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Research

Preoperative total bile acid can be used as a prognostic biomarker in patients with operable biliary tract cancers

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Abstract

Background Biliary tract cancers (BTCs) are highly invasive malignancies with poor prognoses. However, reliable biomarkers for survival prediction remain lacking. Notably, abnormal lipid metabolism has elicited increasing interest in digestive tract tumors, with the liver playing an important role in lipid metabolism.

Objective To explore the relationship between hepatic lipid metabolism-related indicators, assessed through routine clinical biochemical testing and survival prognosis in patients with BTCs.

Methods Overall, 109 patients with a pathological diagnosis of BTC from 2017 to 2023 were included in this study. Univariate and multivariate Cox regression analyses were performed using R Studio software, and survival curves were plotted.

Results Univariate analysis revealed that tumor location and preoperative total bile acid (TBA), carcinoembryonic antigen, cancer antigen (CA)125, and CA19-9 levels were correlated with patient survival ($P < 0.05$). Multivariate Cox regression analysis identified increased TBA level [hazard ratio (HR) = 0.445, $P = 0.004$] as an independent prognostic factor for longer survival. Conversely, tumor location [intrahepatic cholangiocarcinoma (iCCA) and/or extrahepatic cholangiocarcinoma (eCCA)] (HR = 2.463, $P = 0.036$) and increased CA125 and CA19-9 levels (HR = 2.549, $P = 0.008$ and HR = 2.100, $P = 0.019$) were independent prognostic factors for shorter survival. Additionally, Kaplan−Meier survival curves revealed significantly longer survival in patients with increased TBA levels than those in the normal group ($P = 0.012$). Conversely, patients with iCCA and/or eCCA tumor location and increased CA125 and CA19-9 levels had significantly shorter median survival ($P = 0.044$, $P = 0.013$, and $P = 0.012$, respectively).

Conclusion TBA may be a biomarker for predicting survival in patients with operable BTC, highlighting its clinical significance and application potential.

Keywords Biliary tract cancer · Lipid metabolism · Bile acid · Prognosis · Survival

1 Introduction

Biliary tract cancers (BTCs) are highly aggressive tumors with a low incidence rate. However, their incidence has notably increased in recent years. Most patients are diagnosed at advanced stages, and the overall 5-year survival rate across all stages is < 20% [1]. BTCs are anatomically classified into intrahepatic cholangiocarcinoma (iCCA), extrahepatic

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cholangiocarcinoma (eCCA), and gallbladder cancer (GBC) [2]. Treatment methods for BTCs include surgery [3], chemotherapy [4], immunotherapy [5], targeted therapy [6], and local therapy [7].

Abnormal metabolism in tumor cells has been associated with the occurrence and development of tumors [8], and recent basic and clinical studies have focused on the correlation between abnormal lipid metabolism and tumors [9]. The liver plays a crucial role in lipid metabolism [10]. Although tumor markers such as carcinoembryonic antigen (CEA) [11] and carbohydrate antigen (CA)19-9 [12] are commonly used, reliable biomarkers for survival prediction in BTCs remain lacking. Therefore, this study aimed to explore the correlation between common liver lipid metabolism-related indicators, assessed through routine blood biochemical tests and the prognosis of patients with BTCs.

2 Methods

2.1 Study design and patients

In this retrospective study, we recruited 208 patients who were diagnosed with BTCs at Beijing Chao-yang Hospital, Capital Medical University, from 2017 to 2023. The inclusion criteria included a clear pathological diagnosis and no antitumor medical therapy prior to enrollment. The exclusion criteria included ineligibility for surgical resection, pathological types other than adenocarcinoma, and incomplete data. Ultimately, 109 patients with BTCs were included in the study (Fig. 1). Baseline clinical data and blood test results were collected 1 week before surgery. Patients were followed up for survival outcomes via telephone or outpatient visits, with the last follow-up conducted in July 2024.

2.2 Blood detection

Red-top vacuum blood collection tubes were used to collect 3 mL of fasting blood in the morning within 1 week before BTC surgery. Serum total cholesterol and triglyceride levels were measured using enzymatic methods, whereas low-density lipoprotein cholesterol levels were measured using the direct method. Total bile acid (TBA) content was measured via the enzyme cycling method. Carcinoembryonic antigen (CEA), cancer antigen (CA)125, and CA19-9 levels were determined using direct chemiluminescence (ADVIA® 2400; Siemens, Munich, Germany).

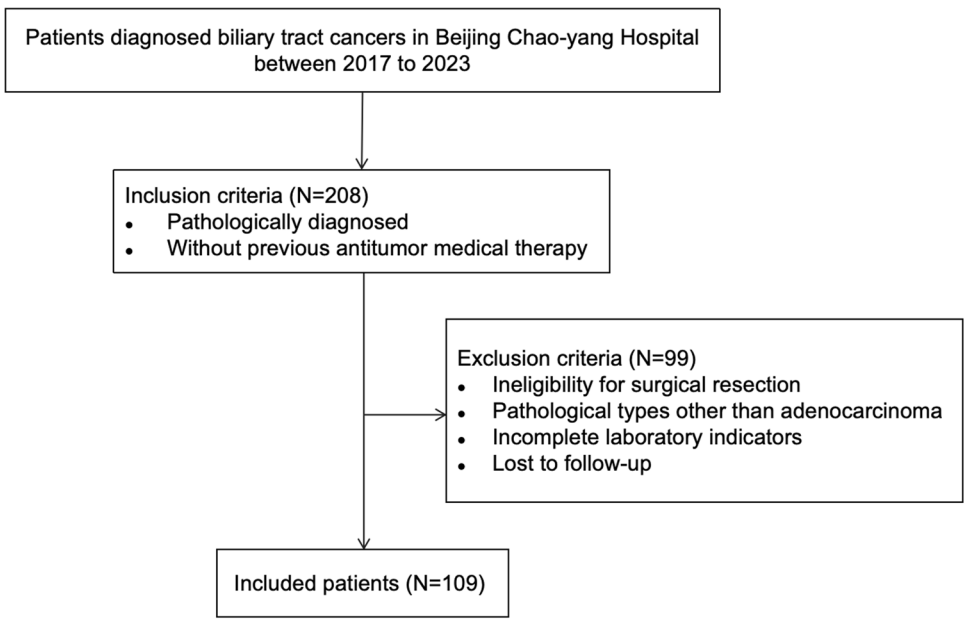

Fig. 1 Patient inclusion and exclusion process

2.3 Statistical analysis

R Studio version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for Cox univariate and multivariate regression analyses, as well as survival analyses, using the "survival," "survminer," and "rms" packages. Cox regression was performed using the "coxph" function. Survival curves were plotted using the "ggsurvplot" function. Categorical variables were presented as percentages. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

General information, personal history, pathological characteristics, and laboratory test results of 109 enrolled patients with BTC were recorded as categorical variables (percentages) (Table 1).

3.2 Univariate and multivariate Cox regression analyses

Various factors were assessed, including patients' age, sex, smoking and drinking status, tumor location, G grade, TNM stage, liver lipid metabolism-related biochemical indicators, and tumor markers. Univariate Cox regression analysis revealed that tumor location (iCCA and/or eCCA) [hazard ratio (HR) = 2.221, 95% confidence interval (CI): 1.003–4.918, $P = 0.049$], TBA (HR = 0.517, 95% CI: 0.305–0.876, $P = 0.014$), CEA (HR = 2.161, 95% CI: 1.167–4.002, $P = 0.014$), CA125 (HR = 2.075, 95% CI: 1.156–3.725, $P = 0.015$), and CA19-9 (HR = 2.088, 95% CI: 1.162–3.751, $P = 0.014$) were significantly correlated with patient overall survival and prognosis ($P < 0.05$).

All variables with $P < 0.05$ were included in the multivariate Cox regression model. The results revealed increased TBA level (HR = 0.445, 95% CI: 0.255–0.775, $P = 0.004$) as an independent protective factor. However, tumor location (iCCA and/or eCCA) (HR = 2.463, 95% CI: 1.063–5.708, $P = 0.036$), as well as increased CA125 (HR = 2.549, 95% CI: 1.282–5.067, $P = 0.008$) and CA19-9 levels (HR = 2.100, 95% CI: 1.133–3.895, $P = 0.019$), were identified as independent risk factors for poorer survival in patients with BTC (Table 2).

3.3 Kaplan–Meier survival curves

R studio software was used to analyze and plot survival curves for independent prognosis factors, including tumor location ($P = 0.044$) and TBA ($P = 0.012$), CA125 ($P = 0.013$), and CA19-9 levels ($P = 0.012$). (Fig. 2a–d).

4 Discussion

Bile acids are synthesized from cholesterol in the liver, stored in the gallbladder, and secreted into the duodenum after ingestion to promote fat digestion and the absorption of fat-soluble vitamins. Subsequently, most bile acids are reabsorbed by intestinal cells. This cycle plays a crucial role in lipid digestion, absorption, and metabolism [13].

This study included 109 patients with operable BTC. Notably, increased serum TBA levels were significantly associated with longer survival. Previous studies have linked abnormally high TBA levels to poor prognosis in hepatocellular carcinoma (HCC) [14, 15] and colorectal cancer [16]. Conversely, other studies have associated increased TBA levels with improved prognosis in breast cancer [17]. TBA serves as a sensitive indicator of liver function [18, 19], as even slight damage to liver cells can elevate TBA levels [20]. Increased TBA levels in patients with BTC may facilitate timely intervention, promoting early diagnosis and appropriate treatment to improve prognosis. Additionally, all patients in this study underwent surgery, which often leads to abnormal digestive function and frequent diarrhea owing to partial surgical resection of the pancreas [21]. Consequently, doctors routinely administer intestinal probiotics to alleviate diarrhea symptoms. Alterations in the intestinal flora may lead to changes in bile acid metabolism and composition. Furthermore, the surgical approaches for HCC and BTC differ. HCC surgery involves fewer digestive organs and gastrointestinal symptoms such as diarrhea, potentially leading to differences in intestinal flora alterations compared to those following BTC surgery. Consequently, HCC and BTC surgeries may result in different degrees of bile acid metabolism variations.

Table 1 Patient demographic and disease characteristics

Characteristics	Patients (N = 109) No. (%)
Age (year)	
≤ 65	41 (37.6)
> 65	68 (62.4)
Sex	
Male	61 (56.0)
Female	48 (44.0)
Smoking status	
No	82 (75.2)
Yes	27 (24.8)
Drinking status	
No	93 (85.3)
Yes	16 (14.7)
Tumor location	
GBC	16 (14.7)
iCCA and/or eCCA	93 (85.3)
G grade	
G1 + G2	68 (62.4)
G3	41 (37.6)
TNM stage	
I + II	59 (54.1)
III	50 (45.9)
TC	
< 5.18 mmol/L	74 (67.9)
≥ 5.18 mmol/L	35 (32.1)
LDL-C	
< 3.30 mmol/L	68 (62.4)
≥ 3.30 mmol/L	41 (37.6)
TG	
< 1.70 mmol/L	54 (49.5)
≥ 1.70 mmol/L	55 (50.5)
TBA	
0.0–10.0 μmol/L	59 (54.1)
> 10.0 μmol/L	50 (45.9)
CEA	
< 5.0 ng/mL	93 (85.3)
≥ 5.0 ng/mL	16 (14.7)
CA 19-9	
< 37 U/mL	36 (33.0)
≥ 37 U/mL	73 (67.0)
CA125	
< 30.2 U/mL	91 (83.5)
≥ 30.2 U/mL	18 (16.5)

GBC gallbladder cancer, *iCCA* intrahepatic cholangiocarcinoma, *eCCA* extrahepatic cholangiocarcinoma, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *TBA* total bile acid, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CA125* carbohydrate antigen 125

TBA composition is complex, involving intestinal microorganisms that convert primary bile acids into several secondary bile acids. However, the full diversity of secondary bile acids remains poorly understood [22]. Režen et al. found that different bile acids exert opposite effects in the carcinogenic process [23]. Several studies have reported highly hydrophobic BAs, such as lithocholic acid, deoxycholic acid, and chenodeoxycholic acid (CDCA), as major liver cancer promoters that may contribute to HCC development [24]. However, high concentrations of CDCA, ursodeoxycholic acid and taurursodeoxycholic acid can inhibit HCC cell growth and induce apoptosis [25]. Additionally, farnesoid X receptor

Table 2 Cox regression analysis of independent predictive factors for overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (> 65 year)	0.988	0.585–1.669	0.965			
Sex (Female)	0.931	0.563–1.537	0.779			
Smoking (Yes)	0.765	0.407–1.438	0.405			
Drinking (Yes)	0.895	0.441–1.815	0.758			
Tumor location (iCCA and/or eCCA)	2.221	1.003–4.918	**0.049***	2.463	1.063–5.708	**0.036***
G grade (G3)	1.553	0.934–2.583	0.090			
TNM stage (III)	1.577	0.958–2.596	0.073			
TC (≥ 5.18 mmol/L)	0.823	0.476–1.423	0.485			
LDL-C (≥ 3.30 mmol/L)	0.994	0.587–1.681	0.980			
TG (≥ 1.70 mmol/L)	1.190	0.724–1.956	0.492			
TBA (>10.0 μmol/L)	0.517	0.305–0.876	**0.014***	0.445	0.255–0.775	**0.004***
CEA (≥ 5.0 ng/mL)	2.161	1.167–4.002	**0.014***	0.895	0.416–1.923	0.775
CA19-9 (≥ 37 U/mL)	2.088	1.162–3.751	**0.014***	2.100	1.133–3.895	**0.019***
CA125 (≥ 30.2 U/mL)	2.075	1.156–3.725	**0.015***	2.549	1.282–5.067	**0.008***

HR hazard ratio, *CI* confidence interval, *iCCA* intrahepatic cholangiocarcinoma, *eCCA* extrahepatic cholangiocarcinoma, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *TBA* total bile acid, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CA125* carbohydrate antigen 125

*Significant difference ($P < 0.05$)

Bold font indicates statistical significance

activity is a major inhibitor of HCC carcinogenesis [26]. Furthermore, the cancer-promoting or -inhibiting activity of BAs varies in different tumors [27], most likely because of differences in the expression of BA receptors and transporters and cell-specific differences in receptor activation outcomes. The mechanism of the occurrence and development of BA and BTC currently remains unclear.

Our findings also indicated poorer prognosis of patients with iCCA and/or eCCA than those with GBC. This finding is consistent with the results of previous clinical research [28, 29]. A possible explanation is that gallbladder inflammation is a known risk factor for GBC [30], and its early inflammatory symptoms can facilitate the early diagnosis of the disease. However, the early symptoms of iCCA and/or eCCA are often atypical, with most patients being diagnosed at an advanced stage—typically after the onset of jaundice [31].

Serum CA125, a transmembrane mucin encoded by the mucin 16 (*MUC16*) gene [32], is associated with the prognosis of multiple malignancies, including ovarian [33] and pancreatic cancers [34]. Furthermore, CA125 is typically associated with adenocarcinoma [35], which is the predominant pathological type of BTC. Our findings suggest that CA125 serves as an independent predictive biomarker for poor prognosis in patients with BTC, corroborating previous findings [36–38]. Serum CA19-9 is a recognized tumor marker for monitoring therapeutic efficacy and predicting prognosis in patients with BTC [39, 40]. The results of the present study are also consistent with these previous findings.

Considering that this was a retrospective study with a small sample size, our future research will focus on increasing the sample size for a multicenter prospective study to validate these findings. Additionally, we will further explore the effects of intestinal microorganisms on bile acid metabolism and the related mechanisms.

5 Conclusions

Elevated preoperative TBA level is an independent predictive biomarker for longer survival in patients with operable BTC, exhibiting a potential clinical value, which may help guide patients with a poor prognosis toward stronger treatment strategies and more intensive follow-up monitoring.

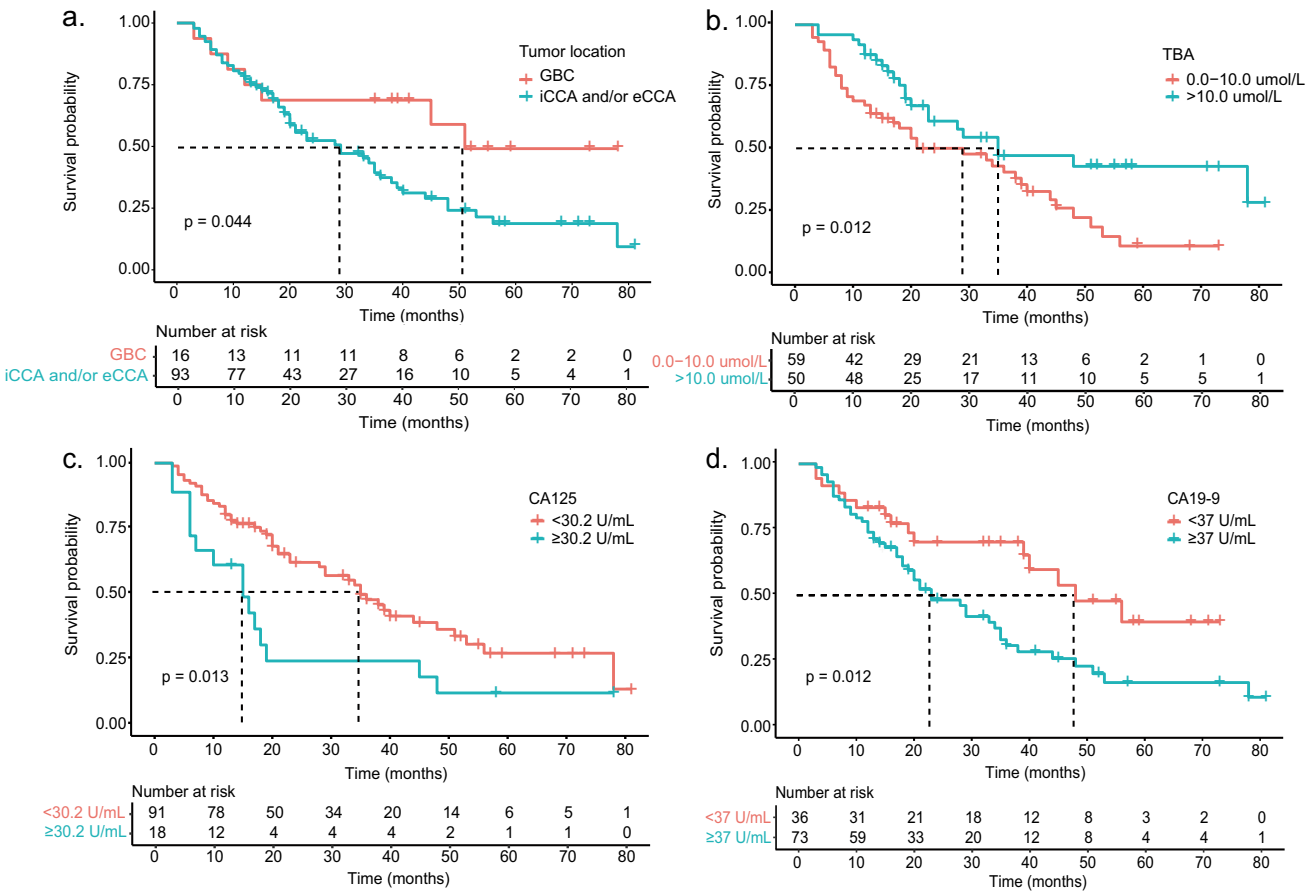

Fig. 2 Kaplan–Meier survival curves. **a** Tumor location, **b** TBA, **c** CA125, and **d** CA19-9 concentration as independent predictive biomarkers. *CA125* carbohydrate antigen 125, *CA19-9* carbohydrate antigen 19-9; *TBA* total bile acid

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Author contributions Conceptualization and project administration: Shanshan Fan, Yang Ge; Data curation: Shanshan Fan, Kexin Zhao, Jiabao Lei; Formal analysis: Shanshan Fan; Writing – original draft: Shanshan Fan, Kexin Zhao; Writing – review & editing: Shanshan Fan. All authors have reviewed the manuscript.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The participants provided informed consent prior to their inclusion in the study. This study was approved by the Ethics Committee of Beijing Chao-yang Hospital and was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments.

Competing interests The authors declare no competing interests.

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