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Liver cirrhosis: a risk factor for gallstone disease in chronic hepatitis C patients in China

Xu Li, PhD, Zhongfeng Wang, PhD, Le Wang, MD, Meng Pan, MD, Pujun Gao, PhD*

Abstract

We investigated the possible link between liver cirrhosis and gallstone risk in chronic hepatitis C (CHC) patients in China.

To analyze the association between liver cirrhosis and gallstone development, we compared outcomes of 133 Chinese CHC patients with gallstones and an age-, sex-, and hepatitis C virus RNA level-matched control group of 431 CHC patients without gallstones.

We found that liver cirrhosis was more prevalent in gallstone patients (40.6%) than in the control group (24.4%). Logistic regression analyses adjusting for demographic features and other gallstone risk factors revealed that liver cirrhosis increased the risk of gallstone development 2-fold (adjusted odds ratio [AOR]: 2.122; 95% confidence interval [CI]: 1.408–3.198). Moreover, multivariate analyses comparing the risk of gallstone development in liver cirrhosis patients with decompensated or compensated liver cirrhosis yielded an estimated AOR (95% CI) of 2.869 (1.277–6.450) in patients with decompensated liver cirrhosis. Gallstone risk also increased significantly with older age (>60 years) (AOR: 2.019; 95% CI: 1.017–4.009).

Liver cirrhosis significantly correlates with increased risk of gallstone development in CHC patients in China. Decompensated liver cirrhosis and older age further heighten this risk in patients diagnosed with hepatitis C-related cirrhosis.

Abbreviations: AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, GGT = gamma-glutamyl transpeptidase, HCV = hepatitis C virus, TBIL = total bilirubin.

Keywords: gallbladder stone, hepatitis C, liver cirrhosis

1. Introduction

Gallstone disease (GD) is one of the most prevalent and costly digestive disorders in the world[1–3]and is diagnosed in 10% to 20% of adults in developed countries. The main risk factors for gallstone formation are sex (females), advanced age, obesity, alcohol use, diabetes mellitus (DM), and hypertriglyceridemia.[4,5] Determining the potential relationship between gallstones and chronic liver disease is of great interest, as previous research indicates cirrhosis is a relevant risk factor for gallstone development.[6,7]

Liver cirrhosis exemplifies end-stage chronic liver disease and exhibits a rising worldwide prevalence.[8,9] Recent studies have found that gallstones may occur more frequently in liver cirrhosis patients than in nonliver cirrhosis patients.[10] Moreover, gallstone formation in cirrhotic patients often leads to a poorer prognosis than cirrhotic patients without gallstones. Therefore, further study of the relationship between cirrhosis and gallstones is critical for predicting clinical outcomes in patients with liver disease.

In China, major known causes of liver cirrhosis include infection with hepatitis B virus or hepatitis C virus (HCV) and excessive alcohol consumption. Thus, we conducted the current study to specifically analyze the association between HCV-related liver cirrhosis and gallstone occurrence in Chinese chronic hepatitis C (CHC) patients, as well as possible relationships between liver cirrhosis severity and gallstone formation.

2. Patients and methods

2.1. Patients

We conducted a retrospective case–control study of patients from The First Hospital of Jilin University in China between January 2010 and June 2016. Patients with chronic HCV infection diagnosed by the presence of anti-HCV antibodies and serum HCV RNA for ≥6 months were recruited for our study. Case patients were matched with control participants based on sex, age, and HCV RNA level.

Potential participants were excluded based on the following criteria: coinfection with human immunodeficiency virus or hepatitis B virus; history or evidence of any cancer; history or evidence of hepatitis other than hepatitis C; or presence of other liver disease, such as alcoholic liver disease.

The Independent Institutional Review Board of The First Hospital of Jilin University approved the recruitment of human participants and our study protocol. Each participant provided written informed consent prior to enrollment in the study.

2.2. Diagnosis of liver cirrhosis and GD

We confirmed each patient's liver cirrhosis diagnosis with a liver biopsy or based on a combination of clinical, biochemical, and radiological findings. Diagnosis of GD relied on ultrasonographic

Editor: Huitao Fan.

The authors have no funding and conflicts of interest to disclose.

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

* Correspondence: Pujun Gao, Department of Hepatology, The First Hospital of Jilin University, Changchun, Jilin, 130021, China (e-mail: gpj0411@163.com).

Medicine (2017) 96:26(e7427)

Received: 21 March 2017 / Received in final form: 16 May 2017 / Accepted: 12 June 2017

http://dx.doi.org/10.1097/MD.0000000000007427

detection of an echogenic structure within the gallbladder lumen that caused a posterior acoustic shadow[11] or cholecystectomy findings.

2.3. Diagnosis of DM

DM was diagnosed in patients with known history of DM under antidiabetic therapy or at least one of the following criteria: fasting glucose level ≥7.0 mmol/L; random glucose level ≥11.1 mmol/L; or 2-hour post-load plasma glucose ≥11.1 mmol/L.[12]

2.4. Study variables

Demographic and clinical presentation variables in this study included sex, age, presence of type 2 diabetes, and cirrhosis. We also analyzed patient biochemical parameters, such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, prothrombin time, cholesterol, triglycerides, gamma-glutamyl transpeptidase, alkaline phosphatase, glucose, HCV RNA, and cholinesterase. In addition, the Child–Pugh score was calculated in patients with liver cirrhosis for the classification of cirrhosis severity. Abdominal ultrasound was also performed in cirrhosis patients to determine the number of ascites and the presence of cirrhosis.

2.5. Statistical analysis

Continuous variable values were shown as the mean (25th and 75th percentiles), whereas categorical variables were displayed as numbers and percentages; 2-tailed independent samples *t* tests and Chi-squared analysis were employed to investigate each type of variable, respectively. Multivariate logistic regression analysis was used to adjust for possible confounding effects among the variables. We also calculated adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for these comparisons. We used SPSS v. 13.0 (SPSS Inc., Chicago, IL) for data analysis, and $P < .05$ indicated statistical significance.

3. Results

3.1. Demographic and clinical characteristics of case and control participants

Baseline demographic and clinical characteristics of the study participants (n = 564) are presented in Table 1. The case group was comprised of 133 CHC patients with gallstones and included 65 male and 68 female patients with a mean age of 60.04 years. In addition, 54 patients (40.6%) were cirrhotic, and 21 patients (15.8%) had type 2 diabetes. The control group consisted of 431 CHC patients without gallstones and was representative of patients in northeast China. Their mean age was 59.06 years, and approximately half (50.8%) of the control patients were male.

We observed no significant difference in the clinical characteristics, such as levels of triglycerides, cholesterol, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, or alkaline phosphatase, between the 2 groups. Additionally, no significant difference was detected in total bilirubin, albumin, prothrombin time, or glucose between the 2 groups. However, cholinesterase in the case group was significantly lower than in the control group.

3.2. Univariate and multivariate analyses of variables associated with gallstones in CHC patients

Univariate analysis suggested the age and liver cirrhosis distributions were significantly different between case patients and controls. Sex, age, type 2 diabetes, liver cirrhosis, and levels of triglycerides, cholesterol, and HCV RNA were then considered for multivariable analysis. The AOR for patients with liver cirrhosis was 2.122 (95% CI: 1.408–3.198; $P < .001$) compared to patients without liver cirrhosis (Table 2).

3.3. Liver disease severity and gallstones

Because liver cirrhosis was a potential major risk factor for gallstone development in CHC patients, we evaluated the association between gallstone formation and severity of liver cirrhosis (Child–Pugh score) in 159 cirrhosis patients. We further

Table 1

Demographic and clinical characteristics of case and control participants.

Variable	No gallstones N = 431	Gallstones N = 133	*P*
Male, N, %	219 (50.8)	65 (48.9)	.696
Age, y	59.06 (53.00, 64.00)	60.04 (54.50, 68.00)	.282
Type 2 diabetes, N, %	73 (16.9)	21 (15.8)	.756
Liver cirrhosis, N, %	105 (24.4)	54 (40.6)	<.001
Triglycerides, mmol/L	1.28 (0.80, 1.49)	2.45 (0.72, 1.40)	.328
Cholesterol, mmol/L	4.89 (3.17, 4.48)	3.76 (3.07, 4.22)	.515
AST, IU/L	85.34 (35.90, 95.00)	101.39 (37.85, 100.00)	.222
ALT, IU/L	110.51 (33.00, 118.40)	121.40 (30.00, 125.00)	.566
GGT, IU/L	120.81 (28.00, 107.00)	99.02 (28.75, 125.30)	.473
ALP, IU/L	114.09 (67.00, 112.00)	113.27 (74.95, 125.00)	.973
TBIL, μmol/L	35.81 (12.10, 27.80)	41.62 (13.20, 32.55)	.385
ALB, g/L	36.54 (33.30, 41.20)	37.30 (31.30, 40.00)	.756
CHE, IU/L	6173.10 (4108.00, 7970.00)	5415.66 (3147.00, 7311.00)	.005
PT, s	12.19 (10.60, 12.70)	12.13 (10.75, 13.15)	.922
Glucose, mmol/L	6.02 (4.90, 6.06)	5.86 (4.75, 6.05)	.485
HCV RNA, IU/mL	2,153,341.52 (4380.00, 1,600,000.00)	2,569,461.56 (1795.00, 2,010,000.00)	.461

Continuous variables are expressed as means (25th, 75th percentiles). Categorical variables were displayed as numbers and percentages.

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHE = cholinesterase, GGT = gamma-glutamyl transpeptidase, HCV = hepatitis C virus, PT = prothrombin time, TBIL = total bilirubin.

Table 2

Univariate and multivariate analyses of variables associated with gallstones in CHC patients.

Variable	No gallstones N = 431	Gallstones N = 133	P*	AOR (95% CI)†	P‡
Sex			.696	–	–
Female, N, %	212 (49.2)	68 (51.1)			
Male, N, %	219 (50.8)	65 (48.9)			
Age, y			.044	–	–
≤60 y, N, %	269 (62.4)	70 (52.6)			
>60 years, N, %	162 (37.6)	63 (47.4)			
HCV RNA			.375	–	–
Negative, N, %	67 (15.5)	25 (18.8)			
Positive, N, %	364 (84.5)	108 (81.2)			
Triglycerides			.415	–	–
≤1.8 mmol/L, N, %	367 (85.2)	117 (88.0)			
>1.8 mmol/L, N, %	64 (14.8)	16 (12.0)			
Cholesterol			.416	–	–
≤6.0 mmol/L, N, %	415 (96.3)	130 (97.7)			
>6.0 mmol/L, N, %	16 (3.7)	3 (2.3)			
Type 2 diabetes			.756	–	–
No, N, %	358 (83.1)	112 (84.2)			
Yes, N, %	73 (16.9)	21 (15.8)			
Liver cirrhosis			<.001	2.122 (1.408–3.198)	<.001
No, N, %	326 (75.6)	79 (59.4)			
Yes, N, %	105 (24.4)	54 (40.6)			

AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, HCV = hepatitis C virus.

* *P*-value for univariate analysis.

† Adjusted for sex, age, liver cirrhosis, type 2 diabetes, and levels of triglycerides, cholesterol, and HCV RNA.

‡ *P*-value for multivariate analysis.

analyzed the relationship between gallstone risk and the following factors in liver cirrhosis patients: sex, age, type 2 diabetes, and levels of cholesterol, triglycerides, and HCV RNA (Table 3).

Univariate analysis suggested severity distributions were significantly different between gallstone patients and controls. Sex, age, type 2 diabetes, cirrhosis severity, and levels HCV RNA, triglycerides, and cholesterol were included in our multivariable analysis. The AOR for patients with decompensated liver cirrhosis (Child–Pugh class B and C) was 2.869 (95% CI: 1.277–6.450; $P = .011$) compared to patients with compensated liver cirrhosis (class A). In addition, the AOR for older patients (age > 60 years) was 2.019 (95% CI: 1.017–4.009; $P = .045$) compared to younger patients. However, we found no significant association between HCV RNA level and gallstone formation in cirrhotic patients.

4. Discussion

Liver cirrhosis is the major risk factor for pigmented gallstone lithogenesis in adults,[13–15] as cirrhotic patients experience a 2-fold greater occurrence of gallstones than other patients.[13,14,16–18] Specifically, Conte et al[19] followed 618 cirrhotic patients and found that the probability of developing gallstones increased in a time-dependent manner. Moreover, Fornari et al[20] determined that cirrhosis is a risk factor for gallstones in males. Here, we further observed a significantly higher prevalence of GD in cirrhotic patients than in CHC without cirrhosis.

Common aberrations leading to gallstone formation include changes in bile composition and impaired gallbladder motility.[13] For example, chronic hemolysis secondary to hypersplenism, hyperestrogenism, changes in biliary lipid proportions, reduced hepatic synthesis and transport of bile salts, and unconjugated bilirubin contribute to gallstone development in cirrhotic patients. Some studies also found decreased gallbladder motility in patients with HCV-related cirrhosis.[21] Pregnancy is another risk factor for gallstone formation, possibly due to high circulating levels of sex steroids that contribute to gallbladder hypomotility.[22] In cirrhotic patients, increased levels of estrogen and progesterone may cause impairment of gallbladder emptying similar to that observed in pregnant women.[20] Moreover, Buzas et al[21] concluded that thicker gallbladder walls in cirrhotic patients compared to controls could account for gallbladder hypomotility observed in patients with liver cirrhosis.

Our data corroborate findings of previous studies that the prevalence of gallstone formation correlates with severity of cirrhosis.[19,20,23] As stated above, the development of GD in liver cirrhosis could be mediated through bile composition and gallbladder hypomotility. In our opinion, these 2 factors are associated with liver cirrhosis severity. Moreover, we conclude that a longer duration of decompensated liver cirrhosis (compared with compensated cirrhosis) allows sufficient time for gallstone formation in liver cirrhosis patients.

Loriot et al[24] found that concentrations of HCV RNA were similar in serum, bile, and cultures of gallbladder epithelial cells from hepatitis patients. Other researchers have also detected postmortem HCV RNA and antigens in gallbladder specimens from deceased HCV-infected patients.[25] These findings suggest that HCV RNA may be associated with the development of gallstones in CHC patients, although we did not observe such an association in cirrhosis patients in our study. One explanation may stem from the fact that gallstone formation is a chronic process that might be related to the average level of HCV RNA across an extended time period, whereas the level of HCV RNA in our study was assessed at only 1 time point. Moreover, the number of patients with no circulating HCV RNA was low; thus, the lack of apparent correlation between HCV RNA levels and gallstone formation should be considered with caution.

Table 3

Univariate and multivariate analyses of variables associated with gallstones in CHC-related liver cirrhosis patients.

Variables	Liver cirrhosis without gallstones N = 105	Liver cirrhosis with gallstones N = 54	P^*	AOR (95% CI)†	$P^‡$
Sex			.349	–	–
Female, N, %	56 (53.3)	33 (61.1)			
Male, N, %	49 (46.7)	21 (38.9)			
Age			.082	2.019 (1.017–4.009)	.045
≤60 y	60 (57.1)	23 (42.6)			
>60 y	45 (42.9)	31 (57.4)			
Type 2 diabetes			.744	–	–
No, N, %	84 (80.0)	42 (77.8)			
Yes, N, %	21 (20.0)	12 (22.2)			
Triglycerides			.677	–	–
≤1.8 mmol/L, N, %	99 (94.3)	50 (92.6)			
>1.8 mmol/L, N, %	6 (5.7)	4 (7.4)			
Cholesterol			.974	–	–
≤6.0 mmol/L, N, %	101 (96.2)	52 (96.3)			
>6.0 mmol/L, N, %	4 (3.8)	2 (3.7)			
HCV RNA			.207	–	–
Negative, N, %	29 (27.6)	10 (18.5)			
Positive, N, %	76 (72.4)	44 (81.5)			
Severity of cirrhosis			.016	2.869 (1.277–6.450)	.011
Compensated (class A), N, %	39 (37.1)	10 (18.5)			
Discompensated (class B, C), N, %	66 (62.9)	44 (81.5)			

AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, HCV = hepatitis C virus.

* *P*-value for univariate analysis.

† Adjusted for sex, age, diabetes, levels of triglycerides, cholesterol, HCV RNA, and the severity of liver cirrhosis based on the Child–Pugh scale (class A, B, or C).

‡ *P*-value for multivariate analysis.

In addition, DM is often associated with an increased risk of GD,[26] which might occur because there is a significant reduction of gallbladder emptying in DM patients[27–31] or obesity and insulin resistance, which are common in DM patients, are also associated with gallbladder stone development. However, we did not find that type 2 diabetes patients were at higher risk for gallstones in this study. This might be because patients enrolled in our study were CHC patients who might adopt bland diets due to abdominal distension or other digestive symptoms. Such kinds of living habits could lead to weight reduction and weaken the influence of obesity on gallstone occurrence, which is one cause of gallstone development resulting from DM. Moreover, many studies have found significant associations between chronic HCV infection and insulin resistance,[32,33] which is another factor associated with gallstone development in DM patients. As mentioned above, factors contributing to gallstones in DM patients might be disturbed by HCV infection, resulting in no significant association between DM and GD as observed in this study.

In conclusion, we found that the risk of gallstone development in Chinese CHC patients was significantly associated with occurrence of liver cirrhosis. Furthermore, patients with decompensated liver cirrhosis are more susceptible to gallstone formation than patients with compensated liver cirrhosis.

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