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Research Article

Association Between Total Bilirubin and Gender-specific Incidence of Cirrhosis with Type 2 Diabetes in Young and Middle-aged People

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Abstract

Cirrhosis is a progressive liver disease related to chronic liver injury and metabolic disorder. Due to the rising global prevalence rate and the short onset time of type 2 diabetes (T2D), it is increasingly recognized as a key problem for young and middle-aged patients with T2D. T2D aggravates liver fat deposition and inflammation, thus increasing the risk of cirrhosis. This study aimed to explore the gender-specific relationship between total bilirubin (TBIL) levels and cirrhosis in young and middle-aged individuals with T2D. With the increasing comorbidity of metabolic diseases and liver disorders, clarifying such associations is crucial for clinical practice. A total of 1064 adult patients with cirrhosis and T2D were recruited from the National Population Health Data Center. Logistic regression models were applied to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) for the association between TBIL levels and cirrhosis with T2D in males and females separately. After adjusting for potential confounding factors, a positive association between TBIL levels and cirrhosis with T2D was identified in the total population (OR=1.026, 95%CI: 1.008-1.044). A similar positive correlation was observed in males (OR=1.021, 95%CI: 1.002-1.041). However, no statistically significant association was found between TBIL levels and the incidence of cirrhosis with T2D in females. These findings indicate that the association between TBIL levels and cirrhosis in T2D patients varies by gender, highlighting the need to consider gender disparities in the management of cirrhosis among young and middle-aged T2D patients.

Keywords

Cirrhosis, Type 2 Diabetes, Young and Middle-aged People, Gender-specific

1. Introduction

As a progressive liver disease, cirrhosis is closely related to chronic liver injury and metabolic disorder [1]. Type 2 diabetes (T2D) is recognized as one of the risk factors of cirrhosis [2]. Research has shown that T2D patients with insulin

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resistance and hyperglycemia can exacerbate liver fat deposition and inflammatory reactions, significantly increasing the risk of liver cirrhosis [3-5]. With the increasing prevalence of T2D worldwide and the trend towards younger onset, the prevention and treatment of liver cirrhosis in young and middle-aged T2D populations has become an important issue in the field of public health [6, 7].

Total bilirubin (TBIL), as a key indicator reflecting liver metabolism and detoxification function, has attracted much attention for its correlation with the progression of chronic liver disease in recent years [8, 9]. Some studies suggest that TBIL may affect the progression of liver injury through mechanisms such as antioxidant and anti-inflammatory effects [10]. However, there is still controversy regarding the association between TBIL and the risk of liver cirrhosis in T2D patients [11], and the role of gender differences in this relationship is not yet clear. Gender, as a core variable in physiological regulation, exhibits significant differences in liver metabolism, hormone levels, and disease susceptibility, which may lead to a sex specific association between TBIL and cirrhosis [12, 13].

Currently, there is a lack of gender stratified research on the association between TBIL and cirrhosis in young and middle-aged T2D populations, which limits the development of individualized prevention and treatment strategies. Based on this, this study relies on large sample data from the National Population Health Data Center, focusing on young and middle-aged T2D patients, aiming to explore the gender specific association between TBIL and the risk of liver cirrhosis, provide theoretical basis for precision prevention and treatment, and reduce the burden of liver cirrhosis disease in this population.

2. Materials and Methods

2.1. Study Participants

The study subjects were selected from the National Population Health Data Center, including 1064 young and middle-aged adults with T2D. The inclusion criteria were: (1) meeting the diagnostic criteria for T2D (fasting blood glucose ≥7.0 mmol/L, or glycosylated hemoglobin ≥6.5%, or typical diabetic symptoms with random blood glucose ≥11.1 mmol/L) [14]; (2) aged 18-65 years (young and middle-aged); (3) complete clinical data including TBIL and cirrhosis diagnosis. The exclusion criteria were: (1) type 1 diabetes, gestational diabetes, or other special types of diabetes; (2) severe liver diseases caused by viruses, drugs, or autoimmune factors (e.g., viral hepatitis, drug-induced liver injury); (3) incomplete clinical indicators or missing key data.

2.2. Data Collection

Demographic data (age, gender, ethnicity, marital status) and clinical indicators were collected through the National Population Health Data Center database. Anthropometric measurements included height and weight, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Clinical indicators included blood lipids [total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL)], liver function indicators [alanine transaminase (ALT), aspartate transaminase (AST), TBIL], C-reactive protein (CRP), and comorbidities [hypertension, hyperlipidemia, fatty liver disease (FLD)]. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or a history of hypertension with current use of antihypertensive drugs [15]. Hyperlipidemia was diagnosed based on the criteria of TC ≥5.72 mmol/L or TG ≥1.7 mmol/L [16]. Cirrhosis was confirmed by imaging (ultrasound, CT, or MRI) or histopathological examination [17].

2.3. Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. Measurement data with normal distribution were expressed as mean ± standard deviation, and comparisons between groups were conducted using independent samples t-test. Count data were expressed as n (%), and comparisons were performed using the chi-square test. Logistic regression models were used to analyze the association between TBIL and the risk of cirrhosis in T2D patients, with odds ratios (OR) and 95% confidence intervals (CI) calculated. Four models were established for stepwise adjustment of confounding factors: Model 1 was crude model; Model 2 adjusted for age, gender, ethnicity, and marital status; Model 3 further adjusted for BMI, hypertension, hyperlipidemia, and FLD based on Model 2; Model 4 further adjusted for blood lipid indicators (TG, TC, HDL, LDL) and liver function indicators (ALT, AST) and CRP based on Model 3. A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics of Participants

Table 1 shows the demographic and clinical characteristics of T2D patients with and without cirrhosis. There was no significant difference in age (53.58 ± 8.09 years vs 55.05 ± 6.01 years, p=0.420), gender distribution (male: 70.2% vs 75.0%, p=0.807), ethnicity (Han: 94.3% vs 95.0%, p=1.000), marital status (married: 98.5% vs 100.0%, p=1.000), or BMI (26.53 ± 3.58 kg/m^2 vs 27.21 ± 5.85 kg/m^2, p=0.405) between the two groups.

In terms of comorbidities, the proportion of hypertension (30.0% vs 60.2%, p=0.010) and hyperlipidemia (5.0% vs 30.2%, p=0.012) in the cirrhosis group was significantly lower than that in the non-cirrhosis group, while there was no significant difference in the proportion of FLD (15.0% vs 35.8%, p=0.060).

For biochemical indicators, the cirrhosis group had significantly lower TC (3.93±1.28 mmol/L vs 4.55±1.26 mmol/L, p=0.030) and TG (1.27±0.50 mmol/L vs 2.16±1.61 mmol/L, p=0.014) than the non-cirrhosis group, but significantly higher AST (38.52±23.24 U/L vs 22.72±32.73 U/L, p=0.032). There was no significant difference in HDL, LDL, ALT, or CRP between the two groups (p>0.05).

Table 1. *Characteristics of the study individuals based on cirrhosis with T2D.*

Group	**Cirrhosis with T2DM (n=1064)**		***p*-value**
	no	**yes**	
Age (year)	53.58±8.09	55.05±6.01	0.420
Sex (n, %)			
male	733 (70.2%)	15 (75.0%)	0.807
female	311 (29.8%)	5 (25.0%)	
Ethnic (n, %)			1.000
Han	985 (94.3%)	19 (95.0%)	
minority	59 (5.7%)	1 (5.0%)	
Marital status (n, %)			1.000
married	1028 (98.5%)	20 (100.0%)	
unmarried	16 (1.5%)	0 (0.0%)	
BMI (kg/m^2)	26.53±3.58	27.21±5.85	0.405
Hypertension (n, %)			0.010
Yes	629 (60.2%)	6 (30.0%)	
No	415 (39.8%)	14 (70.0%)	
Hyperlipidemia			0.012
Yes	315 (30.2%)	1 (5.0%)	
No	729 (69.8%)	19 (95.0%)	
FLD (n, %)			0.060
Yes	374 (35.8%)	3 (15.0%)	
No	670 (64.2%)	17 (85.0%)	
TC (mmol/L)	4.55±1.26	3.93±1.28	0.030
TG (mmol/L)	2.16±1.61	1.27±0.50	0.014
HDL (mmol/L)	1.04±0.29	0.99±0.38	0.473
LDL (mmol/L)	2.78±0.97	2.48±1.00	0.171
ALT (U/L)	29.23±39.37	39.83±25.53	0.231
AST (U/L)	22.72±32.73	38.52±23.24	0.032
CRP (mg/L)	1.43±2.32	1.65±2.38	0.672

3.2. Association Between TBIL and Risk of Cirrhosis in T2D Patients

Table 2 presents the results of logistic regression analysis on the association between TBIL and the risk of cirrhosis in young and middle-aged T2D patients under different adjustment models. In the total population, after adjusting for confounding factors stepwise, TBIL was positively associated with the risk of cirrhosis. In Model 4 (fully adjusted for demographic characteristics, comorbidities, blood lipids, liver function, and inflammation indicators), the association remained significant (OR=1.026, 95%CI: 1.008-1.044, p=0.005), indicating that for each 1 μmol/L increase in TBIL, the risk of cirrhosis increased by 2.6%.

In gender-stratified analysis, the positive association between TBIL and cirrhosis was significant in males across all models. In Model 4, the OR was 1.021 (95%CI: 1.002-1.041, p=0.030), suggesting that each 1 μmol/L increase in TBIL was associated with a 2.1% increase in cirrhosis risk in males. For females, although Model 1 and Model 2 showed a potential positive association, the association became non-significant after adjusting for comorbidities and biochemical indicators. In Model 4, there was no significant association between TBIL and cirrhosis risk in females (OR=1.926, 95%CI: 0.647-5.734, p=0.239).

Table 2. *Association between TBIL and the risk of cirrhosis with T2D in young and middle-aged people.*

Variables	Model1 OR (95%CI)	Model2 OR (95%CI)	Model3 OR (95%CI)	Model4 OR (95%CI)
Overall, TBIL (μmol/L)				
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.028 (1.008~1.049)	1.029 (1.008~1.051)	1.024 (1.006~1.043)	1.026 (1.008~1.044)
P	0.006	0.006	0.008	0.005
Female, TBIL (μmol/L)				
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.127 (1.040~1.221)	1.137 (1.043~1.240)	1.291 (1.013~1.647)	1.926 (0.647~5.734)
P	0.003	0.004	0.039	0.239
Male, TBIL (μmol/L)				
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.018 (1.002~1.034)	1.016 (1.000~1.033)	1.017 (1.001~1.033)	1.021 (1.002~1.041)
P	0.026	0.044	0.038	0.030

Model1: Crude
Model2: Age, Sex, Ethnic, marital status
Model3: Age, Sex, Ethnic, marital status, BMI, hypertension, hyperlipidemia, FLD
Model4: Age, Sex, Ethnic, marital status, BMI, hypertension, hyperlipidemia, FLD, TG, TC, HDL, LDL, ALT, AST, CRP

4. Discussion

This study explored the gender specific association between TBIL and the risk of cirrhosis in young and middle-aged patients with T2D. In the general population, TBIL is positively correlated with the incidence of cirrhosis in T2D patients, and this association is still significant in males, but not statistically significant in females. This discovery provides a new perspective for understanding the gender specific mechanisms of T2D combined with cirrhosis.

From a physiological perspective, TBIL serves as a crucial marker of liver metabolic function [18]. An increase in its level usually reflects liver cell damage or bile excretion disorders [19, 20]. In male T2D patients, the positive correlation between TBIL and cirrhosis may be related to the following factors: men are more prone to liver damage factors such as excessive alcohol intake and non-alcoholic fatty liver disease [21], while insulin resistance caused by T2D can exacerbate liver fat deposition, leading to liver cell inflammation and necrosis, and thus increasing the release of TBIL into the bloodstream [22]. In addition, higher levels of androgens in males may enhance the association between TBIL and cir-

rhosis by affecting bile acid metabolism [23]. In contrast, women are protected by estrogen before menopause, and their liver metabolism is more stable [24]. The antioxidant effect of estrogen may weaken the damaging effect of TBIL elevation on liver cells [25], which may be one of the reasons why no significant association was observed in women.

There is controversy over the association between TBIL and chronic liver disease in existing research. Some studies suggest that TBIL has antioxidant properties, and low levels of TBIL may increase the risk of liver oxidative stress damage [26]. However, the results of another study showed that elevated TBIL is associated with an increased risk of cirrhosis, which may be related to the characteristics of the study population-this study focuses on T2D patients, whose long-term hyperglycemia has caused liver metabolic disorders [27]. At this time, elevated TBIL is more likely to be a result of liver cell damage rather than a protective factor [19, 20]. In addition, the results of gender stratification analysis are similar with previous studies on gender differences [28], suggesting that the role of gender as a confounding factor should be taken seriously in chronic liver disease research.

From a clinical practice perspective, the results of this study have important guiding significance. For young and middle-aged male T2D patients, monitoring TBIL levels may help identify high-risk populations for liver cirrhosis early [29], and combining blood glucose control with liver protective treatment (such as improving insulin resistance and reducing alcohol intake) can reduce the risk of onset [30]. The prevention and treatment of liver cirrhosis in female T2D patients should pay more attention to other risk factors (such as obesity and liver enzyme abnormalities), and avoid excessive reliance on TBIL indicators [31]. This discovery provides a basis for developing gender specific prevention and treatment strategies for T2D combined with cirrhosis.

The strength of our study is as follows. First, the study focuses on the young and middle-aged T2D population, filling the gap in research on the association between TBIL and cirrhosis in this age group. This population has a shorter disease course and a larger intervention window, so the research results have higher clinical value for early prevention and treatment. Second, by using gender stratification analysis, the gender differences in the association between TBIL and liver cirrhosis in T2D patients were identified for the first time, providing data support for individualized diagnosis and treatment. Third, the data is sourced from the National Population Health Data Center, with a large sample size, and potential confounding factors were adjusted for using a logistic regression model. The statistical reliability of the results is high. Fourth, the research design is tailored to clinical needs, establishing a connection between TBIL—a readily detectable indicator—and the risk of liver cirrhosis. This provides a practical reference for screening efforts in primary healthcare settings.

This study has several limitations. Firstly, the study is a cross-sectional design and cannot determine the causal relationship and temporal sequence between elevated TBIL and the onset of liver cirrhosis. Elevated TBIL may be an early manifestation of liver cirrhosis rather than a direct pathogenic factor, and further prospective cohort studies are needed to verify this. Secondly, although the term adjusting for potential confounders was mentioned, variables that were not explicitly included in the model (such as smoking, alcohol consumption, family history of liver disease, etc.) may affect the rigor of the results. Thirdly, the sample source is single and based solely on data from the National Population Health Data Center, which may have regional limitations. Therefore, caution should be exercised when extrapolating the results to other populations.

Based on the observed gender specific associations, several detailed follow-up work recommendations can be proposed. Firstly, longitudinal cohort studies with longer follow-up periods are needed to elucidate the dynamic relationship between changes in TBIL levels and the progression of liver cirrhosis in middle-aged and young T2D patients, particularly to determine the critical value of TBIL in males that may indicate an increased risk of liver cirrhosis. Secondly, mechanism research should be carried out, including basic experiments (for example, exploring gender differences in hepatic bilirubin metabolic pathway, antioxidant effect and inflammatory response) and clinical sub analysis (for example, stratified according to the duration of diabetes, insulin resistance status or fatty liver complications), to reveal the biological basis behind gender differences. Thirdly, it is necessary to conduct translational research, develop gender stratified risk assessment tools that incorporate TBIL, and design targeted interventions (such as providing antioxidant therapy for men with elevated TBIL) to validate the clinical efficacy of these findings in preventing cirrhosis in T2D populations.

5. Conclusions

There is a significant gender difference in the association between TBIL levels and the risk of liver cirrhosis in young and middle-aged T2D patients, with only a significant positive correlation observed in the male population and no significant association observed in the female population. This discovery suggests that in the prevention and treatment of liver cirrhosis in young and middle-aged T2D patients, the influence of gender factors should be fully valued. For male patients, TBIL levels can be considered as a reference indicator for liver cirrhosis risk assessment, and targeted monitoring and intervention strategies can be developed to optimize prevention and treatment effects and reduce the burden of liver cirrhosis disease in this population.

Abbreviations

T2D	Type 2 Diabetes
TBIL	Total Bilirubin

ORs	Odds Ratios
CIs	Confidence Intervals
BMI	Body Mass Index
TC	Total Cholesterol
TG	Triglycerides
HDL	High-density Lipoprotein
LDL	Low-density Lipoprotein
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CRP	C-Reactive Protein
FLD	Fatty Liver Disease

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Author Contribution

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Yafang Bai: Data curation, Software

Wei-xuan Qin: Data curation, Software

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Jing-min Cheng: Conceptualization, Supervision, Writing – review & editing

Conflicts of Interest

The authors declare that there is no conflict of interest.

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