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The Potential Effects of Diabetes Mellitus on Liver Fibrosis in Patients with Primary Biliary Cholangitis

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCEF **Xu Liu**
CD **Hongqin Xu**
E **Mengru Zhan**
A **Junqi Niu**

Department of Hepatology, The First Hospital of Jilin University, Changchun, Jilin, P.R. China

Corresponding Author: Junqi Niu, e-mail: junqi_niu@163.com

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Background: The impact of diabetes mellitus (DM) on the natural progression of primary biliary cholangitis (PBC) has not yet been determined. The objective of this study was to determine whether DM is associated with increased liver damage in PBC.


Material/Methods: There were 168 treatment-naïve PBC patients, including 37 patients with DM, enrolled in this study between 2012 and 2018. Patient demographics, clinical features, and biochemical and histopathological parameters were collected. Disease severity was assessed by pathological data, Child Pugh grade, and noninvasive indicators. Relevant risks for PBC-related cirrhosis were assessed by univariate and multivariate analyses.

Results: The noninvasive scores predicting fibrosis were all significantly higher in PBC-DM versus PBC-only patients (fibrosis-4 score: 4.08 versus 3.21, $P=0.029$; aminotransferase-to-platelet ratio index: 1.46 versus 1.09, $P=0.036$; red blood cell distribution width to platelet ratio: 0.12 versus 0.08, $P=0.016$; Mayo Risk Score: 1.52 versus 0.19, $P=0.011$; the Newcastle model: 2.85 versus 2.07, $P=0.009$; albumin-bilirubin score: -1.92 versus -2.10 , $P=0.023$). Cirrhosis occurred at a higher rate (62.2% versus 42.0%, $P=0.030$) in PBC-DM patients, but Child Pugh grade and pathological differences could not be accurately determined. A multivariate analysis revealed DM increased the risk of PBC-related cirrhosis, with a resulting adjusted odds ratio of 2.351 (95% confidence interval, 1.022–5.409).

Conclusions: The results of this retrospective, single-center study suggest that DM is associated with more severe liver fibrosis in PBC. Consequently, improved management of DM might alter the prognosis of PBC patients.

MeSH Keywords: **Cholangitis • Diabetes Mellitus • Liver Cirrhosis**

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Background

Primary biliary cholangitis (PBC) is an autoimmune-mediated chronic inflammatory disease characterized by intrahepatic cholestasis [1]. The etiology of PBC, which often occurs in middle-aged and elderly females, is thought to be a combination of genetic predisposition and environmental triggers [2]. Serum anti-mitochondrial antibody (AMA) levels are a specific marker for PBC diagnosis, with positive rates of the AMA-M2 subtype reaching 90–95% [3]. In clinical practice, PBC is typically diagnosed based on serological and imaging findings, or by a liver biopsy, if necessary.

In addition to histology, several noninvasive biochemical markers have been developed to predict the extent of liver damage. The fibrosis-4 (FIB-4) score and aminotransferase-to-platelet ratio index (APRI), which effectively evaluate fibrosis and cirrhosis [4,5], have also been used to predict PBC severity [6]. The Newcastle model and albumin-bilirubin (ALBI) scores were also shown to be related to the clinical outcomes in patients with PBC [7–9]. Besides, the red blood cell distribution width to platelet ratio (RPR), a new noninvasive marker, reportedly has the potential to evaluate the histologic severity of PBC [10]. Historically, the Mayo Risk Score (MRS), which was introduced by Dickson, has been the most widely used noninvasive, prognostic assessment for PBC in the absence of a biopsy [11–13].

The prevalence of diabetes mellitus (DM) has become more evident in developing countries, with the number of patients increasing from 108 million in 1980 to 422 million in 2014 [14]. At present, DM is a major cause of blindness, kidney failure, heart attack, stroke, and lower limb amputation [15]. As well, chronic hyperglycemia, which is considered a pre-inflammatory state and could induce hepatic oxidative stress, is closely related to liver inflammation and fibrosis [16]. DM is an established risk factor for hepatic metabolic diseases i.e., non-alcoholic fatty liver disease (NAFLD) [17], and the prevalence of non-alcoholic steatohepatitis (NASH) has reportedly reached 20% in asymptomatic type 2 DM patients with normal liver function [18]. Furthermore, a multiple regression analysis revealed that DM is an independent prognostic factor for major liver-related outcomes among individuals with chronic viral hepatitis and cirrhosis [19–21]. Follow-up investigations have likewise confirmed that DM is associated with an increased risk of developing liver cirrhosis in patients infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV) [22,23].

Metabolic regulation and immune-mediated inflammation are highly integrated and functionally interdependent. In fact, the interaction between metabolism and immunity can be regarded as a fundamental mechanism in the regulation of homeostasis. DM could result in long-term metabolic abnormalities, including the increased generation of advanced glycation end products,

the activation of protein kinase C isoforms, and increased flux through the polyol and hexosamine pathways [24], all of which could lead to the accumulation of superoxide, which activates inflammatory pathways, resulting in immune dysfunction [25]. To this end, humoral immune disorders, neutrophil dysfunction, and inadequate T cell responses have been reported in diabetic patients [26]. Given the complex immune conditions associated with DM and its clinical correlation with liver pathogenesis, we explored the impact of DM on PBC severity for the first time using invasive and noninvasive assessment methods. The risk of DM in PBC-related cirrhosis was further determined by univariate and multivariate analyses.

Material and Methods

Study population

In this retrospective, single-center study, we analyzed data from inpatients diagnosed with PBC at the First Hospital of Jilin University, China, between February 2012 and May 2018. To evaluate the effect of DM on the severity of PBC and to avoid the interference of PBC disease duration, a total of 168 treatment-naïve participants, including 37 patients with DM, were enrolled. Forty-three patients had undergone liver biopsy. The exclusion criteria were: 1) previously diagnosed PBC or use of pharmacotherapy related to PBC; 2) PBC/Autoimmune Hepatitis Overlap syndrome or some other co-existing liver disease, such as infection with HBV and/or HCV, alcoholic liver disease, or NAFLD; or 3) DM diagnosed after the discovery of PBC. The PBC diagnosis was confirmed by histological findings or clinical characteristics according to the guidelines of the European Association for the Study of the Liver [27], and DM was confirmed based on known history of DM, ongoing anti-diabetic therapy, or at least one of the following criteria: 1) fasting blood glucose (FBG) level ≥ 7.0 mmol/L; 2) random blood glucose level ≥ 11.1 mmol/L; or 3) 2 hour post-load blood glucose ≥ 11.1 mmol/L [28]. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the First Hospital of Jilin University.

Study variables

Patient demographics, medical history (including cigarette smoking and alcohol intake), pertinent clinical signs, and laboratory results related to PBC and DM were obtained at the initial stage of admission. Pathological data were obtained from the hospital medical records. The pathological diagnosis was determined based on the Ludwig and Scheuer scoring system (Stage I: cholangitis; Stage II: inflammation around the portal area; Stage III: progressive fibrosis; and Stage IV: cirrhosis) [29]. In our study, Stage I was considered early stage, whereas advanced stage included Stages II, III, and IV. The respective liver

biopsies were reviewed by 2 independent pathologists who were blinded to the patient background information.

To compare the severity of liver fibrosis between PBC patients and those with DM, FIB-4, APRI, RPR, MRS, the Newcastle model, and ALBI scores were chosen and calculated using the listed formulas [6,7,9–11]. In addition, we analyzed the Child Pugh grade in patients with cirrhosis, which is a grading standard commonly used in clinical practice for the quantitative evaluation of hepatic function reserve. Likewise, we performed univariate and multivariate analyses in our study.

Formulas for liver fibrosis severity

APRI=[(AST level/AST Upper limit of normal)/PLT($10^9/L$)] \times 100 [6]

FIB-4=(Age \times AST)/(PLT \times [ALT] $^{1/2}$) [6]

RPR=RDW/PLT ($10^9/L$) [10]

MRS=(0.039 \times age)+(0.859 \times ascites[no=0, yes=1])+(1.02 \times ln[INR])–(0.53 \times ln[albumin{mg/dL}])+(0.871 \times ln[bilirubin{mg/dL}])+6.843 [11]

Newcastle model=(0.0742 \times age)+(0.261 \times ln[ALP/upper limit of normal])–(2.53 \times [albumin/lower limit of normal])+(0.195 \times ln[bilirubin/upper limit of normal]) [7]

ALBI=(–0.085 \times albumin [g/L])+(0.66 \times log[Bilirubin { μ mol/L}]) [9]

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are shown as median (25th/75th percentile) due to the skewed distribution of the data and categorical variables are displayed as numbers or percentages. The nonparametric Mann-Whitney U-test and the chi-squared (χ^2) test were used for statistical comparisons, as appropriate. A 2-tailed $P < 0.05$ was considered statistically significant. Multivariate logistic regression analysis was used to account for possible confounding variables and adjusted odds ratios (AORs) were obtained with 95% confidence intervals (CIs).

Results

Demographic characteristics

Overall, 168 treatment-naïve PBC patients were included in this study, of which 37 had concurrent DM. The baseline patient characteristics are shown in Table 1. The median ages of the PBC-only and PBC-DM patients were 58.0 (interquartile range [IQR], 48.0–64.0) and 63.0 (IQR, 51.5–72.5; P value=0.057), respectively. Furthermore, the median gender distributions were similar. Epidemiological evidence suggests that PBC occurs more frequently in females, with an estimated male-to-female ratio of 1: 9 or greater, depending on the region [20]. In accord with existing data, the prevalence of PBC was higher

in females (77.9% in the PBC-only group and 83.8% in the PBC-DM group) in our study. Alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels were significantly increased, which was consistent with the characteristics of PBC. In addition to total bilirubin (TBIL), platelets, red blood cell distribution width (RDW), fasting blood glucose (FBG), and glycohemoglobin, there were no statistically significant differences between the 2 groups in terms of clinical characteristics. Because the number of female participants was higher, the number of patients with cigarette smoking and alcohol consumption was small; thus, no statistically significant differences in these factors were detected between the groups. For the PBC-DM group, the median duration of DM was 8.0 years (IQR 1.0–10.0). Although some of the patients received anti-diabetic treatment, FBG and glycohemoglobin were still significantly higher than PBC patients without DM. TBIL levels represented the presence of cholestasis in the liver, which is a typical biochemical manifestation of PBC. As well, the platelet and RDW levels indicated that fibrosis was more severe in the PBC-DM group.

Comparison of the severity of liver damage in PBC-only and PBC-DM patients

After consulting the existing literature and related materials, FIB-4, APRI, RPR, MRS, the Newcastle model, and ALBI scores, which are all closely related to the progression of chronic liver disease, were chosen, calculated, and summarized. As shown in Table 2, these noninvasive scores that predict fibrosis were significantly higher in PBC-DM versus PBC-only patients (FIB-4: 4.08 versus 3.21, $P=0.029$; APRI: 1.46 versus 1.09, $P=0.036$; RPR: 0.12 versus 0.08, $P=0.016$; MRS: 1.52 versus 0.19, $P=0.011$; the Newcastle model: 2.85 versus 2.07, $P=0.009$; and ALBI scores: –1.92 versus –2.10, $P=0.023$).

In this study, 43 patients (25.6%) underwent liver biopsy during hospitalization. In the PBC-only group, 14 patients (36.8%) and 24 patients (63.2%) were in the early and advanced stages of histopathology, respectively, compared with 1 patient (20.0%) and 4 patients (80.0%), respectively, in the PBC-DM group. Although relatively fewer patients in the PBC-DM group underwent a liver biopsy compared with the PBC-only group, the results suggested that patients in the PBC-DM group might have had more severe pathological damage. However, no statistically significant differences were detected between the 2 groups ($P=0.807$), which might also be a reflection of the insufficient sample size. Furthermore, we compared the Child Pugh grade among all cirrhosis cases in the enrolled patients. We found that cirrhosis occurred at a higher rate (62.2% versus 42.0%; $P=0.030$) in the PBC-DM group, but the differences in Child Pugh grade between the 2 groups were likewise not statistically significant ($P=0.465$).

Table 1. Demographic and clinical characteristics of patients.

Variables	PBC-only (n=131)		PBC-DM (n=37)		P value
Demographic characteristics					
Age (years)	58.0	(48.0, 64.0)	63.0	(51.5, 72.5)	0.057
Sex, female (%)	77.9		83.8		0.291
Cigarette smoking [n (%)]	26	(19.8)	4	(10.8)	0.205
Alcohol intake [n (%)]	8	(6.1)	2	(5.4)	1.000*
Clinical characteristics					
AST (IU/L)	65.0	(40.2, 100.2)	58.9	(41.6, 117.6)	0.664
ALT (IU/L)	58.2	(33.6, 97.6)	55.0	(35.3, 145.5)	0.472
ALP (IU/L)	250.2	(147.3, 435.0)	278.0	(153.1, 472.1)	0.600
GGT (IU/L)	251.1	(122.6, 478.8)	279.0	(151.9, 569.4)	0.318
TBIL (umol/L)	18.4	(11.4, 52.8)	25.5	(19.1, 76.7)	0.042
Albumin (g/L)	36.1	(30.5, 38.9)	33.0	(29.7, 37.4)	0.070
AMA-M2 (RU/mL)	156.5	(104.0, 200.0)	165.0	(93.4, 200.0)	0.889
FBG (mmol/L)	5.0	(4.5, 5.5)	7.7	(6.0, 9.7)	<0.001
Glycohemoglobin (%)	5.1	(4.3, 6.0)	6.4	(6.2, 7.8)	<0.001
Triglyceride (mmol/L)	1.2	(0.9, 1.7)	1.6	(0.8, 2.1)	0.197
Total cholesterol (mmol/L)	4.7	(3.7, 6.0)	4.7	(3.7, 6.2)	0.857
PLT (10 ⁹ /L)	168.0	(110.0, 225.0)	125.0	(70.0, 198.0)	0.044
RDW (%)	14.0	(13.2, 15.3)	15.0	(13.6, 16.6)	0.022
INR	1.0	(0.9, 1.1)	1.0	(0.9, 1.1)	0.939
PT(s)	11.4	(10.7, 12.2)	11.7	(10.5, 12.9)	0.484
Duration of DM (years)	-		8.0	(1.0, 10.0)	-

Data were expressed as median (25th, 75th percentiles) or percentage. PBC-only represented that the patient only had PBC and PBC-DM represented that the patient had both PBC and DM. * P value came from χ^2 test for continuous correction. PBC – primary biliary cholangitis; DM – diabetes mellitus; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; GGT – gamma-glutamyl transpeptidase; TBIL – total bilirubin; PT – prothrombin time; PLT – platelet; AMA-M2 – antimitochondrial M2 antibody; RDW – red blood cell distribution width; FBG – fasting blood-glucose; INR – international normalized ratio.

Univariate and multivariate analyses of factors associated with PBC-related cirrhosis

The results of our univariate analysis revealed that the differences in age, DM, and GGT levels were statistically significant between the PBC patients with or without cirrhosis, and that the resulting odds ratio (OR) of DM was 2.27 (95% CI, 1.073–4.804) for the patients with cirrhosis compared with the non-cirrhosis group. Multivariate regression analysis was performed using the indicators in the univariate analysis with a $P < 0.05$ to adjust for confounding factors. Consequently, we found that age and DM increased the risk of cirrhosis, with an AOR of 1.048 (95% CI, 1.018–1.079) and 2.351 (95% CI, 1.022–5.409), respectively (Table 3).

Discussion

The impact of DM on liver-related diseases has received increased attention in recent years, especially the effects of DM on NAFLD. To this end, previous findings have shown that DM is significantly associated with severe fibrosis and hepatocellular carcinoma (HCC) [4,5,14,21,22]. The interaction between metabolism and immunity is complex, and has thus become a topical focus of ongoing research. The detection of PBC, an autoimmune liver disease, is not rare clinically. In fact, the current study was motivated by estimates that up to 30% of PBC patients will suffer from cirrhosis or liver failure [23]. Further, although DM has been associated with metabolic and immune disorders, to date no reports have described the relationship

Table 2. Comparisons of the severity of liver damage between PBC patients and those with DM.

Parameters	PBC-only (n=131)		PBC-DM (n=37)		P value
Noninvasive scores					
FIB-4	3.21	(1.75, 5.36)	4.08	(2.90, 8.37)	0.029
APRI	1.09	(0.51, 1.96)	1.46	(0.77, 2.60)	0.036
RPR	0.08	(0.06, 0.15)	0.12	(0.08, 0.23)	0.016
MRS	0.19	(-0.58, 1.77)	1.52	(0.08, 2.30)	0.011
The Newcastle model	2.07	(1.39, 3.01)	2.85	(2.11, 3.37)	0.009
ALBI	-2.10	(-2.55, -1.63)	-1.92	(-2.24, -1.32)	0.023
Histological stages [n (%)]					
Early stage	14	(36.8)	1	(20)	0.807*
Advanced stage	24	(63.2)	4	(80)	
Cirrhosis [n (%)]	55	(42.0)	23	(62.2)	0.030
Child Pugh grade [n (%)]					
A	19	(34.6)	6	(26.1)	0.465**
B	34	(61.8)	15	(65.2)	
C	2	(3.6)	2	(8.7)	

Data were expressed as median (25th, 75th percentiles) or percentage. PBC-only represented that the patient only had PBC and PBC-DM represented that the patient had both PBC and DM. * P value came from χ^2 test for continuous correction. ** To avoid the expected value <5 of χ^2 test in 3x2 contingency table, we combined the cases of grade B and C. PBC – primary biliary cholangitis; DM – diabetes mellitus; FIB-4 – fibrosis index based on the 4 factors; PRI – aminotransferase-to-platelet ratio index; RPR – red blood cell distribution width to platelet ratio; MRS – Mayo Risk Score; ALBI – albumin-bilirubin scores.

Table 3. Univariate and multivariate analyses of factors associated with PBC-related cirrhosis.

Variables	PBC (n=90)		PBC-related cirrhosis (n=78)		Univariate analysis P value*	Multivariate analysis	
						AOR (95% CI)	P value**
Age (years)	55.0	(47.0, 63.0)	62.0	(53.8, 72.0)	<0.001	1.048 (1.018, 1.079)	0.001
Sex, Female (%)	73	(81.1)	69	(88.5)	0.189		
DM [n (%)]	14	(15.6)	23	(29.5)	0.030	2.351 (1.022, 5.409)	0.044
Cigarette smoking [n (%)]	15	(16.7)	15	(19.2)	0.665		
Alcohol intake [n (%)]	5	(5.6)	5	(6.4)	1.000 [#]		
ALP	279.5	(145.6, 428.3)	250.2	(156.6, 476.3)	0.982		
GGT	323.0	(160.0, 660.6)	209.0	(89.8, 354.3)	0.003	0.999 (0.997, 1.000)	0.009

Data were expressed as median (25th, 75th percentiles) or percentage. PBC represented the patients without cirrhosis and PBC-related cirrhosis represented the patients with cirrhosis. * P value came from χ^2 test or nonparametric Mann-Whitney U-test. ** P value came from multivariate logistic regression analysis. [#] For continuous correction. PBC – primary biliary cholangitis; DM – diabetes mellitus; ALP – alkaline phosphatase; GGT – gamma-glutamyl transpeptidase; AOR – adjusted odds ratio; CI – confidence interval.

between DM and the severity of liver damage in PBC. Due to our strict inclusion and exclusion criteria and the fact that concomitant DM only accounted for a small proportion of PBC patients, only 37 PBC-DM patients were included in our study. NAFLD patients were excluded from our retrospective analysis,

and blood lipid level was likewise considered an influencing factor. After analysis, triglyceride and total cholesterol levels were balanced between the 2 groups.

Histopathological examination is conducive to determining the disease stage and prognosis. The primary pathological change observed in PBC is chronic, destructive inflammation of the small bile ducts (<100 µm), which leads to a progressive decrease in the small bile ducts, intrahepatic cholestasis, liver fibrosis, and eventually cirrhosis. Considering the invasiveness and complications associated with PBC, only 43 patients (25.6%) who were enrolled in our study underwent liver biopsy during hospitalization. Therefore, pathological differences between the 2 groups could not be accurately determined.

Due to the limitations associated with liver biopsies, noninvasive assessment methods for hepatic fibrosis have been developed. In this study, we compared PBC disease stage between patients with and without DM using noninvasive markers that are predictive of fibrosis. FIB-4, APRI, RPR, MRS, the Newcastle model, and ALBI scores are indirect serum biomarkers based on algorithmic evaluations of commonly observed functional alterations of the liver that are widely used to assess stage of liver fibrosis. In addition, these scores are based on the results of routine laboratory tests, are easy and economical to calculate, and might be a predictor of PBC severity [34]. Our results showed that the scores of all fibrosis evaluation models were higher in the PBC-DM group, suggesting that more severe fibrosis occurred in the PBC-DM patients. The indication that fibrosis was more severe in the PBC-DM patients was likewise supported by the higher incidence of cirrhosis in the PBC-DM group.

To further confirm DM is a risk factor for cirrhosis in PBC, factors associated with PBC-related cirrhosis (Table 3) were evaluated. In addition to gender, age, DM, and medical history, ALP and GGT levels, which represent the severity of PBC and might be potential risks for developing cirrhosis in PBC patients, were also included in the univariate analysis. The findings showed that age and DM were both independent risk factors and DM doubled the risk of cirrhosis, which supported our preliminary conclusions. Interestingly, ALP and GGT levels were not increased in the cirrhosis group, which might have been due to the poor reactivity of ALP and GGT caused by severe liver fibrosis and bile duct damage in the cirrhosis patients.

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Our study had several limitations. First, although 6 years of data were collected, the number of patients enrolled in the study and the resulting sample size was small, especially in regard to the PBC-DM group. Consequently, our conclusions require validation in large-scale studies. Second, due to the retrospective nature of the study, it was difficult to obtain body mass index (BMI) scores of the enrolled patients from the hospital medical records. Hence, we could only infer obesity based on blood lipid levels and NAFLD diagnoses. Third, the 168 patients enrolled were newly diagnosed with PBC, 37 of whom had a history of DM; thus, it was difficult to confirm that DM occurred before PBC and that all PBC patients did not have relative medication history.

Conclusions

Despite the inherent limitations, the findings from our study supplemented existing data indicating the negative impact of DM on the natural progression of PBC, and suggested that improving the management of DM by treating the underlying disease might slow the progression of fibrosis in PBC patients. Larger studies are nonetheless recommended to assess the effects of DM on the treatment and prognosis of PBC patients.

Conflicts of interest

None.

Abbreviations

PBC – primary biliary cholangitis; DM – diabetes mellitus; APRI – aminotransferase-to-platelet ratio index; FIB-4 – fibrosis-4; RPR – red blood cell distribution width to platelet ratio; MRS – Mayo Risk Score; ALBI – albumin-bilirubin; AMA – anti-mitochondrial antibody; AMA-M2 – anti-mitochondrial M2 antibody; ALP – alkaline phosphatase; RDW – red blood cell distribution width; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transpeptidase; TBIL – total bilirubin; PLT – platelet; FBG – fasting blood glucose; INR – international normalized ratio; PT – prothrombin time; IQR – interquartile range; CI – confidence interval; IQR – interquartile range; OR – odds ratio; AOR – adjusted odds ratio.

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