



# Prognostic value of preoperative prealbumin levels in patients with unresectable hepatocellular carcinoma undergoing transcatheter arterial chemoembolisation

Kai Lei, Jia-Guo Wang, Yin Li, Hong-Xiang Wang, Jie Xu, Ke You, Zuo-Jin Liu\*

Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400000, China

## ARTICLE INFO

### Keywords:

Hepatocellular carcinoma (HCC)  
OS (overall survival)  
Prealbumin (PAB)  
Prognosis  
Transcatheter arterial chemoembolisation (TACE)

## ABSTRACT

**Background:** This retrospective study analyzed the prognostic value of preoperative prealbumin (PAB) levels in patients with unresectable hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolisation (TACE).

**Methods:** Four hundred and two patients diagnosed with unresectable HCC were included in this retrospective study. All patients underwent their first TACE procedure. Based on PAB levels before the first TACE, 402 patients were classified as having low PAB levels and high PAB levels. Potential confounding factors between the two groups were eliminated using Propensity Score Matching (PSM) analysis. The time to progression (TTP) and overall survival (OS) of the two groups were compared using Kaplan-Meier curves before and after PSM. Risk factors for poor prognosis were determined using univariate and multivariate Cox proportional hazards models.

**Results:** Before PSM, the high PAB level group had a significantly longer median TTP and OS than the low PAB level group (all P values < 0.0001). After PSM, the high PAB level group still had a significantly longer median TTP and OS than the low PAB level group (all P values < 0.05). After PSM, low PAB level was found to be an independent predictor of shorter OS (HR = 0.656; 95% CI: 0.448–0.961; P = 0.03). The subgroup analysis before PSM showed that low PAB levels increased the risk of poor prognosis in most subgroups.

**Conclusions:** Low preoperative PAB levels are associated with poor prognosis in patients with unresectable HCC after TACE.

## 1. Introduction

Liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-related death. Between 70% and 80% of primary liver cancers are hepatocellular carcinoma (HCC) [1,2]. The preferred treatments for early stage HCC include radical resection and liver transplantation. After adopting the Barcelona Clinic Liver Cancer (BCLC) staging system, when many HCC patients were first diagnosed, they were already in the advanced stage [3–5]. For patients with unresectable HCC, interventional and systemic therapies can prolong survival. As an effective local treatment modality, transcatheter arterial chemoembolisation (TACE) can control tumour growth and has significant efficacy in unresectable HCC [6].

Many studies have confirmed a significant association between inflammatory or tumour markers and the prognosis of HCC patients

\* Corresponding author.

E-mail address: [300376@hospital.cqmu.edu.cn](mailto:300376@hospital.cqmu.edu.cn) (Z.-J. Liu).

<https://doi.org/10.1016/j.heliyon.2023.e18494>

Received 31 January 2023; Received in revised form 7 July 2023; Accepted 19 July 2023

Available online 20 July 2023

2405-8440/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

after TACE [7–9]. Another study showed that the platelet (PLT) count before TACE in patients with HCC combined with cirrhosis was significantly associated with tumour recurrence [10]. As a biomarker of suggesting liver synthesis function, prealbumin (PAB) was often found in some nutritional status scores [11,12]. Previous studies have shown that reduced PAB levels can increase the risk of postoperative complications [13]. Moreover, PAB levels have been associated with the prognosis of some cancers, such as ovarian carcinoma [14,15] and lung cancer [16]. Some studies have reported a correlation between the PAB levels and HCC prognosis. Low PAB levels were predictive of liver insufficiency in patients with HCC after liver resection [17]. Some studies have confirmed the association between preoperative prealbumin levels and prognosis of HCC patients undergoing radical resection [18,19]. The relationship between preoperative PAB levels and prognosis of patients with HCC undergoing TACE remains unclear. This retrospective study investigated whether low PAB levels were associated with poor prognosis in patients with HCC after TACE.

## 2. Material and methods

### 2.1. Patient and selection

This retrospective study was approved by the Ethics Committee. All patients were informed of the risks and provided written informed consent prior to treatment. A total of 402 patients were included in this study. All patients were initially diagnosed with HCC and underwent their first TACE between January 2013 and December 2018. Inclusion criteria for all clinical cases were as follows: 1) between the ages of 18 and 80; 2) had a definite diagnosis of HCC confirmed either by characteristic imaging examination or liver biopsy; 3) no other liver disease background except for hepatitis B or C; 4) preoperative liver function in Child-Pugh class A or B; 5) BCLC stage B or C; 6) Eastern Cooperative Oncology Group (ECOG) score standard  $\leq 2$ ; 7) no other malignancies. The exclusion criteria were as follows: 1) patients who underwent radical resection, liver transplantation, or radiofrequency ablation (RFA); 2) patients who received other systemic treatments such as immunotherapy and targeted therapy before the first TACE or during the follow-up period; 3) patients with preoperative liver function in Child-Pugh class C; and 4) patients who were lost to follow-up or had incomplete baseline data.

### 2.2. Transcatheter arterial chemoembolisation procedure

The right femoral artery was punctured using the Seldinger technique. After puncture, a short guidewire was inserted into the 5-Fr micropuncture catheter sheath. Under X-ray fluoroscopy, a 5-Fr angiography catheter was inserted into the abdominal trunk and common hepatic artery to visualise the distribution of tumour vessels using angiography. Using a micro-guidewire, the tumour nutrient artery was superselectively inserted into a 2.7-Fr angiographic microcatheter, which was used to inject a chemotherapeutic agent into the tumour nutrient artery. Doxorubicin (20 mg) and iodised oil (5–20 ml) were used. After embolisation with the iodised oil

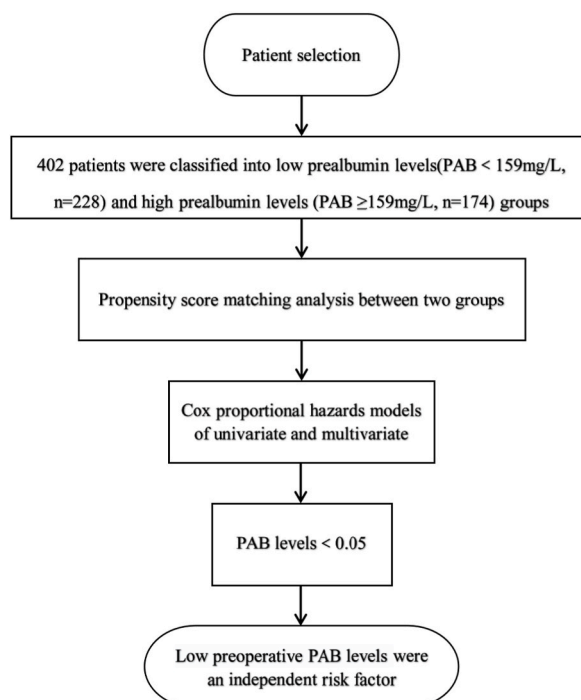


Fig. 1. Flowchart for judging the prognostic value of PAB. PAB, prealbumin.

emulsion, the microsphere diameter was selected based on tumour size and blood supply. Five minutes after drug injection, digital subtraction angiography (DSA) was used to confirm that the arterial flow which provides nutrients to the tumour was stagnant.

### 2.3. Data collection and follow-up

The baseline clinical data for the patients include age, gender, Child-Pugh classification, BCLC stage, portal vessel invasion, tumour number, extrahepatic metastasis, alpha-fetoprotein (AFP) level, longest tumour diameter, alanine aminotransferase (ALT), aspartate transferase (AST), total bilirubin (TBIL), albumin (ALB), haemoglobin (HB), platelet, prothrombin time (PT), and PAB. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were performed to determine the tumour progression 3–4 weeks after the first TACE to determine tumour progression. If the patient did not meet the diagnostic criteria for tumour progression and the lesion was active, re-TACE was performed. If a patient was suspected of having extrahepatic metastasis during follow-up, a relevant examination for extrahepatic metastasis was performed to clarify the diagnosis. After TACE, the Response Evaluation Criteria in Solid Tumours (RECIST) was used to classify tumour response. Tumour response was evaluated for every TACE procedure. Tumour progression was defined as progressive disease (PD) after the first TACE. Complete response (CR), partial response (PR), and stable disease (SD) were not considered as tumour progression. Follow-up via telephone and outpatient and inpatient medical records were provided for all patients after the initial treatment. The deadline for follow-up was June 2022. The primary prognostic endpoint of this study was overall survival (OS). OS was defined as the time between the first TACE and death, or the time between the first TACE and the deadline of follow-up if death did not occur. The second clinical endpoint was the time to progression (TTP). TTP was defined as the time between the first TACE and tumour progression or the time between the first TACE and the deadline of follow-up if tumour progression did not occur.

### 2.4. Cut-off value and group

A flowchart for determining the prognostic value of PAB is shown in Fig. 1. The cut-off value of PAB levels in this study was obtained using the X-tile software [Fig. 2(A-C)]. The cutoff value was used to classify 402 patients with unresectable HCC into low prealbumin levels (PAB < 159 mg/L, n = 228) and high prealbumin (PAB ≥ 159 mg/L, n = 174) groups.

### 2.5. Propensity score matching analysis

Propensity score matching analysis was performed to eliminate confounding variables between the low- and high-PAB groups. This analysis matched all variables that may have influenced the prognostic endpoints, including age, sex, BCLC stage, Child-Pugh classification, portal vessel invasion, extrahepatic metastasis, AST, TBIL, ALB, HB, PLT, and PT. A matching calliper of 0.05 and 1:1 nearest neighbour matching were used in the analysis.

### 2.6. Statistical analysis

SPSS 26.0 software (IBM, Chicago, IL, USA) was used to analyse the data in this study. The clinical baseline data of the low- and high-PAB groups were analyzed using descriptive statistics. The mean (standard deviation [SD]) was applied to the parametric variables. The median and interquartile range (IQR) were applied to continuous numerical variables that did not meet the normal distribution. Categorical variables were summarised as counts and percentages. Before propensity score matching (PSM), comparisons between the low and high PAB groups were completed using the independent samples *t*-test to compare parametric variables, the Mann-Whitney *U* test to compare nonparametric variables, and the Chi-square test to compare categorical variables. After PSM, comparisons between the two groups were performed using the paired *t*-test to compare parametric variables, the Wilcoxon rank-sum test to compare nonparametric variables, and the McNemar test to compare categorical variables. The median TTP and OS between the low and high PAB groups before and after PSM were compared using Kaplan-Meier curves. Correlations between clinical baseline data

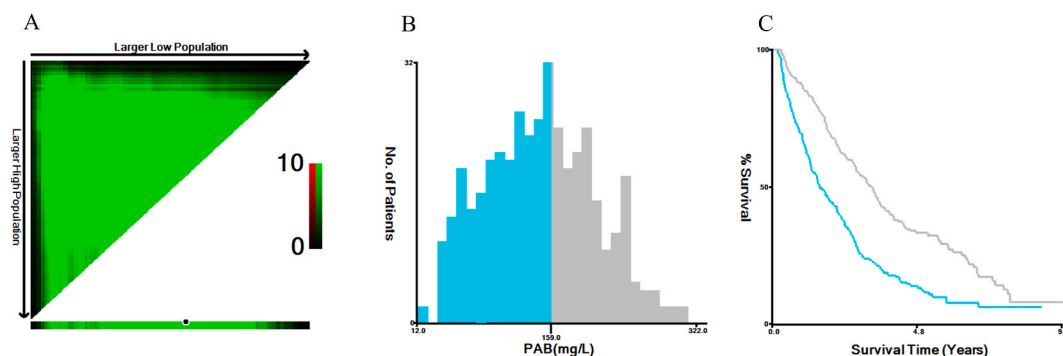


Fig. 2. X-tile analysis of OS according to PAB. OS, overall survival; PAB, prealbumin.

and OS or TTP were tested using univariate and multivariate Cox proportional hazards models. In the univariate Cox proportional hazards models, variables with a *P*-value lower than 0.05 were included in the multivariate Cox proportional hazards models. Significance was set as a *p*-value <0.05. Due to sample size, subgroup analysis was performed before PSM according to sex, age, BCLC stage, Child-Pugh classification, portal vessel invasion, and extrahepatic metastasis.

### 3. Results

#### 3.1. Patient characteristics

The baseline clinical characteristics and descriptive statistics of the 402 patients included in this study are presented in Table 1. The patients were divided into low PAB (PAB < 159 mg/L, n = 228) and high PAB (PAB ≥ 159 mg/L, n = 174) groups based on preoperative PAB levels. The average age of patients in the low PAB group was 55.8 (11.0) years, and the average age of patients in the high PAB group was 53.6 (11.1) years. There were more male than female patients in this study (n = 355, 88.3%). Before PSM, significant differences existed between the low and high PAB groups in clinical baseline data, including age, sex, BCLC stage, Child-Pugh classification, portal vessel invasion, extrahepatic metastasis, AST, TBIL, ALB, HB, PLT, PT, and PAB.

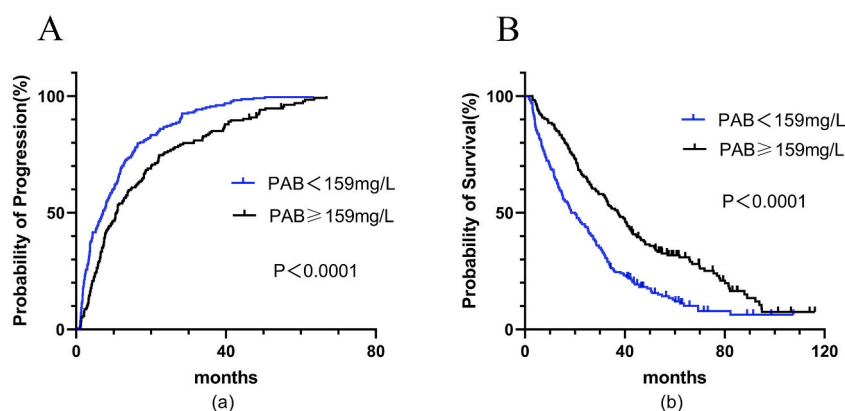
#### 3.2. Survival analysis before PSM

Tumour progression occurred in 228 patients (100%) in the low PAB group and 171 patients (98.3%) in the high PAB group before the follow-up deadline. A total of 199 patients (87.3%) in the low PAB group and 138 (79.3%) in the high PAB group died during follow-up. Before PSM, the median TTP and OS of the low PAB group were 7.2 months and 19.3 months, respectively. The median TTP and OS of the high PAB group were 10.8 months and 37.3 months, respectively. Kaplan–Meier curves with the log-rank test were used to compare the median TTP and OS between the low and high PAB groups before PSM [Fig. 3(A-B)]. The high PAB group had a significantly longer median TTP and median OS than the low PAB group (log-rank test, all *P* values < 0.0001).

**Table 1**  
Patient characteristics before PSM.

Variables		PAB < 159 mg/L (n = 228)	PAB ≥ 159 mg/L (n = 174)	P value
Age (years), Mean (SD)		55.8 (11.0)	53.6 (11.1)	0.048
Sex	Male	195(85.5%)	160(92.0%)	<b>0.047</b>
	Female	33(14.5%)	14(8.0%)	< <b>0.001</b>
BCLC stage	B	135(59.2%)	138(79.3%)	
	C	93(40.8%)	36(20.7%)	
Child-Pugh classification	A	167(73.2%)	171(98.3%)	< <b>0.001</b>
	B	61(26.8%)	39(1.7%)	
Portal vessel invasion	No	144(63.2%)	140(80.5%)	< <b>0.001</b>
	Yes	84(36.8%)	34(19.5%)	
Extrahepatic metastasis	No	215(94.3%)	172(98.9%)	<b>0.017</b>
	Yes	13(5.7%)	2(1.1%)	
Tumor number	Single	39(17.1%)	19(10.9%)	0.080
	Multiple	189(82.9%)	155(89.1%)	
AFP	< 400 ng/ml	153(67.1%)	113(64.9%)	0.650
	≥ 400 ng/ml	75(32.9%)	61(35.1%)	
Tumor longest diameter (mm)		41(56)	40(46)	0.083
Median (IQR)				
ALT (U/L)		35(28)	41(28)	0.057
Median (IQR)				
AST (U/L)		50(42)	38(21)	< <b>0.001</b>
Median (IQR)				
TBIL (umol/L)		17.3(13.3)	13.7(8.2)	< <b>0.001</b>
Median (IQR)				
ALB (g/L), Mean (SD)		35.5(5.0)	42.1(3.7)	< <b>0.001</b>
HB (g/L), Mean (SD)		125.1(22.6)	142.6(15.9)	< <b>0.001</b>
PLT (10 <sup>9</sup> /L)		94(115)	115(74)	<b>0.028</b>
Median (IQR)				
PT (S), Median (IQR)		15.0(2.4)	13.9(1.2)	< <b>0.001</b>
PAB (mg/L), Median (IQR)		108(59)	197(56)	< <b>0.001</b>
Progression	No	0(0%)	3(1.7%)	<b>0.047</b>
	Yes	228(100%)	171(98.3%)	
Survival	No	199(87.3%)	138(79.3%)	<b>0.032</b>
	Yes	29(12.7%)	36(20.7%)	

PSM, propensity score matching; PAB, prealbumin; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transferase; TBIL, total bilirubin; ALB, albumin; HB, haemoglobin; PLT, platelet; PT, prothrombin time; IQR, interquartile range.



**Fig. 3.** Kaplan-Meier curves of TTP (a) and OS (b) in unresectable HCC patients with different pretreatment PAB levels who underwent TACE before PSM. PAB, prealbumin; TTP, time to progression; OS, overall survival; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolisation; PSM, propensity score matching.

### 3.3. PSM analysis for patient data

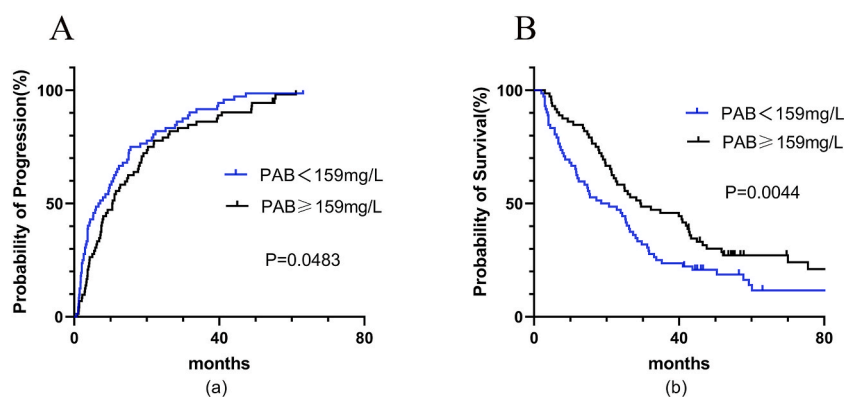
After PSM, the low and high PAB groups each included 72 patients. After PSM, no significant differences were observed between the two groups in the baseline clinical data (Table 2). The respective median TTP and OS of the low PAB group were 7.0 and 19.6 months, and the respective median TTP and OS of the high PAB group were 10.6 and 29.4 months. The median TTP and OS were compared by the Kaplan–Meier curves between the two groups with differences shown in Fig. 4(A–B). The high PAB group still had a significantly longer median TTP and OS than the low PAB group after PSM (log-rank test, all P values < 0.05).

**Table 2**

Patient characteristics after PSM.

Variables		PAB <159 mg/L (n = 72)	PAB ≥159 mg/L (n = 72)	P value
Age (years), Mean (SD)		55.6 (11.3)	56.0 (11.1)	0.818
Gender	Male	65(90.3%)	65(90.3%)	1.000
Stage of BCLC	Female	7(9.7%)	7(9.7%)	0.505
	B	47(65.3%)	51(70.8%)	
	C	25(34.7%)	21(29.2%)	
Child-Pugh classification	A	69(95.8%)	69(95.8%)	1.000
	B	3(4.2%)	3(4.2%)	
Portal vessel invasion	No	48(66.7%)	52(72.2%)	0.505
	Yes	24(33.3%)	20(27.8%)	
Extrahepatic metastasis	No	71(98.6%)	71(98.6%)	1.000
	Yes	1(1.4%)	1(1.4%)	
Tumor number	Single	9(12.5%)	9(12.5%)	0.346
	Multiple	63(87.5%)	63(87.5%)	
AFP	< 400 ng/ml	47(65.3%)	51(70.8%)	0.480
	≥400 ng/ml	25(34.7%)	21(29.2%)	
Tumor longest diameter (mm)		50(40)	48(52)	0.911
Median (IQR)				
ALT (U/L)		38(30)	40(28)	0.575
Median (IQR)				
AST (U/L)		49(42)	40(21)	0.114
Median (IQR)				
TBIL (umol/L)		14.6(7.0)	14.9(10.0)	0.996
Median (IQR)				
ALB (g/L), Mean (SD)		39.4(3.3)	39.7(3.3)	0.434
HB (g/L), Mean (SD)		137.8(14.8)	136.1(16.1)	0.461
PLT (10 <sup>9</sup> /L)		116(93)	125(92)	0.969
Median (IQR)				
PT (S), Median (IQR)		14.3(1.3)	14.4(1.0)	0.838
PAB (mg/L), Median (IQR)		138(29)	193(39)	< 0.001
Progression	No	0(1.4%)	1(1.4%)	0.317
	Yes	72(100%)	71(98.6%)	
Survival	No	62(86.1%)	57(79.2%)	0.317
	Yes	10(13.9%)	15(20.8%)	

PSM, propensity score matching; PAB, prealbumin; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transferase; TBIL, total bilirubin; ALB, albumin; HB, haemoglobin; PLT, platelet; PT, prothrombin time; IQR, interquartile range.



**Fig. 4.** Kaplan-Meier curves of TTP (a) and OS (b) in patients with unresectable HCC with different pretreatment PAB levels who underwent TACE after PSM. TTP, time to progression; OS, overall survival; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolisation; PSM, propensity score matching.

### 3.4. Univariate and multivariate analysis for OS after PSM

After PSM, univariate and multivariate Cox proportional hazards models were used to analyse risk factors for poor prognosis (Table 3). In the univariate analysis of OS, Variables with significant effects on OS included PAB level (HR = 0.648; 95% CI:0.451–0.931; P = 0.019), age (HR = 0.982; 95% CI:0.965–1.000; P = 0.046), stage of BCLC (HR = 2.443; 95% CI:1.675–3.563; P < 0.001), portal vessel invasion (HR = 2.570; 95% CI:1.752–3.769; P < 0.001), extrahepatic metastasis (HR = 6.313; 95% CI:1.503–26.508; P = 0.012), AFP level (HR = 1.784; 95% CI: 1.217–2.616; P = 0.003), tumour longest diameter (HR = 1.015; 95% CI:1.010–1.020; P < 0.001), TBIL (HR = 0.971; 95% CI:0.945–0.997; P = 0.031), PLT (HR = 1.003; 95% CI: 1.001–1.005; P = 0.011). Because BCLC stage was associated with portal vessel invasion and extrahepatic metastasis, multiple collinearities could cause errors in the multivariate analysis. Therefore, portal vessel invasion and extrahepatic metastasis were excluded from the multivariate analysis. Variables included in the multivariate analysis of OS included PAB level, age, BCLC stage, AFP level, longest tumour diameter, TBIL, ALB [20], and PLT. In the analysis of multivariate variables, PAB level (HR = 0.656; 95% CI:0.448–0.961; P = 0.03), stage of BCLC (HR = 1.681; 95% CI:1.044–2.704; P = 0.032), AFP level (HR = 1.569; 95% CI:1.038–2.371; P = 0.033) and longest tumour diameter (HR = 1.008; 95% CI:1.001–1.015; P = 0.036) were significant and independent factors of prognosis in unresectable HCC patients undergoing TACE.

### 3.5. Subgroup analysis of OS before PSM

To exclude the interference of PAB level by other variables before PSM, subgroup analysis was performed according to sex, age,

**Table 3**

Survival analysis of OS for all patients after PSM.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
PAB(≥159 mg/L)	0.648 (0.451–0.931)	<b>0.019</b>	0.656 (0.448–0.961)	<b>0.03</b>
Gender(Female)	1.190 (0.654–2.164)	0.568		
Age(years)	0.982 (0.965–1.000)	<b>0.046</b>	0.988 (0.970–1.007)	0.205
Stage of BCLC(C )	2.443 (1.675–3.563)	<b>&lt; 0.001</b>	1.681 (1.044–2.704)	<b>0.032</b>
Child-Pugh classification(B)	0.632 (0.231–1.727)	0.371		
Portal vessel invasion (Yes)	2.570 (1.752–3.769)	<b>&lt; 0.001</b>		
Extrahepatic metastasis (Yes)	6.313 (1.503–26.508)	<b>0.012</b>		
AFP (≥400 ng/ml)	1.784 (1.217–2.616)	<b>0.003</b>	1.569 (1.038–2.371)	<b>0.033</b>
Tumor number (Multiple)	0.682 (0.425–1.094)	0.112		
Tumor longest diameter (mm)	1.015 (1.010–1.020)	<b>&lt; 0.001</b>	1.008 (1.001–1.015)	<b>0.036</b>
ALT(U/L)	0.998 (0.994–1.002)	0.291		
AST(U/L)	0.999 (0.995–1.002)	0.388		
TBIL(umol/L)	0.971 (0.945–0.997)	<b>0.031</b>	0.985 (0.958–1.014)	0.313
ALB(g/L)	0.962 (0.910–1.018)	0.178	0.992 (0.934–1.053)	0.792
HB(g/L)	1.002 (0.990–1.014)	0.766		
PLT(10 <sup>9</sup> /L)	1.003 (1.001–1.005)	<b>0.011</b>	1.001 (0.998–1.003)	0.681
PT(S)	0.818 (0.667–1.004)	0.055		

OS, overall survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; PAB, prealbumin; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; HB, haemoglobin; PLT, platelet; PT, prothrombin time.

BCLC stage, Child-Pugh classification, portal vessel invasion, extrahepatic metastasis, longest tumour diameter, AFP level, and tumour number (Fig. 5). Except for the subgroups of stage C BCLC, portal vessel invasion, Child-Pugh classification B liver function, extrahepatic metastasis, and tumour number, because of the size of the sample, analysis of the other subgroups demonstrated a significant association between preoperative PAB levels and OS (all  $P < 0.05$ ). Therefore, low preoperative PAB levels are associated with poor prognosis in patients with unresectable HCC after TACE.

#### 4. Discussion

Transarterial chemoembolisation (TACE) is an effective modality for the treatment of liver cancer, particularly unresectable HCC [6]. Evaluating the prognosis after TACE in patients with unresectable HCC is an important question. Relevant studies have found that the Child-Pugh classification, inflammatory cytokines, and some tumour markers are associated with the prognosis of patients with HCC after receiving TACE [8,9,21–23].

As a protein of liver synthesis that can reflect liver function, PAB was not included in the Child-Pugh classification [24]. PAB levels are commonly used as indicators of nutritional status. PAB levels can indicate the level of protein consumption, which in turn can identify patients at risk of malnutrition [13]. Several studies have found that PAB-based nutritional assessment is associated with prognosis of patients with tumours [25–29]. Poor preoperative nutritional status in patients with lung cancer who undergo radical resection can increase the risk of postoperative complications [16]. Nutritional assessment including prealbumin could determine whether patients with ovarian cancer can undergo radical resection [14,15].

PAB is a protein synthesised in the liver that is associated with the prognosis of various liver diseases. Previous studies had demonstrated a significant association between PAB levels before partial hepatectomy and the occurrence of postoperative hepatic insufficiency, including hepatic failure [17,30]. Combining the PAB and Child-Pugh classification could improve the predictive accuracy of prognosis in patients with HCC undergoing radical resection [24]. A score based on PAB levels can effectively predict the risk of early recurrence and mortality in patients who underwent TACE plus locoregional ablative therapy [31]. Fibrinogen to prealbumin ratio (FPR) is considered a potential prognostic indicator for HCC patients receiving RFA and TACE [32]. It has also been demonstrated that a reduction in the ratio of the non-protein respiratory quotient and PAB might be related to the deterioration of liver function after TACE in patients with HCC [33]. Some studies have confirmed the association between preoperative prealbumin levels and the prognosis of patients with HCC undergoing radical resection. Patients with low preoperative PAB levels often have a poor prognosis [18,19,34].

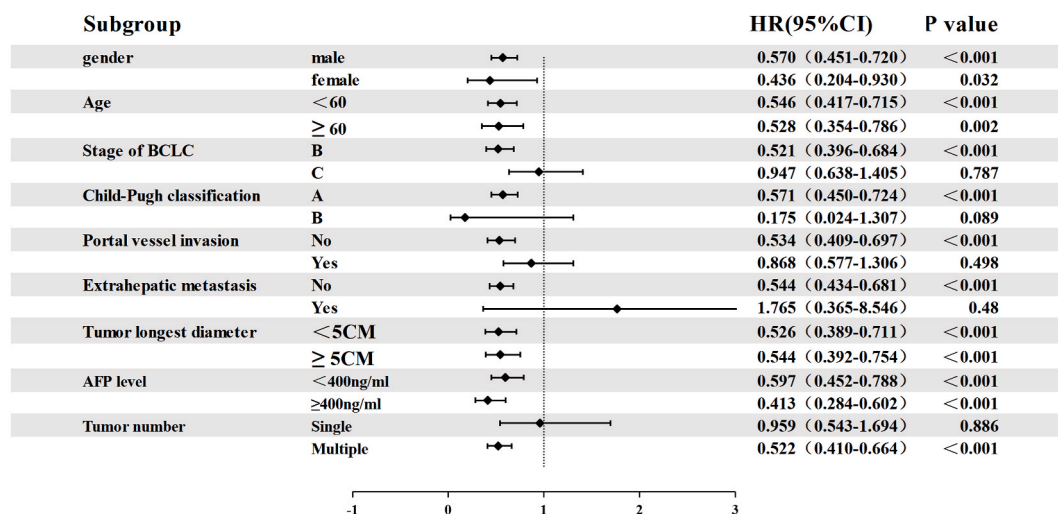
This retrospective study aimed to investigate the association between preoperative PAB levels and prognosis of patients with unresectable HCC. This study has the following advantages. First, this study aimed to determine the association between PAB levels before TACE and the prognosis of patients with unresectable HCC. After determining the grouping cutoff value, the patients were divided into low- and high-PAB groups based on preoperative PAB levels. Second, a PSM analysis was performed to reduce the interference of confounding variables between the low- and high-PAB groups. Survival analysis was performed for both groups before and after PSM. Subgroup analysis was performed before PSM. Third, two clinical endpoints, TTP and OS, were set up simultaneously to explore the long-term survival of patients with unresectable HCC after TACE. By grouping, using PSM to eliminate the interference of confounding variables, and using Cox proportional hazards models, this study is the first to demonstrate that low preoperative PAB levels are an independent predictor of poor prognosis in patients with unresectable HCC after TACE. To exclude the interference of the sample size, a subgroup analysis of OS before PSM was performed. The analysis still demonstrated a significant association between low preoperative PAB levels and shortened OS. This finding indicates that low PAB levels still have an important predictive value for the long-term survival of patients with unresectable HCC after TACE.

Low preoperative PAB levels might represent poor liver function and nutritional status, which indicate poor physical condition in patients with tumours. Albumin is more widely used in the clinical setting; however, it has better specificity and sensitivity in nutritional assessment and judgment of liver function [35,36]. Low PAB levels may indicate a greater tumour burden [13,17,37]. Therefore, poor nutritional status is associated with a poor prognosis in patients with different tumours [14–16]. Low PAB levels can lead to an increased incidence of postoperative complications. Serious postoperative complications can significantly affect the prognosis of patients with tumours. This phenomenon has been confirmed in related studies [18]. Among patients with HCC who underwent radical resection, those with low preoperative PAB levels had higher short-term mortality. In addition, TACE has a detrimental effect on liver function in HCC patients with low PAB levels [6]. Reduced PAB levels have been shown to be associated with the long-term deterioration of liver function in patients undergoing TACE [33]. These reasons suggest that low preoperative PAB levels could cause a poor prognosis in patients with HCC after TACE.

This study has some limitations. First, this was a single-centre, retrospective study and lacked a substantial sample to support the conclusion. Second, relatively few studies have demonstrated that improving PAB levels in patients with HCC can improve the prognosis after TACE. Therefore, further studies are required to validate these results.

#### 5. Conclusions

In summary, low preoperative PAB levels are independent risk factors in patients with unresectable HCC after TACE. Poor nutritional status in patients with HCC before TACE may lead to poor prognosis. This finding provides an important basis for nutritional support in patients with HCC prior to TACE.



**Fig. 5.** Subgroup analysis of OS before PSM. OS, overall survival; PSM, propensity score matching; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; HR, hazard ratio; CI, confidence interval.

## Declarations

### Author contribution statement

Kai Lei: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.  
 Zuo-Jin Liu: Conceived and designed the experiments.  
 Jia-Guo Wang; Yin Li; Hong-Xiang Wang: Performed the experiments; Analyzed and interpreted the data.  
 Jie Xu; Ke You: Performed the experiments.

### Data availability statement

Data will be made available on request.

### Funding statement

This work was supported by the National Natural Science Foundation of China (No.82070678) and the Chongqing Medical University Program for Youth Innovation in Future Medicine (grant number W0084).

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- [1] L.A. Torre, et al., Global cancer statistics, 2012, *CA Can. J. Clin.* 65 (2) (2015) 87–108, <https://doi.org/10.3322/caac.21262>.
- [2] D.M. Parkin, et al., Estimating the world cancer burden: globocan 2000, *Int. J. Cancer* 94 (2) (2001) 153–156, <https://doi.org/10.1002/ijc.1440>.
- [3] A. Forner, M. Reig, J. Bruix, Hepatocellular carcinoma, *Lancet* 391 (10127) (2018) 1301–1314, [https://doi.org/10.1016/s0140-6736\(18\)30010-2](https://doi.org/10.1016/s0140-6736(18)30010-2).
- [4] V. Mazzaferro, et al., Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis, *N. Engl. J. Med.* 334 (11) (1996) 693–699, <https://doi.org/10.1056/nejm199603143341104>.
- [5] A. Forner, et al., Current strategy for staging and treatment: the BCLC update and future prospects, *Semin. Liver Dis.* 30 (1) (2010) 61–74, <https://doi.org/10.1055/s-0030-1247133>.
- [6] J.M. Llovet, et al., Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial, *Lancet* 359 (9319) (2002) 1734–1739, [https://doi.org/10.1016/s0140-6736\(02\)08649-x](https://doi.org/10.1016/s0140-6736(02)08649-x).
- [7] Z.L. Huang, et al., Blood neutrophil-to-lymphocyte ratio predicts survival in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization, *J. Vasc. Intervent. Radiol.* 22 (5) (2011) 702–709, <https://doi.org/10.1016/j.jvir.2010.12.041>.
- [8] C.H. Jun, et al., Impact of serum C-reactive protein level on the prognosis of patients with hepatocellular carcinoma undergoing TACE, *Clin. Mol. Hepatol.* 19 (1) (2013) 70–77, <https://doi.org/10.3350/cmh.2013.19.1.70>.
- [9] A. Hiraoka, et al., Prediction of prognosis of intermediate-stage HCC patients: validation of the tumor marker score in a nationwide database in Japan, *Liver Cancer* 8 (5) (2019) 403–411, <https://doi.org/10.1159/000495944>.
- [10] S.P. Li, et al., High platelet count predicts poor prognosis in HCC patients undergoing TACE: a propensity score-matched analysis, *Expet Rev. Gastroenterol. Hepatol.* 16 (2) (2022) 193–199, <https://doi.org/10.1080/17474124.2022.2031977>.



- [11] G. Devoto, et al., Prealbumin serum concentrations as a useful tool in the assessment of malnutrition in hospitalized patients, *Clin. Chem.* 52 (12) (2006) 2281–2285, <https://doi.org/10.1373/clinchem.2006.080366>.
- [12] F.K. Beck, T.C. Rosenthal, Prealbumin: a marker for nutritional evaluation, *Am. Fam. Physician* 65 (8) (2002) 1575–1578.
- [13] J.A. Windsor, G.L. Hill, Protein depletion and surgical risk, *Aust. N. Z. J. Surg.* 58 (9) (1988) 711–715, <https://doi.org/10.1111/j.1445-2197.1988.tb01101.x>.
- [14] J.P. Geisler, et al., Nutritional assessment using prealbumin as an objective criterion to determine whom should not undergo primary radical cytoreductive surgery for ovarian cancer, *Gynecol. Oncol.* 106 (1) (2007) 128–131, <https://doi.org/10.1016/j.ygyno.2007.03.008>.
- [15] C.G. Mähle, K. Grankvist, Plasma prealbumin in women with epithelial ovarian carcinoma, *Gynecol. Obstet. Invest.* 37 (2) (1994) 135–140, <https://doi.org/10.1159/000292542>.
- [16] R.T. Jagoe, T.H. Goodship, G.J. Gibson, Nutritional status of patients undergoing lung cancer operations, *Ann. Thorac. Surg.* 71 (3) (2001) 929–935, [https://doi.org/10.1016/s0003-4975\(00\)02005-1](https://doi.org/10.1016/s0003-4975(00)02005-1).
- [17] L. Huang, et al., Prealbumin is predictive for postoperative liver insufficiency in patients undergoing liver resection, *World J. Gastroenterol.* 18 (47) (2012) 7021–7025, <https://doi.org/10.3748/wjg.v18.i47.7021>.
- [18] J.D. Li, et al., Association between preoperative prealbumin level and postoperative mortality and morbidity after hepatic resection for hepatocellular carcinoma: a multicenter study from a HBV-endemic area, *Am. J. Surg.* 221 (5) (2021) 1024–1032, <https://doi.org/10.1016/j.amjsurg.2020.08.036>.
- [19] J.D. Li, et al., Preoperative prealbumin level as an independent predictor of long-term prognosis after liver resection for hepatocellular carcinoma: a multi-institutional study, *HPB (Oxford)* 21 (2) (2019) 157–166, <https://doi.org/10.1016/j.hpb.2018.06.1803>.
- [20] M.T. Wu, et al., Clinical and prognostic implications of pretreatment albumin to C-reactive protein ratio in patients with hepatocellular carcinoma, *BMC Cancer* 19 (1) (2019) 538, <https://doi.org/10.1186/s12885-019-5747-5>.
- [21] L. Müller, et al., Immunonutritive scoring for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: evaluation of the CALLY index, *Cancers* 13 (19) (2021), <https://doi.org/10.3390/cancers13195018>.
- [22] M.E. McNally, et al., Inflammatory markers are associated with outcome in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization, *Ann. Surg. Oncol.* 20 (3) (2013) 923–928, <https://doi.org/10.1245/s10434-012-2639-1>.
- [23] I. Waked, et al., Transarterial chemo-embolisation of hepatocellular carcinoma: impact of liver function and vascular invasion, *Br. J. Cancer* 116 (4) (2017) 448–454, <https://doi.org/10.1038/bjc.2016.423>.
- [24] X. Wen, et al., Integration of prealbumin into child-pugh classification improves prognosis predicting accuracy in HCC patients considering curative surgery, *J. Clin. Trans. Hepatol.* 6 (4) (2018) 377–384, <https://doi.org/10.14218/JCTH.2018.00004>.
- [25] J.F. Feng, et al., C-reactive protein to prealbumin ratio (CPR): a novel inflammatory-nutritional prognostic factor for predicting cancer-specific survival (CSS) and overall survival (OS) in patients with resectable esophageal squamous cell carcinoma, *JAMA Oncol.* 2019 (2019), 4359103, <https://doi.org/10.1155/2019/4359103>.
- [26] T. Matsunaga, et al., Prognostic significance of C-reactive protein-to-prealbumin ratio in patients with esophageal cancer, *Yonago Acta Med.* 63 (1) (2020) 8–19, <https://doi.org/10.33160/yam.2020.02.002>.
- [27] D.W. Sun, L. An, G.Y. Lv, Albumin-fibrinogen ratio and fibrinogen-prealbumin ratio as promising prognostic markers for cancers: an updated meta-analysis, *World J. Surg. Oncol.* 18 (1) (2020) 9, <https://doi.org/10.1186/s12957-020-1786-2>.
- [28] Z. Wang, et al., Prealbumin-to-Globulin ratio can predict the chemotherapy outcomes and prognosis of patients with gastric cancer receiving first-line chemotherapy, *J. Immunol. Res.* 2020 (2020), 6813176, <https://doi.org/10.1155/2020/6813176>.
- [29] Y. Li, et al., Use of the alkaline phosphatase to prealbumin ratio as an independent predictive factor for the prognosis of gastric cancer, *World J. Gastroenterol.* 26 (44) (2020) 6963–6978, <https://doi.org/10.3748/wjg.v26.i44.6963>.
- [30] W.C. Zhao, et al., Preoperative predictors of short-term survival after hepatectomy for multinodular hepatocellular carcinoma, *World J. Gastroenterol.* 18 (25) (2012) 3272–3281, <https://doi.org/10.3748/wjg.v18.i25.3272>.
- [31] Q. Wang, et al., Combination of the gamma-glutamyltransferase-to-prealbumin ratio and other indicators may be a novel marker for predicting the prognosis of patients with hepatocellular carcinoma undergoing locoregional ablative therapies, *Infect. Agents Cancer* 14 (2019) 49, <https://doi.org/10.1186/s13027-019-0266-1>.
- [32] Y. Shen, et al., The prognostic role of circulating FPR before operation in patients with BCLC A-C hepatocellular carcinoma: a retrospective cohort study, *J. Hepatocell. Carcinoma* 9 (2022) 467–476, <https://doi.org/10.2147/jhc.S369168>.
- [33] M. Saito, et al., Short-term reductions in non-protein respiratory quotient and prealbumin can be associated with the long-term deterioration of liver function after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma, *J. Gastroenterol.* 47 (6) (2012) 704–714, <https://doi.org/10.1007/s00535-012-0535-x>.
- [34] Y. Fan, et al., Preoperative serum prealbumin level and adverse prognosis in patients with hepatocellular carcinoma after hepatectomy: a meta-analysis, *Front. Oncol.* 11 (2021), 775425, <https://doi.org/10.3389/fonc.2021.775425>.
- [35] N. Collins, The difference between albumin and prealbumin, *Adv. Skin Wound Care* 14 (5) (2001) 235–236, <https://doi.org/10.1097/00129334-200109000-00009>.
- [36] M.S. Crestani, T. Grassi, T. Steemburgo, Methods of nutritional assessment and functional capacity in the identification of unfavorable clinical outcomes in hospitalized patients with cancer: a systematic review, *Nutr. Rev.* 80 (4) (2021) 786–811, <https://doi.org/10.1093/nutrit/nuab090>.
- [37] R.R. Huo, et al., Dose-response between serum prealbumin and all-cause mortality after hepatectomy in patients with hepatocellular carcinoma, *Front. Oncol.* 10 (2020), 596691, <https://doi.org/10.3389/fonc.2020.596691>.