

# Nutritional prognostic scores in patients with hilar cholangiocarcinoma treated by percutaneous transhepatic biliary stenting combined with <sup>125</sup>I seed intracavitary irradiation

## A retrospective observational study

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### Abstract

We mainly aimed to preliminarily explore the prognostic values of nutrition-based prognostic scores in patients with advanced hilar cholangiocarcinoma (HCCA).

We retrospectively analyzed 73 cases of HCCA, who underwent percutaneous transhepatic biliary stenting (PTBS) combined with <sup>125</sup>I seed intracavitary irradiation from November 2012 to April 2017 in our department. The postoperative changes of total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin (ALB) were observed. The preoperative clinical data were collected to calculate the nutrition-based scores, including controlling nutritional status (CONUT), C-reactive protein/albumin ratio (CAR), and prognostic nutritional index (PNI). Kaplan–Meier curve and Cox regression model were used for overall survival (OS) analyses.

The serum levels of TBIL, DBIL, ALT, AST, and ALP significantly reduced, and ALB significantly increased at 1 month and 3 months postoperatively. The median survival time of the cohort was 12 months and the 1-year survival rate was 53.1%. Univariate analysis revealed that the statistically significant factors related to OS were CA19-9, TBIL, ALB, CONUT, and PNI. Multivariate analysis further identified CA19-9, CONUT, and PNI as independent prognostic factors.

Nutrition-based prognostic scores, CONUT and PNI in particular, can be used as predictors of survival in unresectable HCCA.

**Abbreviations:** ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CA19-9 = carbohydrate antigen 19-9, CAR = C-reactive protein/albumin ratio, CEA = carcino-embryonic antigen, CONUT = controlling nutritional status, CRP = C-reactive protein, DBIL = direct bilirubin, DSA = digital subtraction angiography, HCCA = hilar cholangiocarcinoma, OS = overall survival, PLT = platelet count, PNI = prognostic nutritional index, PTBS = percutaneous transhepatic biliary stenting, PTCD = percutaneous transhepatic cholangial drainage, TBIL = total bilirubin.

**Keywords:** <sup>125</sup>I seed, biliary stent, controlling nutritional status, hilar cholangiocarcinoma, prognostic nutritional index

## 1. Introduction

Cholangiocarcinoma is a rare malignancy arising from bile duct epithelial cells, with an incidence of approximately 1 to 2 per

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100,000 population.<sup>[1]</sup> Surgical resection and liver transplantation remain the only radical therapies for hilar cholangiocarcinoma (HCCA, also known as Klatskin tumors). Unfortunately, up to 80% of HCCA patients present with unresectable stage at the time of diagnosis.<sup>[2]</sup> Because of the vital location of tumor, the prognosis of unresectable HCCA remains dismal, with a median survival time of less than 1 year.<sup>[2]</sup>

To date, chemotherapy remains the preferred treatment for locally advanced, recurrent, or metastatic HCCA, while it has limited improvements in patients' survival.<sup>[3]</sup> Biliary drainage, especially via the percutaneous transhepatic approach, has been proposed to relieve cholestasis and improve survival in HCCA.<sup>[4]</sup> Recently, percutaneous transhepatic biliary stenting (PTBS) has also been applied to patients with HCCA due to the effective relief of biliary obstruction.<sup>[4,5]</sup> However, as the ingrowth of tumor, the biliary stent alone is associated with a high risk of biliary reobstruction and a poor survival.<sup>[6]</sup> In contrast, the PTBS combined with <sup>125</sup>I seed intracavitary irradiation shows a longer stent patency time and a better survival for patients with HCCA,<sup>[7,8]</sup> while further research is still needed to determine the efficacy of this technique and factors associated with outcome.

Malnutrition may result in wound healing delay, immune function disorder, and the dysfunction of neutrophils, macrophages, and lymphocytes.<sup>[9]</sup> It has been reported that malnutri-

tion involves in the cancer progression, and is associated with an increased risk of postoperative complications and a prolonged hospital stay in cancer patients.<sup>[10,11]</sup> In addition, preoperative poor nutritional condition leads to an adverse survival in patients with malignant tumors.<sup>[9,12]</sup> On the basis of the above findings, in recent years, several nutrition-based scores have been identified as possible prognostic markers in various cancers. Details of these scores are all easily available from peripheral blood sample, including the controlling nutritional status (CONUT), C-reactive protein (CRP)-to-albumin (ALB) ratio (CAR), and prognostic nutritional index (PNI).<sup>[12–14]</sup> To our knowledge, the values of the 3 nutrition-based prognostic scores have rarely been investigated in unresectable HCCA patients. In this study, we preliminarily explored the prognostic significance of the above 3 nutritional scores in HCCA patients treated with PTBS combined with <sup>125</sup>I seed intracavitary irradiation.

## 2. Materials and methods

### 2.1. Study population

We retrospectively reviewed the data of HCCA patients who undergone PTBS combined with <sup>125</sup>I seed implantation from November 2012 to April 2017 in our department. Eligible patients were HCCA diagnosed by pathological or clinical method; unresectability or refusal to resection; and treated with PTBS followed by <sup>125</sup>I seed implantation. Exclusion criteria were benign bile duct stricture; with a history of surgery, endoscopic biliary stenting, or chemotherapy for HCCA; intrahepatic or distal cholangiocarcinoma; and incomplete data or follow-up information. In total, 73 patients met the selection standard and were included. We reported the current study according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD).<sup>[15]</sup> Our study was in compliance with the Declaration of Helsinki<sup>[16]</sup> and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. In addition, written informed consent was given by all patients.

### 2.2. Instruments

The Innova 3100 digital subtraction angiography (DSA) device (General Electric, Fairfield, Connecticut) was used during the operation. Percutaneous transhepatic cholangial drainage (PTCD) was performed by using pigtail catheters (Guangzhou Leadgem Medical Devices Co., Ltd., China). The self-expandable metal stent was purchased from Micro-Tech Co., Ltd (Nanjing, China) and the catheter with various sizes (8 × 40 mm, 8 × 60 mm, 8 × 80 mm, 8 × 100 mm, 10 × 40 mm, 10 × 60 mm, 10 × 80 mm, and 10 × 100 mm, as appropriate) was applied. The <sup>125</sup>I brachytherapy particles (Beijing Atomic Hi-Tech Co., Ltd., China) were cylindrical, with the length of 4.5 mm, the diameter of 0.8 mm, the radioactivity of 33.3 MBq, and the half-life of 59.43 days.

### 2.3. Surgical procedures

About a week after PTCD, the PTBS and <sup>125</sup>I seed implantation were performed under DSA. The process of PTBS has been described previously.<sup>[17]</sup> Briefly, cholangiography through the PTCD tube was first performed to observe the situation of biliary stricture and expansion. The guidewire was then inserted through PTCD tube, which was then replaced by catheter sheath. The cholangiographic catheter was further inserted pass through the guidewire and the direction was repeatedly adjusted so that the catheter can completely reach the duodenum. Subsequently, we measured the length and the diameter of the obstructed bile duct

to select suitable stent. Under DSA guidance, the cholangiographic catheter was withdrawn and the biliary stent was slowly inserted through the guidewire.

The number of <sup>125</sup>I particles was calculated according to the following formula: (length + width + height of tumor) (cm)/3 × 5 ÷ activity per particle (mCi). The “P” type tube was used as the particles source applicator. The distribution of <sup>125</sup>I particles in the “P” type tube was determined by the situation of biliary obstruction. The <sup>125</sup>I particles were separated with the average particle space 0.6 to 1.0 cm. Under the guidance of the guidewire, the “P” type tube that contains <sup>125</sup>I particles was inserted into the stent cavity of the obstructive location.

### 2.4. Data collection and follow-up

We reviewed the electronic medical records to collect the following clinical data: age, gender, and preoperative laboratory tests. Preoperative measurements included serum total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ALB, total cholesterol, neutrophil count, lymphocyte count, CRP, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA). The scores of CONUT, CAR, and PNI were calculated according to the following formulas:

- CONUT: ALB (g/L):  $\geq 35$  g/L = 0; 30–34.9 = 2; 25–29.9 = 4;  $< 25$  = 6. Lymphocyte count ( $10^9$ /L):  $> 1.6$  = 0; 1.2–1.6 = 1; 0.8–1.2 = 2;  $< 0.8$  = 3. Total cholesterol (mg/dL):  $> 180$  = 0; 140–179 = 1; 100–139 = 2;  $< 100$  = 3. The CONUT score is the sum of the above 3 variables and therefore is varied from 0 to 12.
- CAR: CRP (mg/L)/ALB (g/L).
- PNI: ALB (g/L) + 5 × lymphocyte count ( $10^9$ /L).

Patients were followed up until September 2017 or until death. The follow-up contents included routine biochemical measurements and imaging examinations. The levels of TBIL, DBIL, ALT, AST, ALP, and ALB at 1 month and 3 months postoperatively were compared with the preoperative levels.

### 2.5. Statistical analysis

SPSS version 21.0 (IBM Corp., Armonk, New York) was used to collect and analyze the data. Continuous variables were described as median (range) for these with non-normal distribution and mean ± standard deviation for the normally distributed variables. Different subgroups were compared by using the *t* test, Wilcoxon test, or  $\chi^2$  test, as appropriate. Paired-sample *t* test was used to evaluate the postoperative changes of liver function and bilirubin. We used the receiver operating characteristic (ROC) curve to determine the optimal cut-off point (the maximum of specificity and sensitivity) of nutrition-based scores for discriminating between deceased and living patients.

The primary outcome we observed was overall survival (OS), which was estimated by the Kaplan–Meier curve. Factors possibly affecting OS were assessed by COX regression. It was considered statistically significant provided  $P < .05$ .

## 3. Results

### 3.1. Characteristics of patients and the assessment of efficacy

Demographic data, laboratory tests, and evaluation of nutrition-based scores of the 73 patients are presented in Table 1. There

**Table 1**  
**Basic characteristics of the 73 HCCA patients.**

Variables	Overall
Gender (male/female)	44/29
Age (≥70/<70 y)	27/46
CA19-9, ng/mL	624.3 (0.6–2068)
CEA, ng/mL	4.13 (0.92–294.8)
ALT, U/L	169 (24–513)
AST, U/L	182 (35–373)
ALP, U/L	697 (152–2556)
Total cholesterol, mg/L	206 (56–809)
PT-INR	1.01 (0.65–1.50)
TBIL, μmol/L	242.3 (47.3–706.2)
DBIL, μmol/L	185.7 (23.0–649.0)
ALB, g/L	34.2 (23.6–45.3)
CRP, mg/L	16.80 (0.69–197.4)
PLT, 10 <sup>9</sup> /L	247 (93–489)
Neutrophil count, 10 <sup>9</sup> /L	4.71 (1.59–35.55)
Lymphocyte count, 10 <sup>9</sup> /L	1.49 (0.40–4.16)
CONUT (0–1/2–3/4–5/≥6)	21/21/18/13
CAR	0.52 (0.02–6.19)
PNI	43.5 (28.0–61.0)
Outcome (death/no)	62/11
Survival time, mo	12 (1–30)

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CA19-9 = carbohydrate antigen 19-9, CAR = C-reactive protein/albumin ratio, CEA = carcino-embryonic antigen, CONUT = controlling nutritional status, CRP = C-reactive protein, DBIL = direct bilirubin, PLT = platelet count, PNI = prognostic nutritional index, PT-INR = prothrombin time-international normalized ratio, TBIL = total bilirubin.

were 44 men and 29 women, with the mean age of 64.7 ± 10.6 years. All patients successfully received the implantations of biliary stent and <sup>125</sup>I seed.

After the operation, the clinical symptoms such as jaundice and fever were significantly improved in all patients. The levels of TBIL, DBIL, ALT, AST, and ALP significantly reduced, and ALB

significantly increased at 1 month and 3 months postoperatively, compared with the preoperative levels (Fig. 1, all *P* < .05).

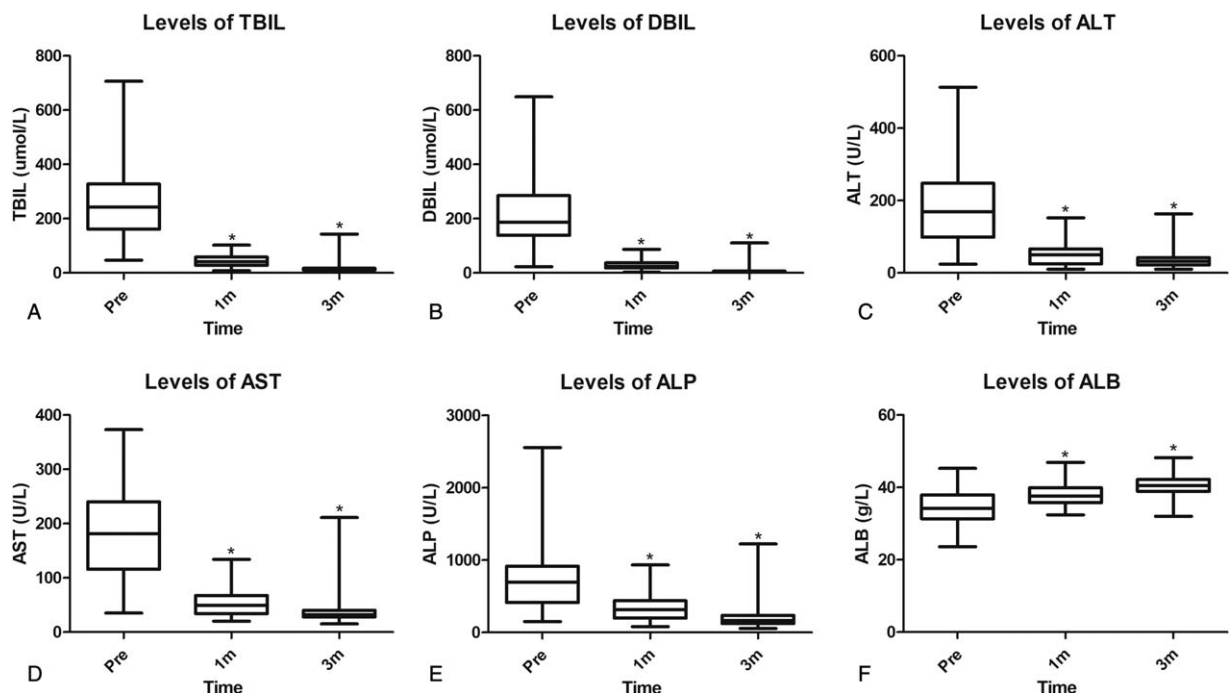
**3.2. Determination of the cut-off values for the CONUT, CAR, and PNI**

The ROC curves of CONUT, CAR, and PNI revealed that 2, 0.31, and 47.4 were the optimal cut-off values, with 77.4% sensitivity and 63.6% specificity, 72.6% sensitivity and 54.5% specificity, and 54.5% sensitivity and 85.5% specificity, respectively. In particular, CONUT and PNI were significant models for determining dead from living cases, with the area under the curve (AUC) values 0.710 [95% confidence interval (95% CI): 0.526–0.893, *P* = .022] and 0.693 (95% CI: 0.521–0.864, *P* = .036), respectively.

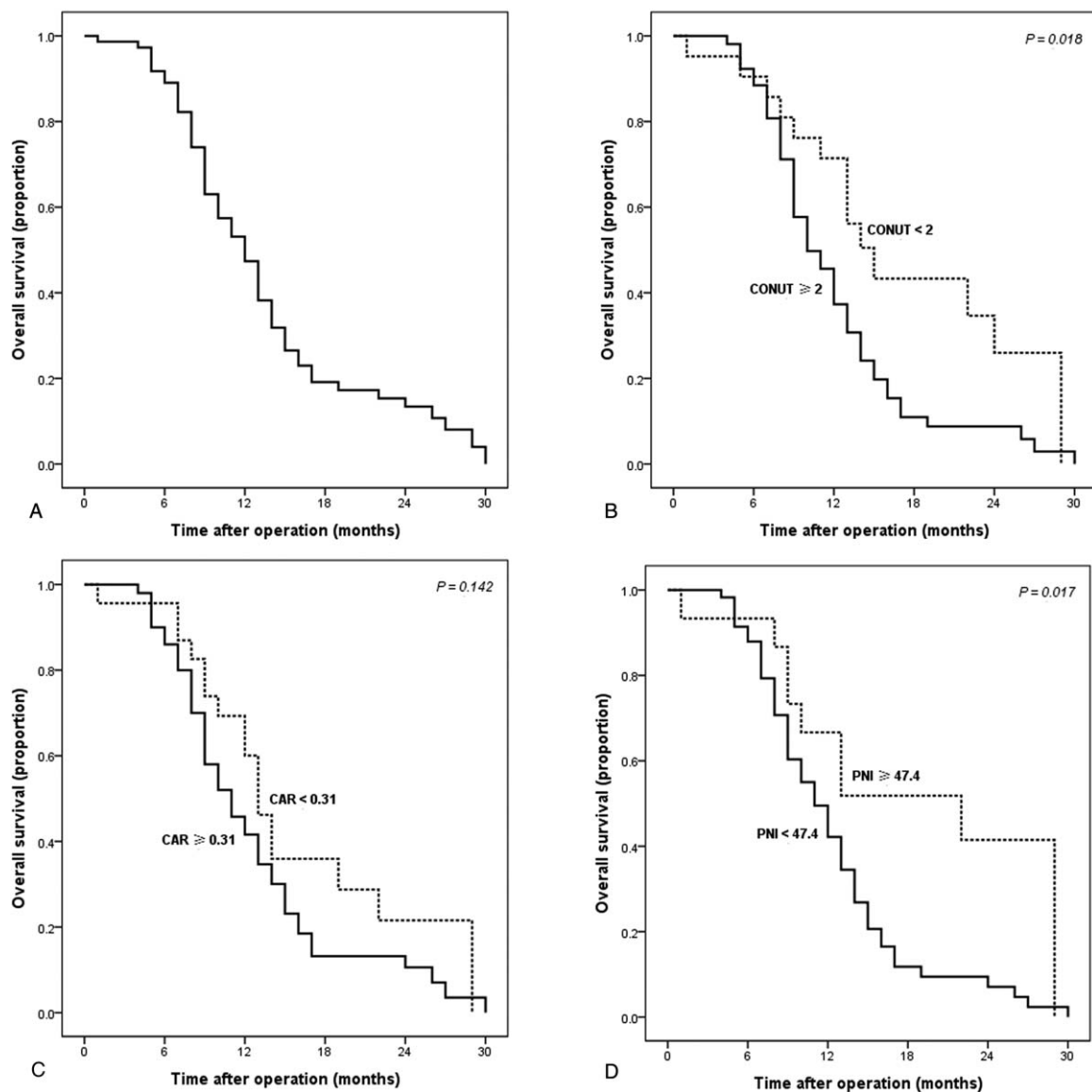
**3.3. Predictors of the OS**

During the follow-up period, there were 62 deaths (84.9%). Figure 2A showed the Kaplan–Meier cumulative OS curve of the whole cohort. The median survival time was 12 months and the 1-year OS rate was 53.1%. Figure 2B to D further revealed the Kaplan–Meier OS curves of patients stratified according to nutrition-based prognostic scores. More specifically, patients with a higher level of CONUT (Fig. 2B, *P* < .05) and a lower level of PNI (Fig. 2D, *P* < .05) had significantly worse OS. Accordingly, the median survival time of patients with lower versus higher CONUT scores was 15 versus 10 months, and the 1-year OS rates were 71.4% versus 45.6%. With regard to PNI, the median survival time of patients with higher versus lower levels was 22 versus 11 months, and the 1-year OS rates were 66.7% versus 49.5%. However, no statistically significant association was demonstrated between CAR and OS in HCCA (Fig. 2C, *P* > .05).

Preoperative CA19-9, TBIL, ALB, CONUT, and PNI were significant factors associated with OS in univariate analysis.



**Figure 1.** Comparison of liver function between preoperation and postoperation. Compared with the preoperative data, the levels of TBIL (A), DBIL (B), ALT (C), AST (D), ALP (E), and ALB (F) significantly improved at 1 month and 3 months postoperatively (*P* < .05).



**Figure 2.** The survival curves of HCCA patients after the implantations of biliary stent and  $^{125}\text{I}$  seed. The survival curves of the whole cohort (A), and the survival curves stratified according to the CONUT (B), CAR (C), and PNI (D).

Multivariate analysis was further performed, and CA19-9, CONUT [hazard ratio (HR)=2.02, 95% CI: 1.08–3.80], and PNI (HR=2.08, 95% CI: 1.01–4.28) were identified as independent prognostic markers of HCCA (Table 2).

### 3.4. Associations between the nutrition-based scores and CA19-9, TBIL

According to the above-mentioned results, CA19-9 and TBIL were crucial prognostic markers for HCCA, which were in accordance with previous reports.<sup>[18–20]</sup> We subsequently investigated the associations between nutrition-based scores and CA19-9, TBIL. We found that patients with abnormal CONUT and PNI scores had significantly higher levels of CA19-9 and TBIL (Fig. 3).

## 4. Discussion

HCCA is a devastating malignancy with a poor prognosis. To date, surgical resection and liver transplantation are the

radical options for HCCA. However, the majority of patients lose the opportunity of surgery at the time of diagnosis. Biliary drainage has become one of the primary treatments in unresectable HCCA due to the alleviation of jaundice and the improvement of the quality of life.<sup>[21]</sup> Biliary stenting is also an effective palliative therapy, and is associated with a decreased risk of complications and a shorter hospital stay compared with surgery.<sup>[6]</sup> However, as a result of the ingrowth or overgrowth of tumor, biliary stent implantation alone leads to a high risk of stent occlusion and repeated procedures may be needed.<sup>[6]</sup> In contrast, biliary stenting combined with radiotherapy significantly relieves stent occlusion.<sup>[22,23]</sup> Moreover, compared with biliary stent alone, the combination of biliary stenting with  $^{125}\text{I}$  seed intracavitary irradiation significantly prolongs stent patency time and improves prognosis in patients with unresectable HCCA.<sup>[7,24–26]</sup> The implanted  $^{125}\text{I}$  seed has a direct effect on the local lesion, and the radioactivity inside the tumor is much higher than the surrounding normal tissues. Therefore, radiation-induced complications, such as gastrointestinal ulcer,

**Table 2**  
**Univariate and multivariate analyses of factors associated with OS of HCCA patients.**

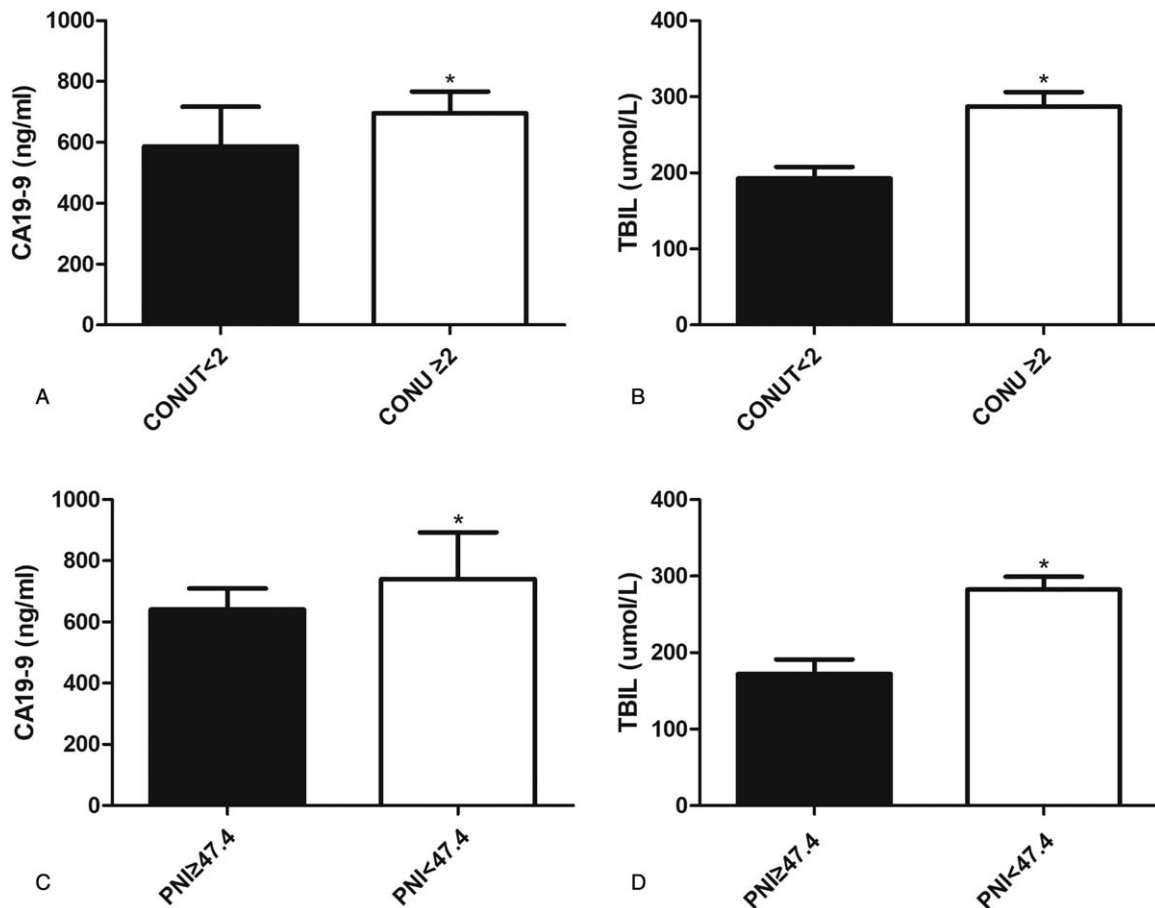
Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male vs female)	1.255 (0.745–2.113)	.394		
Age (≥70 vs <70 y)	1.410 (0.839–2.372)	.195		
CA19-9 (≥819 vs <819 ng/mL)	2.026 (1.171–3.506)	.012	2.005 (1.122–3.580)	.019
CEA (≥5 vs <5 ng/mL)	1.153 (0.670–1.987)	.607		
ALT (≥176 vs <176 U/L)	1.438 (0.867–2.383)	.159		
AST (≥173 vs <173 U/L)	1.078 (0.635–1.829)	.782		
ALP (≥489 vs <489 U/L)	1.002 (0.600–1.675)	.993		
TBIL (≥161 vs <161 μmol/L)	2.087 (1.024–4.253)	.043	1.896 (0.798–4.505)	.147
ALB (≤35 vs >35 g/L)	1.762 (1.025–3.030)	.041	1.241 (0.657–2.345)	.506
Total cholesterol (≤180 vs >180 mg/L)	1.256 (0.741–2.129)	.397		
INR (≥1.1 vs <1.1)	1.284 (0.879–3.135)	.420		
CRP (≥10 vs <10 mg/L)	1.660 (0.798–2.105)	.118		
PLT (≥173 vs <173 × 10 <sup>9</sup> /L)	0.935 (0.423–2.067)	.869		
Neutrophil count (≥4.16 vs <4.16 × 10 <sup>9</sup> /L)	1.384 (0.823–2.329)	.221		
Lymphocyte count (<1.57 vs ≥1.57 × 10 <sup>9</sup> /L)	1.283 (0.771–2.136)	.338		
CONUT (≥2 vs <2)	1.977 (1.083–3.610)	.026	2.023 (1.078–3.800)	.028
CAR (≥0.31 vs <0.31)	1.493 (0.851–2.621)	.162		
PNI (<47.4 vs ≥47.4)	2.264 (1.105–4.639)	.026	2.075 (1.006–4.280)	.048

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CA19-9 = carbohydrate antigen 19-9, CAR = C-reactive protein/albumin ratio, CEA = carcino-embryonic antigen, CONUT = controlling nutritional status, CRP = C-reactive protein, DBIL = direct bilirubin, HR = hazard ratio, PLT = platelet count, PNI = prognostic nutritional index, PT-INR = prothrombin time-international normalized ratio, TBIL = total bilirubin.

hemorrhage, and enteritis, significantly decreased compared with external irradiation. We have adopted the combination of PTBS with <sup>125</sup>I seed implantation in unresectable HCCA since 2012. In the current study, the combined therapy displayed significant

benefits in the relief of symptoms and the improvement of liver function.

Identifying the potential prognostic factors is crucial not only for improving outcomes but also for stratifying patients for



**Figure 3.** Associations between CONUT and CA19-9 (A), TBIL (B), and associations between PNI and CA19-9 (C), TBIL (D) (\**P* < .05).

treatment. Unfortunately, the majority of previous studies have assessed prognostic factors only in patients who underwent surgical resection, while relevant data remain limited in unresectable HCCA.<sup>[27]</sup>

Malnutrition is highly prevalent in inpatients, especially in cancer patients. Increasing evidence indicates that postoperative complications and long-term outcomes of cancer patients are not only affected by the malignant features of the tumor cells but also by the preoperative nutritional status.<sup>[9,14,28]</sup> In recent years, several nutrition-based scores have been identified as predictors of postoperative complications and survival in various malignancies.<sup>[12,13,29]</sup> In the current study, we summarized the clinical data of 73 HCCA patients with the combination of PTBS and <sup>125</sup>I seed implantation, and found that CONUT and PNI were independent predictors of survival. Our study further supports the view that the measurements of preoperative nutrition-based scores can predict outcomes in patients with HCCA.

The CONUT score is originally used as a tool to assess patients' nutritional status.<sup>[30]</sup> A recent meta-analysis with 4 studies showed that patients with a higher preoperative CONUT score had a worse survival in several solid tumors.<sup>[31]</sup> In the current study, we first demonstrated that CONUT was an independent prognostic model in HCCA.

PNI has been recently advocated as a significant predictive indicator of postoperative morbidity and prognosis in some kinds of tumors.<sup>[32,33]</sup> However, with regard to HCCA, there was no significant association between PNI and prognosis in patients who underwent surgical resection.<sup>[34]</sup> Interestingly, however, we found that PNI was significantly correlated with the prognosis of HCCA patients who underwent PTBS combined with <sup>125</sup>I seed implantation.

The mechanisms underlying the association between abnormal nutritional scores and poor outcomes in HCCA remain unclear, and several hypotheses have been proposed. First, poor nutritional status is associated with cancer progression, complications, infections, and thus may lead to delayed treatment.<sup>[35,36]</sup> Second, oxidative stress is involved in the development and progress of various chronic inflammations and malignancies.<sup>[11,37,38]</sup> It is reported that malnutrition can induce oxidative stress, augment a cascade of molecular reactions, and thus play a crucial role in carcinogenesis.<sup>[11]</sup> Third, the prognostic predictive value of nutrition-based scores in HCCA might be clarified by the roles of the 3 original variables, including serum ALB, total cholesterol, and lymphocyte count.

Hypoalbuminemia is one of the most commonly used methods to assess malnutrition and disease progress in cancer patients.<sup>[36]</sup> Activated pro-inflammatory cytokines, such as tumor necrosis factor and interleukin-6, can inhibit the production of ALB from hepatocytes.<sup>[39]</sup> In turn, low serum ALB is correlated with increased inflammatory response in cancer patients.<sup>[40]</sup> In addition, recent studies show that lower serum level of ALB is associated with worse survival in various malignancies.<sup>[29,41,42]</sup> Waghray et al<sup>[27]</sup> analyzed 116 cases of histologically confirmed HCCA, and demonstrated that low level of ALB implied a poor prognosis. In the current study, we also found that pretreatment level of ALB < 35 g/L was associated with worse survival in unresectable HCCA.

Total cholesterol, an essential component of the cell membrane, has also been identified as a useful biomarker of malnutrition.<sup>[36]</sup> The activity of low-density lipoprotein receptor is reported to be elevated in cholangiocarcinoma cells, indicating that hypocholesterolemia may result from excessive uptake of

cholesterol by tumor cells.<sup>[43]</sup> In addition, chronic depletion of cholesterol can induce the activation of NF- $\kappa$ B and promote the proliferation of tumor cells.<sup>[44]</sup> It is also reported that hypocholesterolemia is significantly associated with fewer circulating total T cells and CD8<sup>+</sup> T cells.<sup>[45]</sup> Therefore, low total cholesterol may not only affect intracellular signaling but also impair immune system. Recently, several epidemiological studies further demonstrated that a lower level of serum total cholesterol was associated with worse prognosis in various cancers.<sup>[28,46,47]</sup>

In contrast, as a crucial component of immune system, lymphocyte can eradicate tumor cells by regulating cytokines secretion and inducing cytotoxic cell death.<sup>[48]</sup> A low lymphocyte count contributes to a weakened defense against tumor, an advanced stage, and an unfavorable outcome in cancer patients.<sup>[49,50]</sup>

There are several limitations in the current study. First, it was designed as a single-center, relatively small sample size, and retrospective cohort study. The level of evidence of retrospective study is relatively low, and confounding bias, and missing values may be inevitable. Therefore, further multicenter, larger randomized controlled trials or prospective studies are required to validate our findings. Second, the results of the current study can be influenced by several potential factors, such as tumor stage, tumor size, performance status, postoperative adjuvant therapy, and so forth. In addition, concomitant nutritional diseases, preoperative use of anti-infective medications, blood transfusion, and ALB infusion can affect the estimation of nutrition-based scores. Third, due to the lack of the relative information, several other nutrition-based markers, such as body mass index,<sup>[36]</sup> were not assessed in our study.

In summary, the preoperative nutrition-based scores that can be obtained from routine laboratory examinations, CONUT and PNI in particular, were independent prognostic tools for patients with unresectable HCCA. These simple and inexpensive models may not only contribute to evaluate the outcomes but also help to formulate an individual treatment strategy for HCCA.

## Author contributions

**Data curation:** Yong Wang, Zhen Qian, Wei Wang, Song Yang.

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**Funding acquisition:** Hao Jin, Huichun Liu.

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**Resources:** Wei Wang, Zongkuang Li.

**Software:** Qing Pang, Zhongran Man.

**Supervision:** Lei Zhou, Hao Jin, Huichun Liu.

**Validation:** Peiyuan Cui, Lei Zhou.

**Writing – original draft:** Yong Wang.

**Writing – review & editing:** Peiyuan Cui, Qing Pang, Xiaosi Hu, Huichun Liu.

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