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Relationship Between Diabetes Mellitus and Cirrhosis Risk in Chronic Hepatitis B Patients in Wuhan, China

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Background: The objective of our research was to assess the possible link between diabetes mellitus (DM) and liver cirrhosis in chronic hepatitis B (CHB) patients in Wuhan, China.

Material/Methods: Individuals with a diagnosis of both liver cirrhosis and chronic HBV infection (n=257), and CHB-only patients (n=514) were matched 1: 2 by age and sex. Demographic, lifestyle, laboratory, and clinical characteristics were reviewed. Univariate and the multiple logistic regression analysis were conducted to investigate the association between DM and HBV-related liver cirrhosis.

Results: The prevalence of DM was higher among CHB patients with liver cirrhosis than in those without liver cirrhosis (22.2% *vs.* 12.8%, P=0.001), yielding an adjusted odds ratio (AOR) of 2.317 and a 95% confidence interval (CI) of 1.528–3.513. Among them, 87.7% of liver cirrhosis patients were diagnosed with DM before liver cirrhosis diagnosis, yielding an AOR (95% CI) of 2.386 (1.533–3.714). In comparison to patients with a DM duration of 2–5 years, the AOR (95% CI) for those with a DM duration >5 years was 2.073 (0.701–6.132). In DM treatment, the AOR (95% CI) for those treated with insulin was 4.746 (1.329–16.949).

Conclusions: DM was associated with cirrhosis risk in CHB patients in Wuhan, China.

MeSH Keywords: Diabetes Mellitus • Hepatitis B, Chronic • Liver Cirrhosis • Risk Factors

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Background

Liver cirrhosis, a late stage of liver fibrosis caused by a variety of liver diseases and conditions, is recognized as being pertinent to end-stage liver disease-related mortality around the world [1]. In China, several known factors, including viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and parasitic infection, can contribute to liver cirrhosis. Among these factors, viral hepatitis-associated end-stage liver diseases, especially those caused by hepatitis B virus (HBV) infection, have increased in recent years, leading to high mortality from liver diseases in China [2]. An estimated 300 000 individuals die annually of HBV-related liver cirrhosis and hepatocellular carcinoma (HCC), and many of these infected patients do not know of their disease [3]. Considering the major impact on the global burden of liver diseases, it is crucial to recognize the associated risk factors of HBV-related liver cirrhosis to decrease its incidence.

The pathogenesis of liver cirrhosis is multifactorial and not fully understood at present. Several host or viral factors, including older age, male sex, alcohol consumption, and viral co-infections [4,5], are thought to promote the progression of liver fibrosis. Recently, the association between diabetes mellitus (DM) and end-stage liver diseases have been reported; these include liver cirrhosis and HCC [6–9]. DM is a global health problem. In 2014, the International Diabetes Federation estimated that 963 million people had diabetes in China, accounting for 25% of the estimated world population of diabetics [10]. Emerging evidence suggests that DM is a potential predictor for the progression of liver cirrhosis and HCC, both in NAFLD and in HCV infection [11–14]. However, the role of DM in end-stage liver diseases in CHB patients remains controversial. Some studies concluded DM emerged as an independent risk factor for HCC in CHB patients and increased mortality in patients with HBV cirrhosis [6,7], while no such association was demonstrated in other studies [8,9].

These published studies were carried out in different countries and failed to reach a consensus. Moreover, no information was available about the link between DM and HBV-related liver cirrhosis, particularly in mainland China, where the natural history of chronic HBV infections differs significantly from those in Taiwan and Western countries [2]. Thus, the present study assessed whether DM increases the risk of HBV-related liver cirrhosis while adjusting for other known risk factors for liver cirrhosis in mainland China.

Material and Methods

Study population

This retrospective research was carried out on patients diagnosed and hospitalized at Renmin Hospital of Wuhan University in China from January 2018 to February 2019. A total of 1536 participants, diagnosed as having CHB by the existence of HBV DNA and HBsAg in the serum for more than 6 months, were recruited in our study. After careful review and analysis of medical records, 129 patients were excluded due to incomplete clinical data. Another 469 patients were excluded according to the criteria in the next paragraphs. Of these, 257 patients who had liver cirrhosis were assigned to the case group, and 514 CHB patients without liver cirrhosis matched 2: 1 with cases for age (±3 years) and sex were assigned to the control group. To further explore the relationship between DM and HBV-related liver cirrhosis, all patients without a history or evidence of DM were withdrawn from the analysis. To ensure DM was not induced by liver cirrhosis, the study of the relationship between diabetes-related variables and the cirrhosis risk was limited to patients diagnosed with DM for more than 1 year before diagnosis of liver cirrhosis. Diabetes-related variables were considered, including age at diabetes diagnosis, duration of diabetes, complications of diabetes (e.g., retinopathy, nephropathy, and neuropathy), whether the patient was treated with exogenous insulin, and lifestyle factors.

Exclusion criteria were: (a) below 18 years of age; (b) co-infection with HCV or other types of hepatitis virus; (c) co-infection with human immunodeficiency virus; (d) history or proof of any category of malignancy; (e) history or proof of schistosomiasis infection; (f) history or evidence of drinking or alcoholic liver disease; (g) existence of other liver disease, including NAFLD, autoimmune liver disease, and primary biliary cirrhosis (PBC), and drug-induced liver injury.

The study was approved by the Renmin Hospital Ethics Committee [(2013) E-lun word (KY-035)]. All participants gave written consent and agreed to have their information stored in the hospital database for research purposes.

Evidence for liver cirrhosis diagnosis

The proof of liver cirrhosis diagnosis was based on physical examination, evidence from biochemistry or radiology, or by liver biopsy.

Diagnosis of DM

The diagnosis of DM was primarily established according to a known history of diabetes under anti-diabetic therapy or 1 or more of the following criteria: a fasting glucose level ≥7.0 mmol/L, a random glucose level ≥11.1 mmol/L, and a glucose level ≥11.1 mmol/L at 2 h in the 75-g oral glucose tolerance test [15].

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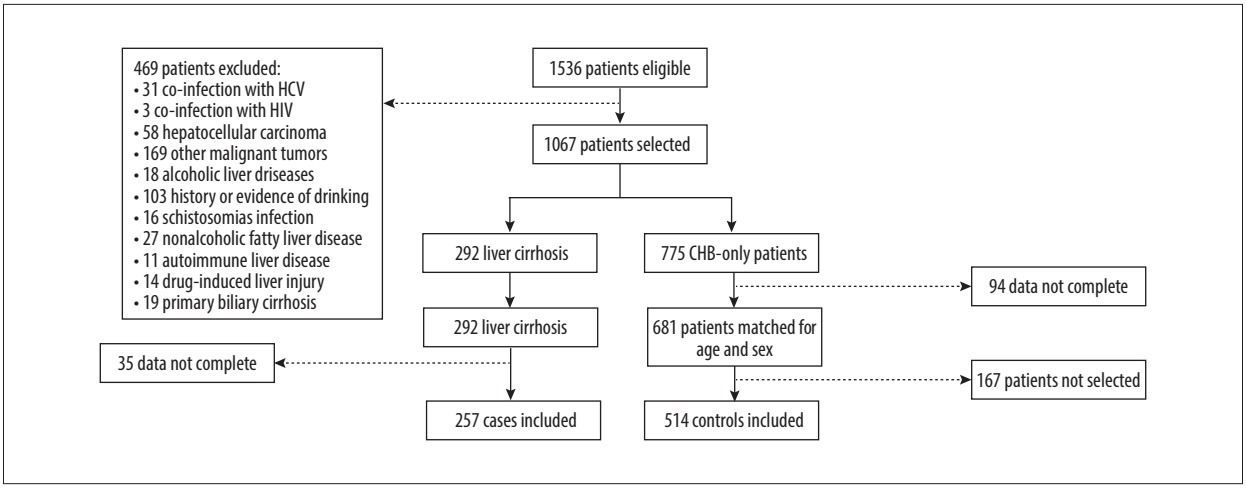

Figure 1. Flowchart of selection of study patients. CHB – chronic hepatitis B; HBV – hepatitis B virus; HIV – human immunodeficiency virus.

Demographic and clinical characteristics

After review of the medical records, the following demographic and clinical characteristics related data were obtained: sex, age, hypertension, gallstones, cigarette smoking, diagnosis of DM, treatment of DM, duration of DM, complications of DM, glucose (GLU), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), g-glutamine transferase (GGT), albumin (ALB), glycated albumin (GA), total bilirubin (TBIL), leucine aminopeptidase (LAP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), small and low-density lipoprotein (sdLDL), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and titer of HBV DNA.

Statistical analysis

Continuous variables are expressed as median and interquartile range, and categorical variables are presented as numbers and percentages. Differences were compared using the independent-samples *t* test for continuous variables and by the chi-square test for categorical variables. We considered two-tailed $P<0.05$ as statistically significant. Univariate logistic regression analysis was performed. Then, some variables were included in the multivariate logistic regression model if the P value was <0.1 according to the results of univariate analysis. Lastly, we calculated adjusted odds ratios (AORs) and 95% confidence intervals (CIs) according to the logistic regression analysis. All statistical analyses were performed in SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patients demographic and clinical characteristics

The selection process of subjects in our study is shown in Figure 1. Patient demographic and clinical characteristics are summarized in Table 1. Among CHB patients with liver cirrhosis (case group), males accounted for 66.5%, with an average age of 55.00 years. Among CHB-only patients (control group), males accounted for 65.6%, with an average age of 53.00 years. We observed significant differences in the prevalence of DM, parameters of liver function, and blood lipid level between the 2 groups. Patients in the case group were more likely to have DM (22.2% *vs.* 12.8%; P=0.001) and gallstones (25.3% *vs.* 15.2%; P=0.001); however, the prevalence of hypertension was lower (16.0% *vs.* 25.7%; P=0.002), and the percentage of smokers exhibited no significant difference between the 2 groups.

Patients in the case group had higher levels of ALP, AST, GGT, ALB, TBIL, LAP, GA, and GLU. However, they had decreased levels of blood lipid profile, including TC, TG, HDL-C, LDL-C, sdLDL, ApoA1, and ApoB. The levels of ALT and HBV DNA in the case group were similar to those in the control group.

Factors associated with development of HBV-related liver cirrhosis

Our univariate analysis suggested that smoking was not associated with HBV-related liver cirrhosis. The incidence of DM and gallstones in CHB patients with liver cirrhosis was higher than in those without liver cirrhosis (Table 2). However, CHB-only patients had a higher prevalence of hypertension, hypercholesteremia (TC >5.72 mmol/L), and hypertriglyceridemia (TG >1.7 mmol/L). Then, DM, hypertension, gallstones,

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Table 1. Demographic and clinical characteristics of study patients.

Characteristics	Liver cirrhosis (N=257)		CHB-only (N=514)		p value
Male, N (%)	171	(66.5)	337	(65.6)	0.788
Age (years)	55.00	(46.00, 63.00)	53.00	(44.00, 62.00)	0.205
Smoking, N (%)	46	(17.9)	73	(14.2)	0.181
Diabetes, N (%)	57	(22.2)	66	(12.8)	0.001
Hypertension, N (%)	41	(16.0)	132	(25.7)	0.002
Gallstones, N (%)	65	(25.3)	78	(15.2)	0.001
ALT (U/L)	23.00	(35.00, 77.00)	25.00	(16.00, 61.00)	0.468
AST (U/L)	47.00	(31.00, 88.00)	26.00	(20.00, 48.25)	0.017
ALP (U/L)	93.00	(71.50, 126.00)	72.00	(58.00, 91.00)	<0.001
GGT (U/L)	44.00	(25.00, 97.50)	23.00	(14.00, 46.00)	0.002
ALB (g/L)	33.19	(28.70, 38.34)	40.35	(36.20, 43.20)	<0.001
GA (g/L)	5.17	(4.37, 6.45)	5.03	(4.24, 5.75)	0.002
TBIL (μmol/L)	25.40	(14.85, 48.75)	13.40	(9.45, 18.49)	<0.001
LAP (U/L)	70.00	(54.95, 89.00)	55.00	(47.32, 65.42)	<0.001
TC (mmol/L)	3.39	(2.87, 3.97)	4.08	(3.44, 4.80)	<0.001
TG (mmol/L)	0.89	(0.68, 1.41)	1.19	(0.86, 1.74)	<0.001
HDL-C (mmol/L)	0.95	(0.60, 1.23)	1.03	(0.81, 1.28)	<0.001
LDL-C (mmol/L)	1.53	(1.17, 2.00)	2.29	(1.72, 2.84)	<0.001
sdLDL (mmol/L)	0.29	(0.17, 0.48)	0.60	(0.41, 0.95)	<0.001
ApoA1 (g/L)	1.10	(0.83, 1.26)	1.26	(1.10, 1.43)	<0.001
ApoB (g/L)	0.65	(0.50, 0.80)	0.80	(0.66, 0.99)	<0.001
GLU (mmol/L)	4.92	(4.25, 5.97)	4.68	(4.24, 5.26)	0.003
HBV DNA (IU/mL)	631.00	(100.00, 130500.00)	478.00	(100.00, 24700.00)	0.057

CHB – chronic hepatitis B; HBV – hepatitis B virus; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; GGT – g-glutamine transferase; ALB – albumin; GA – glycated albumin; TBIL – total bilirubin; LAP – leucine aminopeptidase; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; sdLDL – small and low-density lipoprotein; ApoA1 – apolipoprotein A1; ApoB – apolipoprotein B; GLU – glucose.
The median and interquartile range and independent-samples *t* test were used for continuous variables. The numbers (percentages) and chi-square test were used for categorical variables.

TG levels, and TC levels were incorporated into the multivariate analysis. After adjusting for possible confounding factors, we found that gallstones were related to HBV-related liver cirrhosis, yielding an AOR (95% CI) of 1.733 (1.184–2.538). Interestingly, our multivariate analysis showed a significantly different prevalence of hypertension, hypercholesteremia, and hypertriglyceridemia between the 2 groups. Among them, 87.7% of liver cirrhosis patients were diagnosed as having DM before liver cirrhosis diagnosis, yielding an AOR (95% CI) of 2.386 (1.533–3.714) (Figure 2).

Relationship between diabetes-related variables and HBV-related cirrhosis risk development in diabetes patients

Fifty liver cirrhosis patients with DM and 57 CHB-only patients with DM (controls) remained eligible for the final analysis (Table 3). Univariate analysis indicated that the duration of diabetes and the treatment of diabetes (insulin treatment and oral treatment) might be related to the development of liver cirrhosis. However, other factors, including sex, age at diabetes diagnosis, presence of diabetes complications, TC levels,

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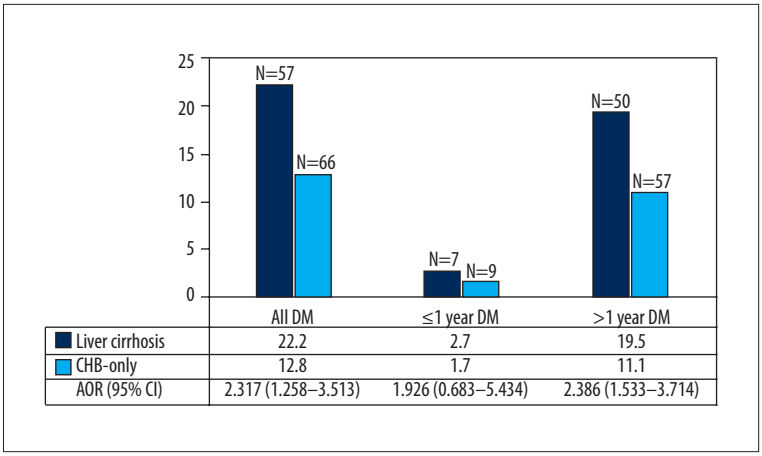

Figure 2. AOR for the relationship between DM and the cirrhosis risk. CHB – chronic hepatitis B; AOR – adjusted odds ratio; DM – diabetes mellitus. The AOR for the association between DM and the risk of liver cirrhosis according to the duration of DM. AORs were adjusted for the effect of hypertension, gallstones, TC levels, and TG levels.

Table 2. Relationship between potential factors and HBV-related liver cirrhosis.

Variable	Liver cirrhosis (N=257)	CHB-only (N=514)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p Value	AOR (95% CI)	p Value
Sex			1.044 (0.761–1.433)	0.788	–	–
Female, N (%)	86 (33.5)	177 (34.4)				
Male, N (%)	171 (66.5)	337 (65.6)				
Smoking			1.317 (0.879–1.972)	0.181	–	–
No, N (%)	211 (82.1)	444 (85.8)				
Yes, N (%)	46 (17.9)	73 (14.2)				
Hypertension			0.549 (0.373–0.810)	0.002	0.521 (0.347–0.781)	0.002
No, N (%)	216 (84.0)	382 (74.3)				
Yes, N (%)	41 (16.0)	132 (25.7)				
Gallstones			1.892 (1.307–2.741)	0.001	1.733 (1.184–2.538)	0.005
No, N (%)	192 (74.7)	436 (84.8)				
Yes, N (%)	65 (25.3)	78 (15.2)				
TC			0.285 (0.127–0.640)	0.002	0.356 (0.155–0.819)	0.015
≤5.72 mmol/L, N (%)	250 (97.3)	468 (91.1)				
>5.72 mmol/L, N (%)	7 (2.7)	46 (8.9)				
TG			0.502 (0.339–0.744)	0.001	0.553 (0.365–0.838)	0.005
≤1.7 mmol/L, N (%)	218 (84.8)	379 (73.7)				
>1.7 mmol/L, N (%)	39 (15.2)	135 (26.3)				
Diabetes			1.935 (1.308–2.862)	<0.001	2.317 (1.528–3.513)	<0.001
No, N (%)	200 (77.8)	448 (87.1)				
Yes, N (%)	57 (22.2)	66 (12.9)				

DM– diabetes mellitus; CHB – chronic hepatitis B; HBV – hepatitis B virus; TC – total cholesterol; TG – triglyceride; OR – odds ratio; 95% CI – 95% confidence interval; AOR – adjusted odds ratio.

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Table 3. Association between diabetes-related variables and liver cirrhosis risk in patients with dual diagnosis of CHB and DM.

Variable	Liver cirrhosis (N=50)	CHB-only (N=57)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p Value	AOR (95% CI)	p Value
Sex			0.816 (0.369–1.804)	0.615	–	–
Female, N (%)	19 (38.0)	19 (30.3)				
Male, N (%)	31 (62.0)	38 (69.7)				
Age at diabetes diagnosis (years)			1.304 (0.609–2.793)	0.494	–	–
≤50	23 (54.0)	30 (52.6)				
>50	27 (46.0)	27 (47.4)				
Duration of diabetes			2.474 (1.075–5.694)	0.033	2.073 (0.701–6.132)	0.187
2–5 years, N (%)	12 (24.0)	31 (54.4)				
>5 years, N (%)	38 (76.0)	26 (45.6)				
Complications of diabetes			0.895 (0.323–2.479)	0.831	–	–
No, N (%)	42 (84.2)	47 (82.5)				
Yes, N (%)	8 (15.8)	10 (17.5)				
Insulin treatment of diabetes			6.527 (2.799–15.219)	<0.001	4.746 (1.329–16.949)	0.016
No, N (%)	16 (32.0)	43 (75.4)				
Yes, N (%)	34 (68.0)	14 (24.6)				
Oral treatment of diabetes			0.205 (0.088–0.480)	<0.001	0.328 (0.094–1.150)	0.082
No, N (%)	39 (78.0)	24 (42.1)				
Yes, N (%)	11 (22.0)	33 (57.9)				
Hypertension			0.464 (0.207–1.040)	0.062	0.243 (0.085–0.691)	0.008
No, N (%)	36 (72.0)	31 (54.4)				
Yes, N (%)	14 (28.0)	26 (45.6)				
Gallstones			2.286 (0.898–5.817)	0.083	3.668 (1.157–11.625)	0.027
No, N (%)	35 (70.0)	48 (84.2)				
Yes, N (%)	15 (30.0)	9 (15.8)				
TC			0.433 (0.080–2.339)	0.331	–	–
≤5.72 mmol/L, N (%)	48 (96.0)	52 (91.2)				
>5.72 mmol/L, N (%)	2 (4.0)	5 (8.8)				
TG			0.941 (0.419–2.116)	0.883	–	–
≤1.7 mmol/L, N (%)	34 (68.0)	38 (66.7)				
>1.7 mmol/L, N (%)	16 (32.0)	19 (33.3)				

CHB – chronic hepatitis B; DM – diabetes mellitus; HBV – hepatitis B virus; TC – total cholesterol; TG – triglyceride; OR – odds ratio; 95% CI – 95% confidence interval; AOR – adjusted odds ratio.

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and TG levels, were not linked to the cirrhosis risk in our univariate analysis. Multivariate analysis was used to examine the role of duration of diabetes, exogenous insulin treatment, oral treatment, presence of gallstones, and presence of hypertension. We found that CHB patients treated with exogenous insulin had higher cirrhosis risk, yielding AORs (95% CI) of 4.746 (1.329–16.949). However, the relationship between oral treatment and risk of liver cirrhosis was not statistically significant (P=0.082), and there was no correlation between cirrhosis risk and duration of DM in our multivariate analysis (P=0.187). However, a significantly different prevalence of hypertension and gallstones was observed between the 2 groups in our multivariate analysis, but not in than univariate analysis.

Discussion

DM was related to cirrhosis risk in CHB patients, independently of other known risk factors. Our results are consistent with the findings of a study conducted in Taiwan that indicated a positive association between diabetes and liver cirrhosis in chronic HBsAg carriers [16], but that study failed to consider the impact of potential factors, including treatment of diabetes and blood lipid levels. The AOR found in our study was somewhat lower after adjustment for hypertension, gallstones, total cholesterol level, and triglyceride level. Likewise, a nationwide cohort study indicated that DM was an independent predictor for liver cirrhosis and its decompensation in CHB patients and provided similar results [17]. Given the detrimental impact of male sex and older age on liver cirrhosis in 2 studies [16,17], our participants were matched by age and sex to eliminate interference.

Interestingly, another study found an independent association between diabetes and more severe fibrosis rather than mild fibrosis, both in CHB and CHC patients [18]. A retrospective study of 145 liver cirrhosis patients with acute upper gastrointestinal bleeding indicated that DM can increase the risk of in-hospital mortality [19], but another study came to the opposite conclusion. In 2016, Han et al. conducted a retrospective case-control study and found that T2DM is not be a risk factor for HCC in HBV cirrhosis patients [20]. The precise mechanism remains unclear and little is known about the associations between age at diabetes diagnosis, diabetes duration, treatment of diabetes, and cirrhosis risk among CHB patients in mainland China.

Our findings indicated that participants treated with exogenous insulin had higher cirrhosis risk compared with those without exogenous insulin treatment, which might be associated with the accretion of circulating insulin levels. Additionally, our univariate analysis found that CHB patients with diabetes for more than 5 years had increased risk of liver cirrhosis. However, this association was not statistically significant when the analysis was restricted to studies adjusting for other diabetes-related variables. These results might be driven by strong results found for insulin treatment, since most diabetics with longer disease duration were treated with insulin. To the best of our knowledge, the relationship between diabetes duration and risk of liver cirrhosis has not been analyzed previously in clinical studies. However, some studies have shown that insulin treatment was associated with increased risk of HCC [21,22], and diabetes duration was not associated with HCC [23,24], which were similar to our findings. Notably, we found no evidence that age at diabetes diagnosis was related to HBV-related liver cirrhosis.

In our study, the presence of gallstones was associated with liver cirrhosis, yielding an AOR (95% CI) of 1.733 (1.184–2.538) for all patients. Notably, in CHB patients with DM, the AOR (95% CI) [3.668 (1.157–11.625)] was slightly higher. The findings of a retrospective study suggested that gallstone diseases are a predictor of diabetes [25]. Therefore, a possible explanation for our study results might be the presence of gallstone diseases, which can influence diabetes status. Interestingly, we found that the association between oral treatment and liver cirrhosis was not statistically significant.

The underlying mechanisms linking DM and liver cirrhosis, particularly in patients with HBV infection, are not clear. The hypothesis of the adverse impact of DM on liver cirrhosis may be related to insulin resistance (IR) [26–28]. IR in hepatocytes directly disturbs glucose metabolism and interferes with cell survival and proliferation. Our findings suggest that insulin induces the hyperphosphorylation of IRS1 and AKT, which was previously reported in activated hepatic stellate cells (HSC) [29]. In addition, high levels of circulating blood glucose or insulin can enhance expression of collagen and other hepatic fibrosis-related precursors in HSC [30]. Furthermore, oxidative stress caused by hyperglycemia may be another factor promoting liver fibrosis [31]. These findings might help explain how DM was associated with liver cirrhosis in CHB patients in our study.

There are some limitations to our study. First, the number of cases was not large, particularly within categories of CHB patients who had diabetes, limiting the interpretation of subgroup analyses. Secondly, no information on specific types of oral hypoglycemic agents was available, so we could not assess their role in liver cirrhosis. Finally, no data were available on family history of cirrhosis.

Conclusions

We found that DM was associated with cirrhosis risk in CHB patients in Wuhan, China. We also found a significant correlation between exogenous insulin treatment and liver cirrhosis among patients dually diagnosed with CHB and DM.

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Conflicts of interest

None.

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