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Retrospective Study

# Correlation between pre-treatment serum total blood bilirubin and unconjugated bilirubin and prognosis in patients with colorectal cancer

Hui Tong, Peng Xing, Zhao-Ning Ji

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## Abstract

### BACKGROUND

Epidemiological studies have found that unconjugated bilirubin (UCB) levels are positively correlated with the incidence of colorectal cancer (CRC). Therefore, bilirubin may also play an important role in the prognosis of CRC.

### AIM

To investigate the predictive value of total bilirubin (TBIL) and UCB in the prognosis of patients with CRC.

### METHODS

A total of 142 CRC patients were selected as the research subjects in Jingxian Hospital, from October 2014 to May 2021. General and tumour-related clinical data at admission and the overall survival at 3 years after surgery were collected. The optimal cut-off values of TBIL and UCB were determined by receiver operating characteristic curve analysis. Univariate and multivariate Cox regression were used to analyse the effect of bilirubin level on the survival of CRC patients. The Kaplan-Meier method was used to assess the survival time.

### RESULTS

The 3-year overall survival rate of CRC patients was significantly higher in the high TBIL ( $> 13.45 \mu\text{mol/L}$ ) group than in the low TBIL ( $\leq 13.45 \mu\text{mol/L}$ ) group (76.4% vs 37.1%;  $P < 0.05$ ). The 3-year overall survival rate of CRC patients in the high UCB ( $> 10.75 \mu\text{mol/L}$ ) group was significantly higher than that in the low UCB ( $\leq 10.75 \mu\text{mol/L}$ ) group (83.3% vs 34.2%;  $P < 0.05$ ). Multivariate Cox regression analysis showed that higher TBIL levels were an independent predictor

of better prognosis in CRC patients (hazard ratio = 0.360, 95% confidence interval: 0.159-0.812,  $P = 0.014$ ).

## CONCLUSION

TBIL levels can be used as a prognostic indicator for CRC patients.

**Key Words:** Bilirubin; Colorectal neoplasms; Prognosis

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**Core Tip:** In this study, we demonstrated that bilirubin levels may be used as a prognostic indicator in colorectal cancer (CRC) patients. Higher total bilirubin (TBIL) and unconjugated bilirubin levels were negatively correlated with 3-year survival in CRC patients. TBIL may be used as a protective prognostic indicator in patients with CRC.

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death[1]. The incidence of CRC is higher in men than in women. The CRC burden is expected to increase by 60%, with more than 2.2 million new cancer cases and more than 1.1 million cancer deaths, by 2030[2].

Some studies have reported that bilirubin, a product of haemoglobin catabolism, and particularly unconjugated bilirubin (UCB), has significant anti-inflammatory and anti-oxidant effects and that it plays a role in several oxidative stress-related diseases, including CRC[3]. Epidemiological studies have found that, in men, UCB levels are positively correlated with the incidence of CRC, while they are negatively correlated with the incidence of CRC in women[4,5].

However, clinical data on the relationship between UCB levels and CRC prognosis are lacking. Therefore, this study aimed to investigate the effect of serum total bilirubin (TBIL) and UCB levels on the prognosis of patients with CRC.

## MATERIALS AND METHODS

### General information

Patients with CRC who attended Jingxian Hospital between October 2014 and May 2021 were selected. The clinical data of 142 study subjects who met the inclusion criteria were retrospectively analysed. Patient inclusion criteria were as follows: (1) Age > 18 years without preoperative antitumor treatment; (2) radical resection of primary CRC; (3) histopathology-confirmed diagnosis of all patients with stage I-III CRC; and (4) complete clinical and pathological data. Patient exclusion criteria were as follows: (1) Colon perforation and peritonitis; (2) history of oncological disease and death from other causes during follow-up; (3) severe cardiovascular disease; (4) primary hepatobiliary diseases that may affect serum bilirubin levels; and (5) incomplete data.

Among the 142 patients finally included, 91 were male and 51 were female, with an average age of ( $64.11 \pm 9.10$ ) years and a follow-up period of (5 to 49 mo). Clinical data of the study subjects at the time of admission were collected by reviewing electronic records. These data included age, sex, smoking status, tumour differentiation, tumour size, tumour location, tumour, node, and metastasis (TNM) staging, and laboratory test data (imaging examination, *etc*). Fasting peripheral blood samples were obtained from patients before surgery to determine TBIL and UCB levels.

### Follow-up methods

Patients included in the study were followed up by telephone, or at inpatient or outpatient visits, starting from the time of patient discharge, with a follow-up interval of once every 2 mo. Patient survival and other conditions were followed up until the patient's death or the study endpoint (October 31, 2022).

### Statistical analysis

SPSS v22.0 (IBM SPSS Inc., Armonk, NY, United States) was used for statistical analysis of the data. Normally distributed quantitative data are expressed as mean  $\pm$  SD and were compared between the two groups using *t*-tests. Quantitative data with a skewed distribution are expressed as median (interquartile interval) and were compared between the two groups using the non-parametric Mann-Whitney U test. Count data were expressed as composition ratios and were compared using the Chi-Square test. Survival curves were plotted using the Kaplan-Meier method and differences in survival between groups were analysed using the log-rank test. A Cox regression model was used to analyse the risk

factors affecting disease prognosis. A *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Determination of optimal cut-off values for TBIL and UCB

To determine the optimal cut-off values for TBIL and UCB, the area under the receiver operating characteristic (ROC) curve for prediction of survival in CRC patients was fitted. The area under the ROC curve predicted by TBIL was 0.660 [95% confidence interval (CI): 0.565-0.755; *P* = 0.001], with a sensitivity of 67.9% and specificity of 72.1%. The maximum Youden index value was 0.400 at a cut-off value of 13.45  $\mu\text{mol/L}$  for TBIL for dividing CRC patients into high TBIL (> 13.45  $\mu\text{mol/L}$ ) and low TBIL ( $\leq$  13.45  $\mu\text{mol/L}$ ) groups. The area under the ROC curve predicted by UCB was 0.735 (95%CI: 0.646-0.82; *P* < 0.001), with a sensitivity of 67.9% and a specificity of 82.0%. The maximum Youden index value was 0.499 at a cut-off value of 10.75  $\mu\text{mol/L}$  for UCB for dividing CRC patients into high UCB (> 10.75  $\mu\text{mol/L}$ ) and low UCB ( $\leq$  10.75  $\mu\text{mol/L}$ ) groups (Table 1).

### Relationship between TBIL level grouping and basic clinical characteristics

The differences between the two groups in the degree of tumour differentiation, presence of lymph node metastasis and pathological TNM stage were statistically significant (*P* < 0.05). However, there were no statistically significant differences (*P* > 0.05) in age, sex, tumour diameter, tumour location, chemotherapy, and smoking ratio (Table 2).

### Survival curve analysis of the TBIL and UCB groups

The 3-year overall survival rate was 37.1% (26/70) in the low TBIL group and 76.4% (55/72) in the high TBIL group, which was statistically significantly different (*P* < 0.001). The 3-year overall survival rate was 34.2% (26/76) in the low UCB group and 83.3% (55/66) in the high UCB group, with a statistically significant difference between the two groups (*P* < 0.001), as shown in Figure 1.

### Cox regression analysis of factors affecting the prognosis of CRC patients

Cox univariate regression analysis was performed on variables collected in this study that had the potential to affect the prognosis of patients, including age and sex. The analysis showed that the degree of tumour differentiation, tumour diameter, lymph node metastasis, pathological stage, smoking, TBIL, and UCB were associated with prognosis (*P* < 0.05). Variables with statistically significant differences were further included in the multivariate regression analysis. The results showed that the degree of tumour differentiation, lymph node metastasis, and TBIL were risk factors affecting the prognosis of patients (*P* < 0.05), as shown in Table 3.

## DISCUSSION

In this study, we demonstrated that bilirubin levels may be used as a prognostic indicator in CRC patients. Higher TBIL and UCB levels were negatively correlated with 3-year survival in CRC. TBIL may be used as a protective prognostic indicator in patients with CRC.

Bilirubin is a product of secondary catabolism of haemoglobin, which is released during the breakdown of aging red blood cells. Bilirubin is present in the circulation mainly in the form of TBIL, direct bilirubin, and UCB[6]. Although abnormally high concentrations of bilirubin are considered harmful, mildly to moderately elevated serum bilirubin concentrations can act as a potent endogenous anti-oxidant with anti-inflammatory, anti-oxidant, and anti-proliferative effects through the process of oxidation of bilirubin itself to biliverdin[7]. Recent evidence suggests that mildly elevated levels of bilirubin, a novel metabolic hormone, may have a protective role in cardiovascular disease and cancer[8]. Several studies have shown a close relationship between serum bilirubin levels and digestive system tumours. Sun *et al*[9] found that low TBIL levels were associated with poor prognosis in gastric cancer, but other studies have shown that high levels of TBIL are a risk factor for poor tumour prognosis[10].

Studies have reported inconsistent results regarding the relationship between circulating bilirubin levels and risk of CRC. In a Mendelian randomization study (67878 cases), TBIL levels were not associated with the risk of CRC[11], which was similar to the findings of a meta-analysis and a prospective survey[12,13]. In an approximately 10-year follow-up study by He *et al*[14], baseline TBIL levels were found to be negatively correlated with the risk of CRC. On the other hand, a nested case-control study by McCullough *et al*[15] found a positive correlation between TBIL levels and the risk of CRC. Although the relationship between bilirubin levels and the risk of CRC remains inconclusive, its potential predictive value for the prognosis of CRC remains a hot topic in the field.

In a prospective study, combining preoperative albumin with bilirubin could predict postoperative complications and overall survival in CRC patients, particularly in stage III patients with tumour metastasis[16]. In the present study, we found that CRC patients with lower levels of TBIL had a worse prognosis and that a lower TBIL level was an independent risk factor for poor survival outcomes in CRC patients, which was consistent with the findings of Sun *et al*[9]. On the other hand, Yang *et al*[17] found that increased TBIL was associated with decreased overall survival in CRC patients. The difference between our study findings and those of Yang *et al*[17] may be related to the inclusion of different study subjects, as their study subjects consisted of stage IV CRC patients, while our study subjects did not include stage IV patients.

**Table 1 Determination of optimal cut-off values for total bilirubin and unconjugated bilirubin (%)**

	Cut-off ( $\mu\text{mol/L}$ )	Sensitivity	Specificity	Jordan index	Area	95%CI
TBIL	13.45	67.9	72.1	0.400	0.660	0.565-0.755
UCB	10.75	67.9	82.0	0.499	0.735	0.646-0.823

TBIL: Total bilirubin; UCB: Unconjugated bilirubin; CI: Confidence interval.

**Table 2 Relationship between total bilirubin level grouping and basic clinical characteristics of patients (mean  $\pm$  SD)**

		TBIL $\leq$ 13.45 $\mu\text{mol/L}$ (n = 70)	TBIL $>$ 13.45 $\mu\text{mol/L}$ (n = 72)	t/ $\chi^2$	P value
Age (yr)		65.21 $\pm$ 8.33	63.03 $\pm$ 9.73	1.437	0.153
TBIL ( $\mu\text{mol/L}$ )		10.65 $\pm$ 2.11	17.70 $\pm$ 4.43	12.163	< 0.001
UCB ( $\mu\text{mol/L}$ )		8.81 $\pm$ 2.42	13.48 $\pm$ 4.10	8.297	< 0.001
Sex	Male	49 (70.0)	42 (58.3)	2.099	0.147
	Female	21 (30.0)	30 (41.7)		
Grade	High	20 (18.6)	26 (36.1)	16.039	< 0.001
	Middle	16 (22.9)	33 (45.8)		
	Low	34 (48.6)	13 (18.1)		
Diameter	< 5 cm	26 (37.1)	38 (52.8)	3.505	0.061
	$\geq$ 5 cm	44 (62.9)	34 (47.2)		
Site	Rectum	26 (37.1)	34 (47.2)	1.508	0.471
	Right	20 (28.6)	18 (25.0)		
	Left	24 (34.3)	20 (27.8)		
Lymph node metastasis	No	27 (38.6)	40 (55.6)	4.108	0.043
	Yes	43 (61.4)	32 (44.4)		
TNM	I	23 (32.9)	34 (47.2)	6.077	0.048
	II	22 (31.4)	25 (34.7)		
	III	25 (35.7)	13 (18.1)		
Smoking	Yes	23 (32.9)	26 (36.1)	0.166	0.683
	No	47 (67.1)	46 (63.9)		
Chemotherapy	Yes	42 (60.0)	38 (52.8)	0.753	0.386
	No	28 (40.0)	34 (47.2)		

T-test for age, total bilirubin, unconjugated bilirubin,  $\chi^2$  for gender, degree of tumour differentiation, tumour diameter, tumour location, presence of lymph node metastasis, pathological tumour, node, and metastasis stage, smoking, whether chemotherapy. TBIL: Total bilirubin; UCB: Unconjugated bilirubin; TNM: Tumor, node, and metastasis.

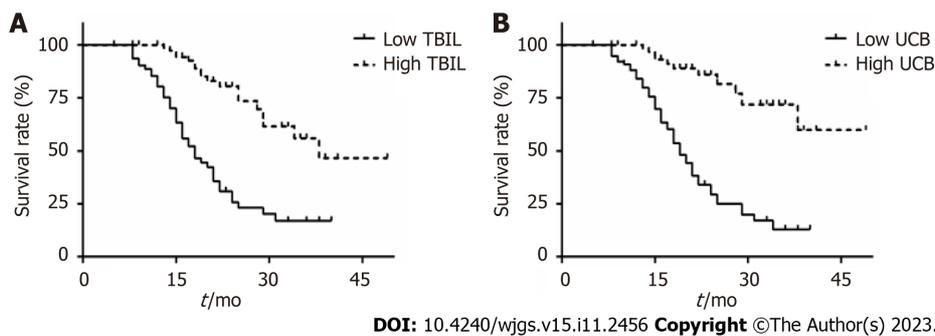
UCB, which is the most active anti-oxidant component of TBIL *in vitro*, comprises a large part of circulating bilirubin [18]. In the present study, lower UCB levels were associated with lower survival rates in CRC patients in univariate, but not in multivariate Cox regression analysis, similar to previous findings[19]. This suggests that UCB, as a prognostic factor, is influenced by other factors and is not suitable as an independent predictor in clinical practice.

In conclusion, our results indicate that circulating TBIL may be used as a prognostic indicator in CRC patients. However, due to the retrospective nature of this study and the small sample size, larger prospective studies are still needed to confirm these findings.

**Table 3** Cox regression analysis affecting the prognosis of colorectal cancer patients

Variable	Univariate analysis			Multivariate analysis			
	HR	95%CI	P value	HR	95%CI	P value	
Age (yr)	1.017	0.989-1.046	0.234	-			
Sex	Male			-			
	Female	0.805	0.468-1.384	0.433	-		
Grade	High	1		1			
	Middle	4.664	1.888-11.521	0.001	2.619	0.939-7.303	0.066
	Low	39.435	16.469-94.427	< 0.001	22.873	7.092-73.769	< 0.001
Diameter	< 5 cm						
	≥ 5 cm	2.287	1.315-3.980	0.003	0.927	0.494-1.741	0.814
Lymph node metastasis	No						
	Yes	17.672	7.815-39.963	< 0.001	9.129	1.157-73.485	0.036
TNM	I	1		1			
	II	7.235	3.023-17.315	< 0.001	0.998	0.121-8.218	0.999
	III	19.778	8.461-46.235	< 0.001	1.124	0.125-10.088	0.917
Smoking	No						
	Yes	2.357	1.424-3.093	0.001	0.800	0.444-1.442	0.458
TBIL (μmol/L)	≤ 13.45						
	> 13.45	0.282	0.160-0.495	< 0.001	0.360	0.159-0.812	0.014
UCB (μmol/L)	≤ 10.75						
	> 10.75	0.178	0.093-0.344	< 0.001	0.986	0.385-2.526	0.977

TBIL: Total bilirubin; UCB: Unconjugated bilirubin; TNM: Tumour, node, and metastasis; CI: Confidence interval; HR: Hazard Ratio.



**Figure 1** Survival curve analysis of colorectal cancer patients in the total bilirubin and unconjugated bilirubin groups. A: Colorectal cancer (CRC) patients in the total bilirubin group; B: CRC patients in the unconjugated bilirubin group. TBIL: Total bilirubin; UCB: Unconjugated bilirubin.

## CONCLUSION

TBIL levels can be used as a prognostic indicator for CRC patients.

## ARTICLE HIGHLIGHTS

### Research background

Epidemiological studies have found that unconjugated bilirubin (UCB) levels are positively correlated with the incidence of colorectal cancer (CRC).

**Research motivation**

Therefore, we speculate that bilirubin may also play an important role in the prognosis of CRC.

**Research objectives**

To investigate the predictive value of total bilirubin (TBIL) and UCB in the prognosis of patients with CRC.

**Research methods**

A total of 142 CRC patients were selected as the research subjects in Jingxian Hospital, from October 2014 to May 2021. General and tumour-related clinical data at admission and the overall survival at 3 years after surgery were collected. The optimal cut-off values of TBIL and UCB were determined by receiver operating characteristic curve analysis. Univariate and multivariate Cox regression were used to analyse the effect of bilirubin level on the survival of CRC patients. The Kaplan–Meier method was used to assess the survival time.

**Research results**

The 3-year overall survival rate of CRC patients was significantly higher in the high TBIL ( $> 13.45 \mu\text{mol/L}$ ) group than in the low TBIL ( $\leq 13.45 \mu\text{mol/L}$ ) group (76.4% *vs* 37.1%;  $P < 0.05$ ). The 3-year overall survival rate of CRC patients in the high UCB ( $> 10.75 \mu\text{mol/L}$ ) group was significantly higher than that in the low UCB ( $\leq 10.75 \mu\text{mol/L}$ ) group (83.3% *vs* 34.2%;  $P < 0.05$ ). Multivariate Cox regression analysis showed that higher TBIL levels were an independent predictor of better prognosis in CRC patients (hazard ratio = 0.360, 95% confidence interval: 0.159-0.812,  $P = 0.014$ ).

**Research conclusions**

TBIL levels can be used as a prognostic indicator for CRC patients.

**Research perspectives**

To investigate the role of TBIL and UCB in the prognosis of patients with CRC.

**FOOTNOTES**

**Author contributions:** Ji ZN designed the research; Tong H performed the research; Ji ZN and Xing P contributed new reagents or analytic tools; Tong H analyzed data and wrote the paper.

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