115	327		
Alcohol consumption history					
With	246	88	158	17.586	<0.001
Without	303	60	243		
Gallstones					
With	70	21	49	0.377	0.539
Without	479	127	352		
Diabetes					
With	32	6	26	1.163	0.281
Without	517	142	375		

Hypertension					
With	43	12	31	0.021	0.884
Without	506	136	370		
HBV infection					
With	415	107	308	1.192	0.275
Without	134	41	93		
Cirrhosis					
With	302	92	210	4.189	0.041
Without	247	56	191		
Portal vein hypertension					
With	94	24	70	0.117	0.732
Without	455	124	331		
Multiple tumor foci					
With	324	87	237	0.005	0.946
Without	225	61	164		
Portal vein tumor thrombus					
With	201	59	142	0.924	0.336
Without	348	89	259		
Distant metastasis					
With	75	23	52	0.607	0.436
Without	474	125	349		
Splenomegaly					
With	132	38	94	0.295	0.587
Without	417	110	307		
Ascites					
With	216	53	163	1.060	0.303
Without	333	95	238		
Collateral circulation					
With	74	13	61	3.830	0.050
Without	475	135	340		
Tumor pathological staging					
Massive	411	116	295	4.678	0.096
Nodular	68	11	57		
Diffuse	70	21	49		
Liver function classification					
A	133	14	119	24.068	<0.001
B	416	134	282		
ECOG score					
0	347	78	269	9.611	0.002
1	202	70	132		
Type of embolic agents					
Microspheres	59	27	32	26.120	<0.001
Iodinated oil	173	25	148		
Mixed	317	96	221		
Age (years)	55.00 [48.00, 63.00]	55.00 [50.00, 61.25]	54.00 [47.00, 63.00]	0.912	0.362
BMI (kg/m^2)	21.61 [19.86, 23.43]	20.68 [19.41, 22.25]	22.05 [20.07, 24.11]	5.346	<0.001
AFP (ng/mL)	705.60 [404.52, 1043.04]	721.14 [417.98, 1105.90]	704.95 [400.02, 1029.57]	0.524	0.600
CA125 (U/mL)	106.56 [51.97, 172.68]	111.06 [49.39, 181.28]	104.69 [53.81, 169.12]	0.183	0.855
CA153 (U/mL)	30.54 [15.90, 51.35]	30.73 [13.04, 49.94]	30.41 [16.17, 51.66]	0.533	0.594
CA199 (U/mL)	89.89 [44.19, 152.25]	87.43 [38.34, 149.22]	90.68 [45.72, 153.30]	0.692	0.489
White blood cells (×10ˆ9/L)	6.72 [4.82, 8.94]	6.69 [4.94, 8.94]	6.75 [4.81, 8.94]	0.126	0.900
Neutrophils (×10ˆ9/L)	4.63 [2.80, 6.16]	4.49 [3.24, 6.02]	4.66 [2.68, 6.21]	0.117	0.907
Lymphocytes (×10ˆ9/L)	1.45 [1.03, 1.82]	1.56 [1.09, 1.88]	1.38 [1.02, 1.76]	1.746	0.081
Monocytes (×10ˆ9/L)	0.66 [0.46, 0.86]	0.64 [0.47, 0.85]	0.66 [0.46, 0.86]	0.080	0.936
Red blood cells (×10ˆ12/L)	4.409±0.930	4.351±0.908	4.431±0.938	0.898	0.370
Hemoglobin (%)	124.231±22.909	127.243±24.197	123.120±22.343	-1.876	0.061

Platelets (×10^9/L)	217.00 [148.00, 281.00]	203.00 [141.50, 274.50]	223.00 [148.00, 283.00]	1.355	0.176
TB (μmol/L)	32.661±9.491	32.377±8.811	32.766±9.739	0.426	0.670
DB (μmol/L)	22.988±7.533	23.224±6.831	22.901±7.783	-0.446	0.656
IDB (μmol/L)	9.39 [5.21, 13.72]	8.61 [5.56, 12.52]	9.48 [5.13, 14.05]	1.220	0.222
ALB (g/L)	34.40 [31.20, 37.70]	31.80 [27.48, 36.92]	34.90 [31.90, 37.70]	5.356	<0.001
ALP (U/L)	180.678±81.667	173.013±79.046	183.507±82.530	1.337	0.182
GGT (U/L)	250.65 [129.87, 404.28]	288.21 [139.44, 420.98]	242.89 [121.94, 387.18]	1.860	0.063
Creatinine (μmol/L)	78.471±20.175	78.196±20.855	78.573±19.943	0.194	0.846
PA (mg/L)	87.40 [59.20, 112.80]	64.20 [37.62, 104.23]	93.00 [69.00, 116.80]	5.626	<0.001
SIRI	1.89 [1.01, 3.60]	1.86 [1.08, 3.29]	1.93 [0.94, 3.61]	0.023	0.982
LMR	2.24 [1.43, 3.35]	2.36 [1.53, 3.53]	2.18 [1.42, 3.34]	1.038	0.299
PLR	155.56 [94.24, 231.68]	149.20 [90.31, 206.32]	160.34 [99.60, 235.77]	1.587	0.112
PNI	41.45 [37.90, 45.30]	39.40 [34.91, 44.54]	41.90 [38.80, 45.45]	3.808	<0.001
Number of TACE sessions (times)	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.233	0.001

Note: PES, post-embolism syndrome; TACE, transcatheter arterial chemoembolization; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; AFP, alpha-fetoprotein; CA125/153/199, cancer antigen 125/153/199; TB, total bilirubin; DB, direct bilirubin; IDB, indirect bilirubin; ALB, albumin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; PA, prealbumin; SIRI, Systemic Inflammatory Response Index; LMR; lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; PNI, Prognostic Nutritional Index.

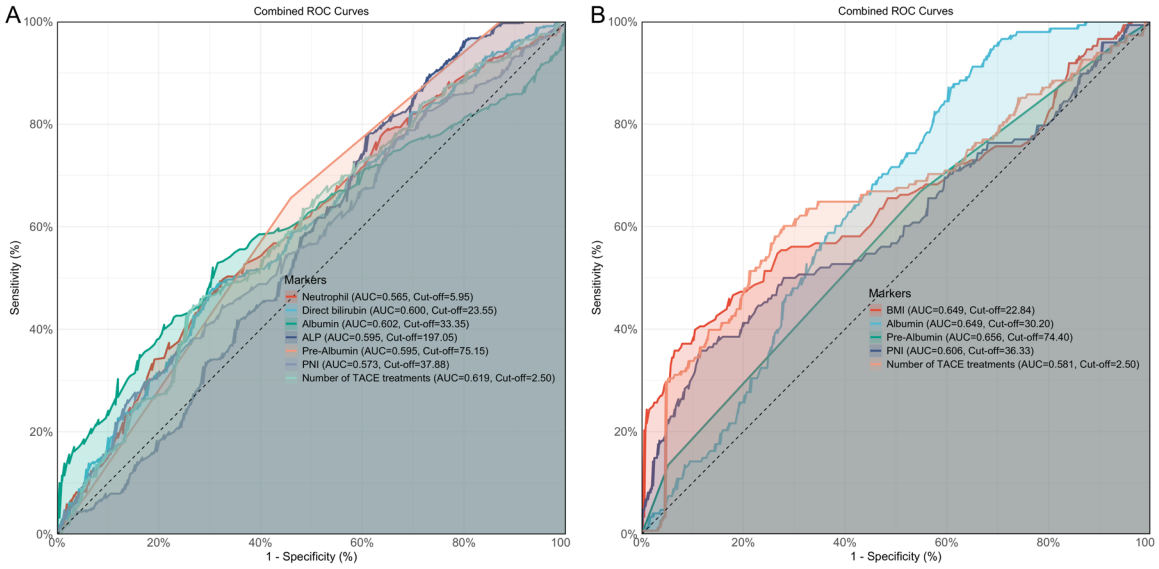


Figure 2. ROC curves for continuous variables associated with liver function impairment and post-embolism syndrome. A: ROC curves of continuous variables related to liver function impairment, including neutrophils, DB, ALB, ALP, PA, PNI, and number of TACE sessions. B: ROC curves of continuous variables associated with PES, including BMI, ALB, PA, PNI, and number of TACE sessions. Note: ROC, receiver operating characteristic; AUC, area under the curve; DB, direct bilirubin; PA, prealbumin; ALB, albumin; ALP, alkaline phosphatase; PNI: prognostic nutritional index; BMI, body mass index.

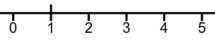
using the Youden index. For liver function impairment, AUC values for neutrophils, DB, ALB, ALP, PA, PNI, and number of TACE sessions were 0.565, 0.600, 0.602, 0.595, 0.595, 0.573, and 0.619, respectively (**Figure 2A**). For PES, AUCs for BMI, ALB, PA, PNI ,and TACE number were 0.649, 0.649, 0.656, 0.606, and 0.581, respectively, indicating moderate predictive performance (**Figure 2B**). These dichotomized variables were included in subsequent multivariate analysis.

Multivariate logistic regression analysis of risk factors

Multivariate logistic regression identified the following independent risk factors for post-TACE liver function impairment: neutrophil count (OR=2.349, P=0.001), DB (OR=0.627, P=0.041), PA (OR=1.674, P=0.028), TACE frequency (OR=0.482, P=0.001), alcohol consumption (OR=0.296, P<0.001), cirrhosis (OR=0.528, P=0.005), ascites (OR=0.548, P=0.011), tumor

A

Variable	Estimate	Std Error	OR(95%CI)	P Value
Neutrophil	0.854	0.249	2.349(1.447−3.841)	0.001
Direct bilirubin	−0.467	0.228	0.627(0.400−0.980)	0.041
Albumin	0.506	0.284	1.658(0.955−2.912)	0.075
Albumin	−0.879	0.237	0.415(0.259−0.656)	<0.001
Pre−Albumin	0.515	0.235	1.674(1.059−2.666)	0.028
PNI	0.480	0.339	1.616(0.835−3.159)	0.156
Number of TACE treatments	−0.731	0.227	0.482(0.307−0.750)	0.001
History of alcohol consumption	−1.216	0.234	0.296(0.186−0.466)	<0.001
Cirrhosis	−0.638	0.226	0.528(0.338−0.822)	0.005
Abdominal fluid	−0.601	0.236	0.548(0.343−0.869)	0.011
Tumor Pathologic Staging	−1.100	0.168	0.333(0.237−0.459)	<0.001
Liver Function Classification	1.143	0.256	3.135(1.905−5.215)	<0.001
ECOG score	−0.462	0.232	0.630(0.399−0.992)	0.046



B

Variable	Estimate	Std Error	OR(95%CI)	PValue
BMI	−1.244	0.284	0.288(0.165−0.502)	<0.001
Albumin	−0.956	0.342	0.384(0.197−0.752)	0.005
Pre−Albumin	−1.245	0.234	0.288(0.182−0.456)	<0.001
PNI	−0.845	0.356	0.429(0.214−0.862)	0.017
Number of TACE treatments	0.388	0.238	1.474(0.924−2.351)	0.103
History of alcohol consumption	0.672	0.230	1.959(1.249−3.072)	0.003
Cirrhosis	0.222	0.234	1.249(0.790−1.975)	0.341
Liver Function Classification	−1.249	0.338	0.287(0.148−0.556)	<0.001
ECOG score	−0.640	0.233	0.527(0.334−0.833)	0.006
Type of embolic agent	−0.088	0.167	0.916(0.660−1.271)	0.6

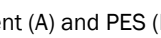


Figure 3. Multivariate logistic regression analysis of risk factors for liver function impairment (A) and PES (B). Note: PES, post-embolism syndrome; PNI, Prognostic Nutritional Index; TACE, transcatheter arterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

stage (OR=0.333, P<0.001), liver function class (OR=3.135, P<0.001), and ECOG score (OR=0.630, P=0.046). Among these, neutrophil count, PA, and liver function grade were positively associated with liver impairment risk, whereas others were protective (**Figure 3A**). For PES, independent predictors included BMI (OR=0.288, P<0.001), ALB (OR=0.384, P=0.005), PA (OR=0.288, P<0.001), PNI (OR=0.429, P=0.017), alcohol consumption (OR=1.959, P=0.003), liver function classification (OR=0.287, P<0.001), and ECOG score (OR=0.527, P=0.006) (**Figure 3B**).

Nomogram construction and risk assessment

Based on multivariate regression results, nomograms were constructed to estimate individual risk for liver function impairment and PES post-TACE. For liver impairment, the most influential predictors were tumor stage and alcohol consumption. Moderate predictors included TACE frequency, DB, ALP, and cirrhosis, while neutrophil count, PA, ascites, liver function classification, and ECOG score had weaker associations. The derived prediction model for liver function impairment was expressed as:

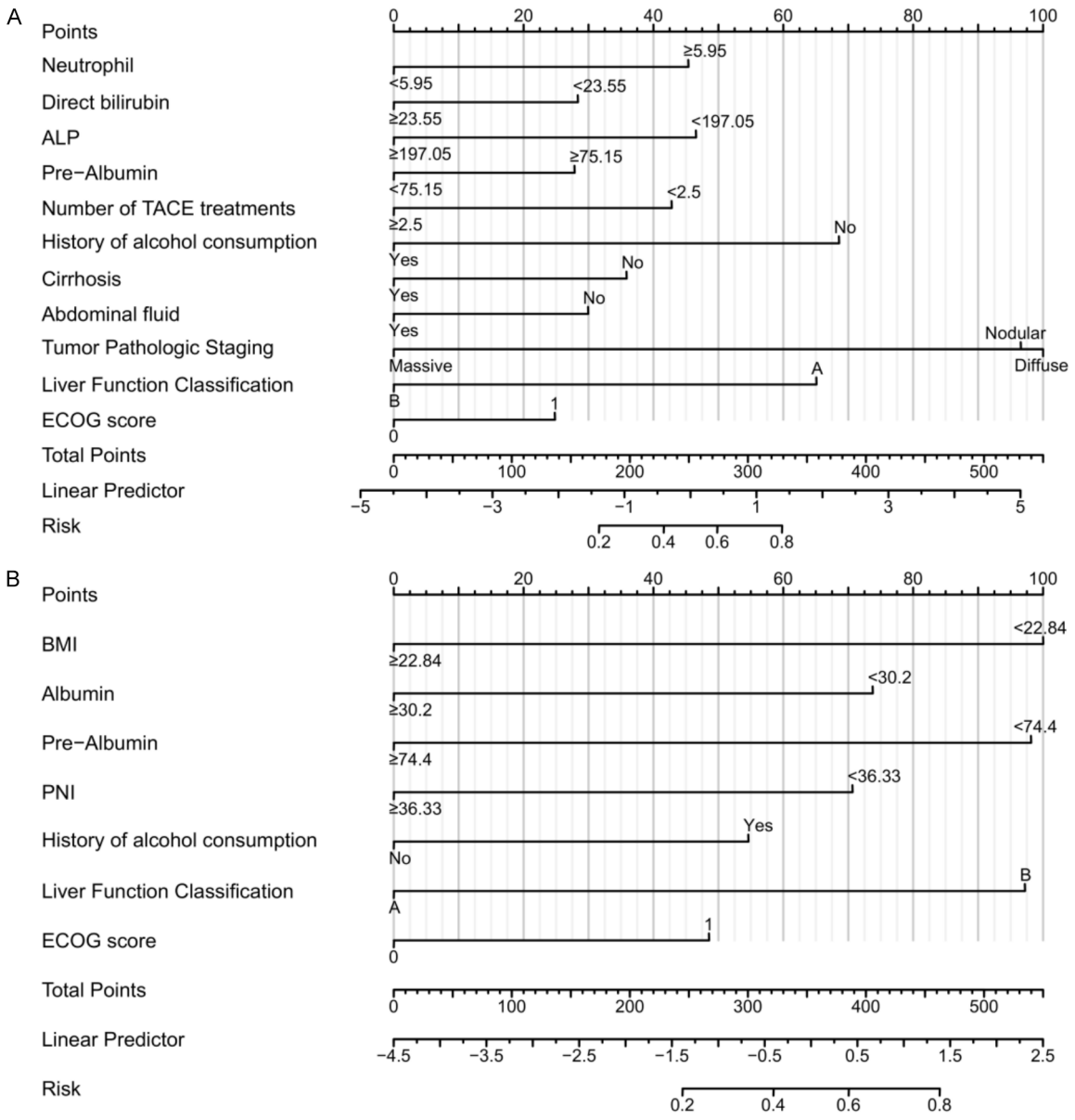


Figure 4. Nomogram models for risk prediction of liver function impairment (A) and PES (B) after TACE treatment. Note: PES, post-embolism syndrome; TACE, transcatheter arterial chemoembolization; PNI, Prognostic Nutritional Index; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

Logit(P) = -2.023 - 0.812 × (Neutrophil count) + 0.507 × (DB) + 0.833 × (ALP) - 0.498 × (PA) + 0.766 × (TACE sessions) + 1.227 × (Alcohol consumption history) + 0.641 × (Cirrhosis) + 0.535 × (Ascites) + 1.727 × (Tumor stage 2) + 1.789 × (Stage 3) - 1.164 × (Liver function classification) + 0.444 × (ECOG) (See **Figure 4A** for Nomogram). For PES, key predictors included BMI, PA, and PNI. Moderate contributors included liver class and ALB, and weaker factors were alcohol consumption and ECOG. The model for PES formula was: Logit(P) = -3.804 + 1.273 × (BMI) + 0.939 × (ALB) + 1.249 × (PA) + 0.899 × (PNI) - 0.695 × (Alcohol consumption history) + 1.237 × (Liver function classification) + 0.618 × (ECOG) (See **Figure 4B** for Nomogram).

Performance and validation of the liver impairment nomogram

The nomogram for liver function impairment prediction exhibited strong predictive capability (AUC=0.854, 95% CI: 0.821-0.886). Calibration analysis showed good fit (χ^2=3.819, P=0.873),

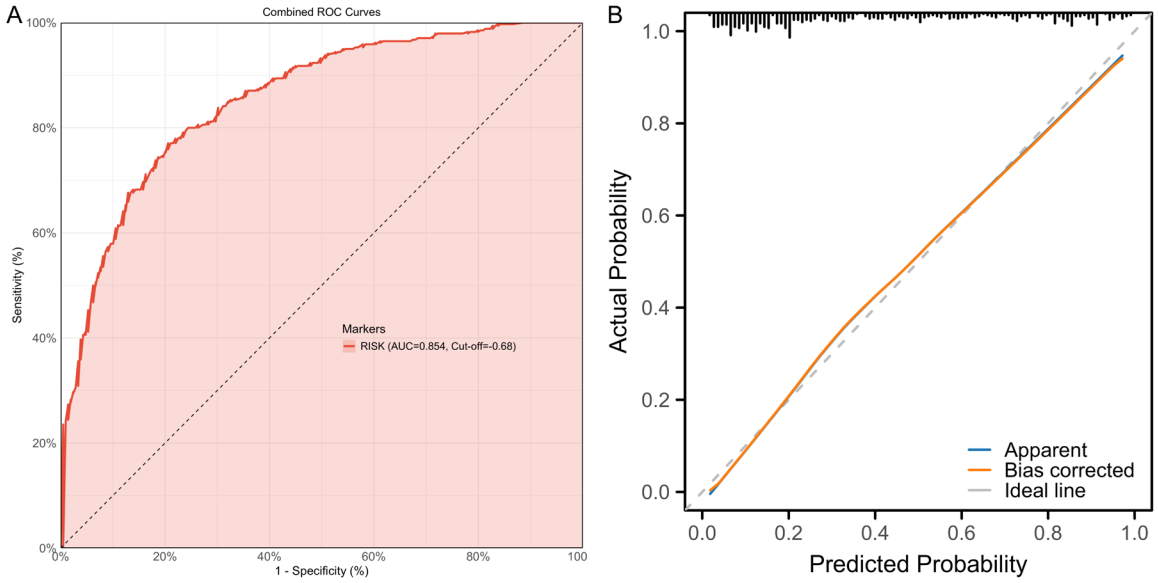


Figure 5. Prediction performance and calibration of the Nomogram for liver function impairment. A: The ROC curve of the Nomogram model for liver function impairment. B: The calibration curve reveals a high degree of consistency between the predicted probability and the actual probability of the model. Note: ROC, receiver operating characteristic; AUC, area under the curve.

and the C-index was 0.854 (P<0.001) (**Figure 5A**, **5B**). For validation, patients were split into training (n=362) and validation (n=187) cohorts, which showed no significant baseline differences (Table S1). In the training set, the Nomogram yielded an AUC of 0.855, χ^2 (likelihood ratio) =225.92 (P<0.001), χ^2 (goodness-of-fit) =3.819 (P=0.873), with calibration curves showing excellent agreement (Figure S1A, S1B). Validation set performance was consistent (AUC=0.852, χ^2=77.14, P<0.001; χ^2=4.815, P=0.777) (Figure S1C, S1D).

Performance and validation of the PES nomogram

The nomogram for PES prediction also exhibited high accuracy (AUC=0.826, 95% CI: 0.788-0.865) and good calibration (χ^2=7.577, P=0.476), with C-index of 0.826 (P<0.001) (**Figure 6A**, **6B**). Training (n=362) and validation (n=187) cohorts had comparable baseline characteristics (Table S2). In the training group, AUC was 0.820 (95% CI: 0.772-0.868), likelihood ratio χ^2=102.24 (P<0.001), and goodness-of-fit χ^2=3.056 (P=0.931) (Figure S2A, S2B). The validation group demonstrated comparable performance (AUC=0.843; χ^2=56.68, P<0.001; χ^2=7.736, P=0.460) (Figure S2C, S2D).

Discussion

This retrospective study analyzed 549 patients with primary PHC who underwent TACE, aiming to identify clinical predictors of liver function impairment and PES. Based on the identified risk factors, nomogram models were established to facilitate individualized risk assessment. The incidence of liver function impairment and PES following TACE were 38.07% and 26.96%, respectively. These complications not only adversely affect patients' quality of life but may also hinder subsequent treatment and, in severe cases, pose life-threatening risks. By identifying independent risk factors for both complications, this study provides a scientific foundation for early risk stratification and personalized treatment planning, ultimately improving therapeutic outcomes.

Liver function impairment was found to be significantly associated with a history of alcohol consumption, cirrhosis, ascites, Child-Pugh grade, and the number of TACE sessions. Among these, alcohol consumption and cirrhosis emerged as the most prominent independent risk factors. Chen et al. [19] highlighted the effects of alcohol consumption and cirrhosis on liver function, with chronic alcohol intake known to directly inducing hepatocellular injury and com-

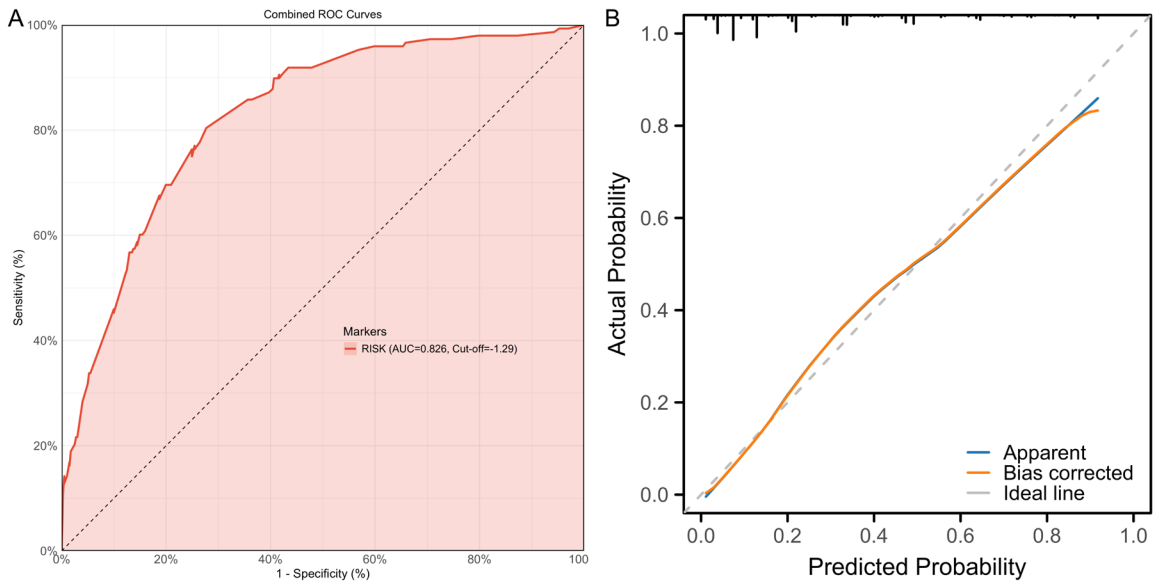


Figure 6. Prediction performance and calibration of the Nomogram for post-embolism syndrome. A: The ROC curve of the Nomogram model for post-embolism syndrome; B: The calibration curve reveals a high degree of consistency between the predicted probability and the actual probability of the model. Note: ROC, receiver operating characteristic; AUC, area under the curve.

promising hepatic reserve. In patients with cirrhosis, impaired regenerative capacity and reduced liver function increase vulnerability to post-TACE decompensation. Liu et al. [20] further emphasized cirrhosis as a key factor affecting liver recovery and complication risk following TACE. Additionally, the Child-Pugh grade and ECOG performance status also serve as critical indicators of liver function reserve and overall physical condition, playing essential roles in liver function assessment. Lower scores reflect poorer tolerance to treatment and higher susceptibility to hepatic injury.

Moreover, repeated TACE procedures, while beneficial for tumor control, may exert cumulative damage to non-tumorous liver parenchyma. Duan et al. [21] reported that TACE induces ischemic necrosis of tumor tissues by occluding hepatic artery blood flow; However, this process may also compromise the blood supply to normal liver tissues, causing ischemic hepatocellular injury. In patients with impaired liver function, especially those with a history of alcohol use or cirrhosis, this ischemic insult may result in irreversible hepatocellular damage due to limited regenerative capacity.

Cheng et al. [22] reported that a greater tumor burden, as defined by "up-to-seven" or "up-to-eleven" criteria, significantly increases the risk of liver function impairment. Similarly, a higher Child-Pugh grade correlates with a higher probability of post-TACE deterioration. Peng et al. [23] identified tumor size, abnormal ALB and total TB levels as key prognostic factors for liver function outcomes. Furthermore, ascites, commonly associated with cirrhosis, signals diminished liver reserve and is thus a reliable indicator of liver dysfunction. Ma et al. [24] concluded that the presence of ascites adversely affects TACE efficacy and is linked to a higher incidence of adverse events.

To improve prediction of post-TACE liver function impairment, Li et al. [25] developed a machine learning-based nomogram incorporating six key risk factors, including the FIB-4 index, tumor burden, portal vein invasion, and gamma-glutamyl transferase (GGT) levels. These findings underscore the importance of thorough preoperative evaluation in patients with alcohol intake or cirrhosis, with special attention paid to Child-Pugh and ECOG scores. Integrating these clinical parameters into nomogram models facilitates early identification of high-risk patients. Clinically, strategies such as reducing the frequency of TACE sessions or opting for milder embolic agents may help mitigate hepatic injury. Park et al. [26] and Jia et al. [27] recommended close postoperative monitoring

of indicators such as DB, ALB, and PA, for early detection of liver function deterioration.

The incidence of PES was significantly associated with BMI, ALB, PA, PNI, alcohol consumption history, Child-Pugh classification, and embolic agent selection. Lower BMI is typically indicative of poor nutritional status and reduced inflammatory response capability, rendering patients more vulnerable to PES. Wang et al. [28] confirmed that a low skeletal muscle index (SMI) is an independent predictor of PES, reinforcing the link between nutritional status and PES risk. Likewise, decreased ALB, PA, and PNI reflect poor liver reserve and nutritional deficiency, all contributing to elevated PES risk. He et al. [29] found low ALB to be a strong predictor of PES, particularly in patients undergoing drug-eluting bead TACE (DEB-TACE).

The choice of embolic agents is also a critical factor influencing the risk of PES. Studies show that microsphere embolization correlates with a higher PES incidence compared to other agents, potentially due to its more complete and sustained embolic effect. Bian et al. [30] identified microsphere agent, prior post-TACE abdominal pain, and vascular invasion as significant contributors to postoperative abdominal discomfort, a hallmark symptom of PES. Du et al. [31] further demonstrated that DEB-TACE and embolization of multiple lesions are independent predictors of PES, highlighting the combined impact of embolic agent and tumor burden.

PES is primarily mediated by inflammatory responses secondary to ischemic tumor necrosis after embolization. This process results in the release of inflammatory mediators and metabolic byproducts, leading to systemic inflammatory response syndrome. Roehlen et al. [32] identified tumor size as the most robust independent predictor of PES. Severe PES, characterized by intense abdominal pain, fever, and nausea, has been linked to lower disease control rates and poorer survival outcomes. Patients with low BMI and ALB levels often lack adequate anti-inflammatory reserves, further exacerbating PES risk.

Although microspheres are effective embolic agents, their high embolic potency can induce intense inflammatory responses and tissue necrosis, thus increasing risk of PES. For high-risk patients, preoperative nutritional support to elevate ALB and PA levels is recommended. A recent study [33] showed that dexamethasone-lipiodol emulsions significantly reduced PES incidence and alleviated symptoms such as pain, fever, and vomiting, suggesting a potential role for intraoperative anti-inflammatory interventions. Additionally, microsphere agents should be used cautiously or in combination with slower-releasing agents to mitigate inflammatory reactions. Postoperatively, vigilant monitoring of inflammatory markers and symptomatic management-including anti-inflammatory medications, nutritional support, and psychological care-are essential to improve patient comfort and outcomes.

The nomogram models developed in this study demonstrated strong predictive capability. Specifically, the AUCs of models for the liver function impairment and PES were 0.854 and 0.826, respectively, showcasing strong discriminatory power and accuracy. Calibration analyses showed high concordance between predicted and observed outcomes, affirming the clinical utility of these models in early identification of high-risk patients. Similar conclusions were reported by Li et al. [25] and Bai et al. [15], whose models yielded AUCs of 0.878 and 0.713, respectively. By translating risk factors into intuitive scoring systems, nomograms facilitate rapid bedside risk assessment. Zeng et al. [34] further demonstrated that early targeted intervention in high-risk PA-TACE patients (with scores >5) significantly improved clinical outcomes, reinforcing the value of personalized treatment approach advocated in this study.

However, this study's retrospective and single-center design introduces certain limitations, including potential selection bias and limited external validity. Additionally, some influential factors-such as tumor molecular characteristics and immune status-were not assessed, possibly affecting the comprehensiveness of the risk prediction models. Future research should address the following key directions: (1) conducting prospective, multi-center validations of these nomograms; (2) exploring molecular and biomarker-based mechanisms to enhance personalized therapy; (3) evaluating the efficacy of interventions such as nutritional support and anti-inflammatory treatment in reducing complication rates; and (4) developing

artificial intelligence-based predictive tools to further enhance model precision and clinical applicability.

Conclusion

This study systematically identified clinical predictors of liver function impairment and PES in PHC patients undergoing TACE and established effective nomogram models for individualized risk assessment. By quantifying key risk indicators, these models offer practical tools for optimizing treatment strategies and improving patient outcomes in clinical practice.

Disclosure of conflict of interest

None.

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Table S1. Comparison of clinical characteristics between training and validation groups for liver function impairment following TACE

Variables	Total	Training group (n=362)	Validation group (n=187)	Statistics	P
Liver function impairment					
With	340	230	110	1.161	0.281
Without	209	132	77		
Neutrophils					
≥5.95	157	102	55	0.092	0.762
<5.95	392	260	132		
DB					
≥23.55	241	161	80	0.144	0.705
<23.55	308	201	107		
ALP					
≥197.05	223	144	79	0.311	0.577
<197.05	326	218	108		
PA					
≥75.15	341	224	117	0.025	0.875
<75.15	208	138	70		
Number of TACE sessions					
≥2.5	319	211	108	0.014	0.904
<2.5	230	151	79		
History of alcohol consumption					
With	246	165	81	0.256	0.613
Without	303	197	106		
Cirrhosis					
With	302	198	104	0.042	0.837
Without	247	164	83		
Ascites					
With	216	142	74	0.006	0.937
Without	333	220	113		
Tumor pathological staging					
Massive	411	269	142	0.351	0.839
Nodular	68	47	21		
Diffuse	70	46	24		
Liver function classification					
A	133	89	44	0.075	0.784
B	416	273	143		
ECOG score					
0	347	228	119	0.023	0.880
1	202	134	68		

Note: DB, direct bilirubin; ALP, alkaline phosphatase; PA, prealbumin; TACE, transcatheter arterial chemoembolization.

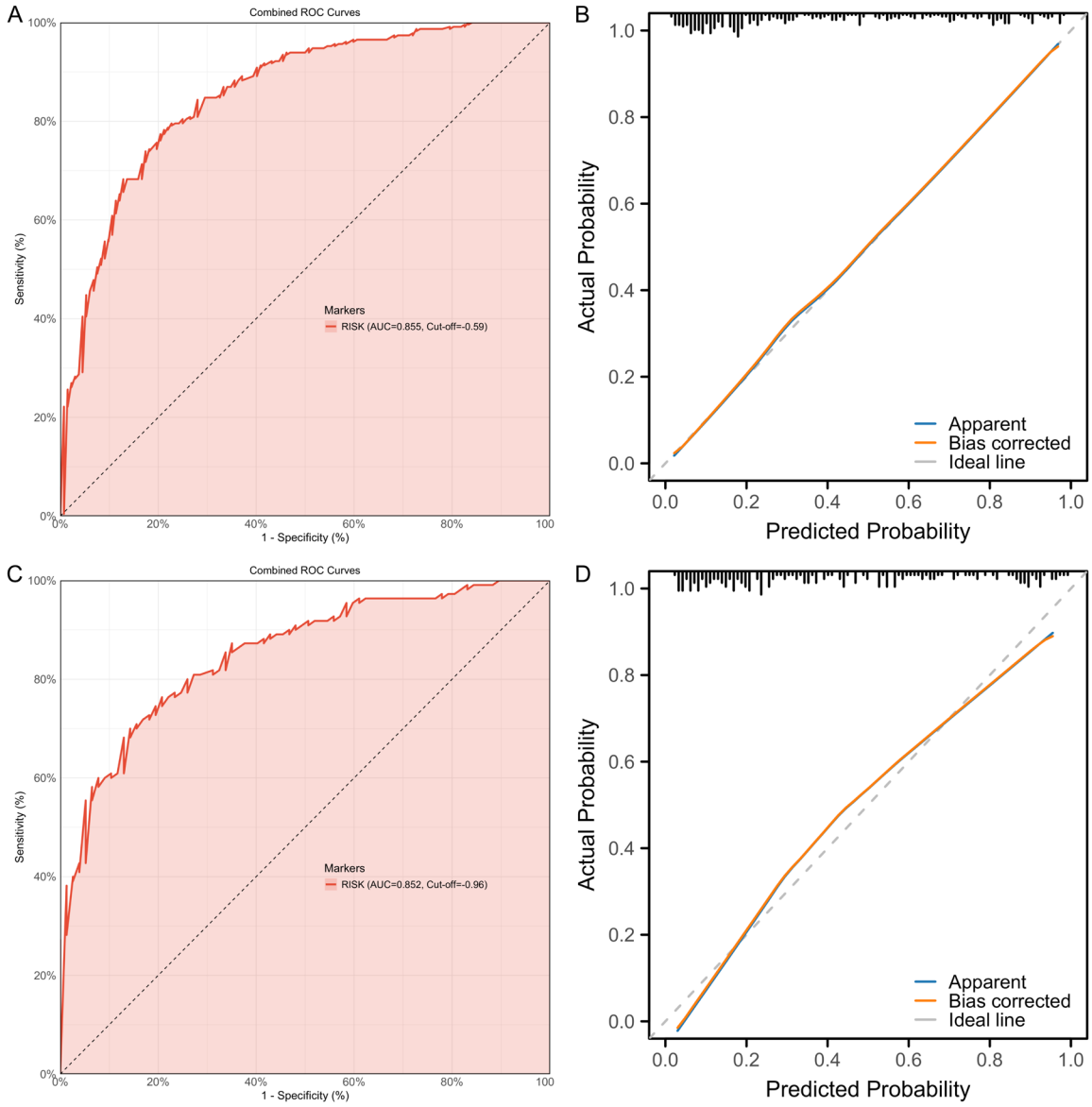

Figure S1. ROC and calibration curves of the nomogram for liver function impairment in the training group (A, B) and validation group (C, D). (A, B) Prediction performance (A) and calibration analysis (B) of the liver function impairment Nomogram in the training group. (C, D) Prediction performance (C) and calibration analysis (D) of the liver function impairment Nomogram in the validation group. Note: ROC, receiver operating characteristic; AUC, area under the curve.

Table S2. Comparison of clinical characteristics between training and validation groups for post-embolism syndrome prediction

Variables	Total	Training group (n=362)	Validation group (n=187)	Statistics	P
Post-embolism syndrome					
With	401	259	142	1.206	0.272
Without	148	103	45	1.206	0.272
BMI					
≥22.84	180	118	62	0.017	0.895
<22.84	369	244	125		
ALB					
≥30.2	448	297	151	0.138	0.710
<30.2	101	65	36		
PA					
≥74.4	348	230	118	0.010	0.920
<74.4	201	132	69		
PNI					
≥36.33	449	294	155	0.231	0.630
<36.33	100	68	32		
History of alcohol consumption					
With	246	164	82	0.105	0.746
Without	303	198	105		
Liver function classification					
A	133	86	47	0.127	0.721
B	416	276	140		
ECOG score					
0	347	229	118	0.001	0.971
1	202	133	69		

Note: BMI, body mass index; ALB, albumin; PA, prealbumin; PNI, Prognostic Nutritional Index; ECOG, Eastern Cooperative Oncology Group.

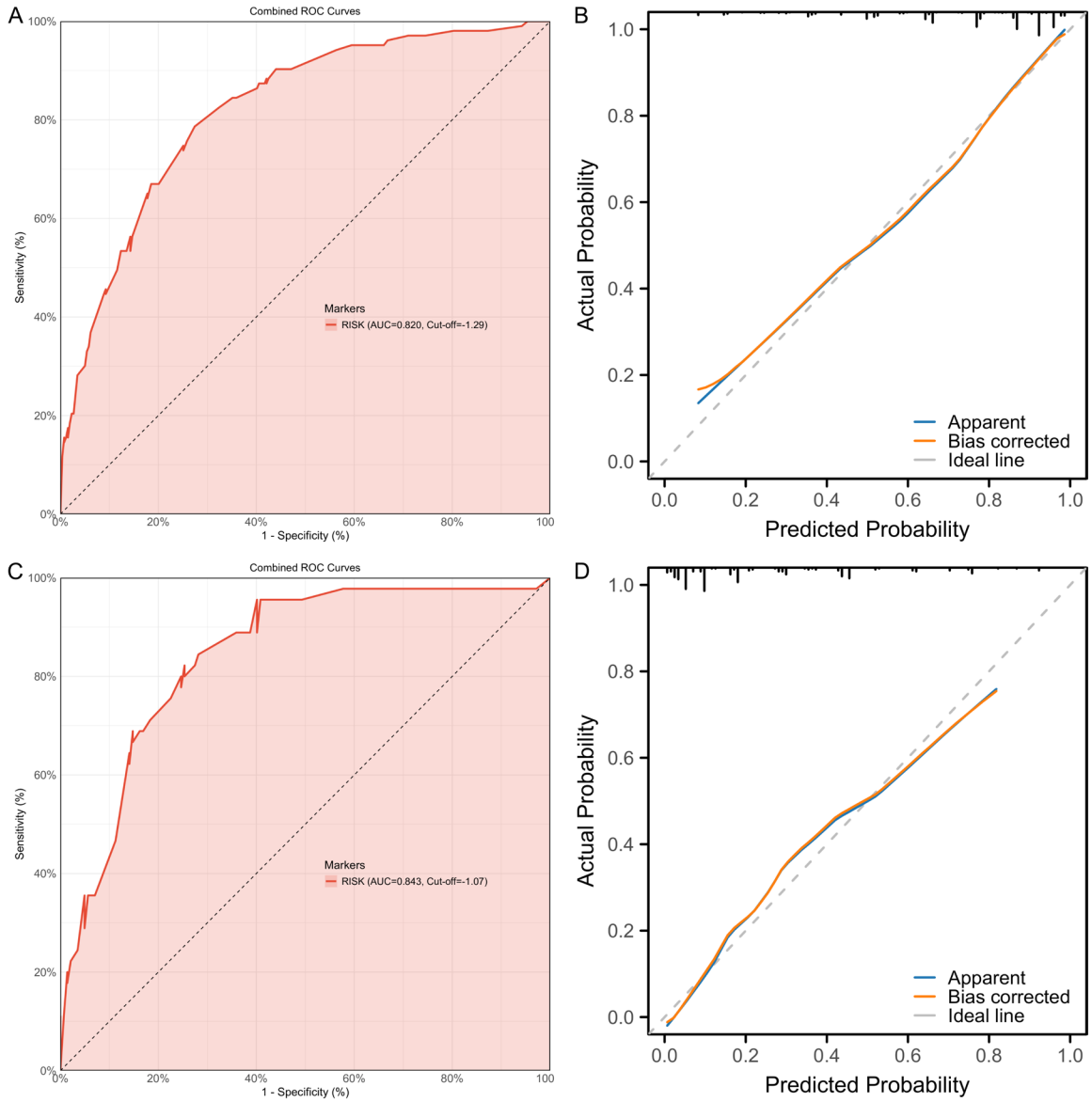

Figure S2. Prediction performance and calibration analysis of nomogram for post-embolism syndrome in the training (A, B) and validation groups (C, D). (A, B) Prediction performance (A) and calibration analysis (B) of the post-embolism syndrome Nomogram in the training group. (C, D) Prediction performance (C) and calibration analysis (D) of the post-embolism syndrome Nomogram in the validation group. Note: AUC, area under the curve.