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High Association between Gallstones and Incidence of Cirrhosis in Chinese Chronic Hepatitis B Patients

Min Liu[1,2], Liyue Zheng[3], Jinyang Zhang[1], Jiawei Geng[2*] and Xueshan Xia[1,4*]

[1]Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, Yunnan 650500, China

[2]Department of Infectious Disease and Hepatic Disease, The First People's Hospital of Yunnan Province, Kunming, Yunnan 650100, China

[3]Department of Digestive, The First People's Hospital of Yunnan Province, Kunming, Yunnan 650100, China

[4]Kunming Medical University, Kunming, Yunnan 650500, China

ABSTRACT

Background: Multiple previous studies have reported that patients with cirrhosis have a higher incidence of gallstone disease, we aimed to investigate the reverse association, that is, whether CHB patients with gallstones are more likely to develop liver cirrhosis.

Methods: This was a historical cohort study. Propensity score matching (PSM) was employed to reduce baseline bias. The 5-year estimated cumulative incidences (Kaplan-Meier) and risks of liver cirrhosis (Cox proportional hazard model) were calculated.

Results: 492 patients with non-cirrhotic adult CHB between January 2014 and December 2019 were finally analyzed after PSM. 60 patients developed cirrhosis during the 3.99 years median follow-up period. Both the annual rates (4.46 cases per 100 person-years versus 1.57 cases per 100 person-years) and the 5-year estimated cumulative incidence of cirrhosis (16.7% vs. 5.7%) were significantly higher among CHB patients with gallstones versus those without gallstones ($p<0.001$). In addition, CHB patients with gallstones were 2.69 times more likely to develop cirrhosis (95% CI, 1.49-4.84, P= 0.001) than patients without gallstones at baseline.

Conclusion: Like the elderly and high viral load, gallstone was also the independent predictor of liver cirrhosis in CHB patients. However, the study couldn't identify whether early cholecystectomy will benefit CHB patients with gallstones.

***Corresponding author's**

Jiawei Geng, Department of Infectious Disease and Hepatic Disease, The First People's Hospital of Yunnan Province, Kunming, Yunnan 650100, China.

XueShan Xia, Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, Yunnan 650500, China.

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Abbreviations
CHB: Chronic Hepatitis B
PSM: Propensity Score Matching
ALT: Alanine Aminotransferase
AST: Aspartate aminotransferase
TBIL: Total Bilirubin
ALB: Albumin

Introduction

Liver cirrhosis due to hepatitis B virus infection is a major challenge of global health, the complications of which often result in hospitalisation, impaired quality of life, and high mortality [1]. Significantly, most previous studies generally reported liver cirrhosis notably correlated with an increased risk of gallstone prevalence [2-4]. Patients with cirrhosis are more likely to suffer with gallbladder emptying impaired, which play an important role in the pathogenesis of gallstone formation [5].

Interestingly, an additional possible explanation might be that patients with gallstones are more likely to develop cirrhosis than patients without gallstones. In 2010, a cohort study up to 21 years of follow-up from American found that cholecystectomy is an independent predictor of cirrhosis occurrence and is associated with elevated serum liver enzymes, however, this study had not yet determined whether gallstone is a risk factor for liver cirrhosis[6]. Chronic hepatitis B (CHB) is the leading cause of liver cirrhosis in China, yet few studies have been conducted on the relationship between cirrhosis and gallstone disease in CHB patients [7,8]. Therefore, we performed a cohort study to determine whether CHB patients with gallstones were more likely to develop cirrhosis in the subsequent follow-up than patients without gallstones at baseline.

Patients and Methods

Patients

Eligible non-cirrhotic adult CHB patients were recruited from the First People's Hospital of Yunnan Province in Kunming, China, between 2014 and 2019. Key exclusion criteria included a past or current history of liver cirrhosis, HCC, decompensated liver function, human immunodeficiency virus, a history or evidence of a form of hepatitis other than that caused by HBV.

This cohort study included CHB patients with gallstone disease and those patients of control without gallstone at baseline. Gallstone disease diagnosis was dependent on the ultrasonographic detection of an echogenic structure within the gallbladder lumen that caused a posterior acoustic shadow [9]. In addition, we conducted a propensity score matching (PSM) test to avoid the influence of potential interferences. The baseline information of two groups was compared using a general model and PSM model.

This study was approved by the institutional review board of The First People's Hospital of Yunnan Province, and the requirement for informed consent from patients was waived.

Endpoints

The end point of interest was the occurrence of liver cirrhosis. The diagnosis of cirrhosis was defined as the presence of any of the following criteria: nodular liver surface on ultrasonography, clinical features of portal hypertension (eg, ascites, splenomegaly and varices) or a platelet count of less than 100x109/L or albumin less than 3.5 g/dL [10].

Follow-up Evaluation

In this trial, all patients were kept in the long-term follow-up. Information about baseline characteristics and clinical outcomes of the patients were obtained from electronic medical records. All patients had regular clinical assessments and received regular surveillance for liver cirrhosis using abdominal ultrasonography every 6–12 months.

The index date was defined as the date when a patient underwent the first test for serum HBV DNA levels. The follow-up period for each patient was calculated from the index date to the date of diagnosis of liver cirrhosis or the last follow-up (31 December 2020). The CHB patients with gallstones who underwent cholecystectomy and those without gallstones at baseline who occur gallstones during follow-up were censored at that time.

Statistical Analysis

Based on features of the baseline data type, normality, and variance, Continuous variable values are presented as the median (25^{th} and 75^{th} percentiles), the nonparametric Mann–Whitney *U* test was selected to evaluate differences in the levels of age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) and albumin (ALB). χ^2 test was used to compare differences for categorical variables.

To reduce the effect of selection bias and potential confounders between the groups, differences in the baseline characteristics were adjusted through PSM analysis based on the following variables: age, ALT, AST, and HBV DNA. In the PSM analysis, we used nearest neighbor matching with a caliper size of 0.01 and matched patients with gallstones and those without gallstones in a 1:1 ratio [11].

Cumulative incidence curves for liver cirrhosis were estimated using the Kaplan-Meier method. We employed a Cox proportional hazards regression model to determine the hazard ratio (HR) for the incidence of liver cirrhosis. All statistical analyses were based on two-sided hypothesis tests with a significance level of $P < 0.05$ by using SPSS 25.0 (SPSS, Chicago, IL, USA).

Results

Demographic and Clinical Characteristics of Study Population

2138 patients were screened, the reasons for 1519 exclusions and the detailed patient flowchart were shown in Figure 1. The primary study population comprised 252 CHB patients with gallstones and 367 without gallstones in the general model. All participants'clinical characteristics have been shown in Table 1. After PSM, there was no significant between-group difference in the baseline.

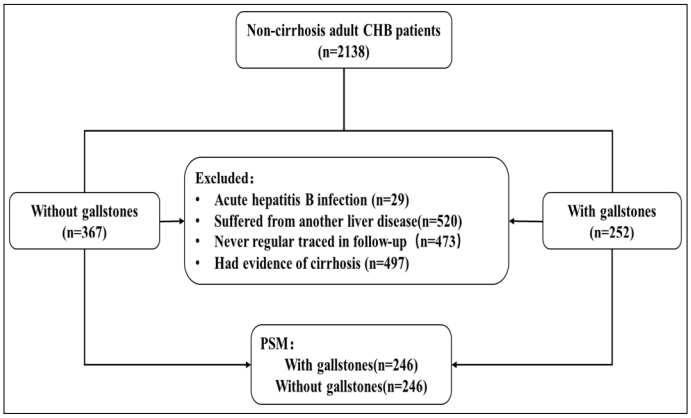


Figure 1: Flowchart Showing Derivation of the Study Population

Table 1: Clinical Characteristics of Participants before and after PSM

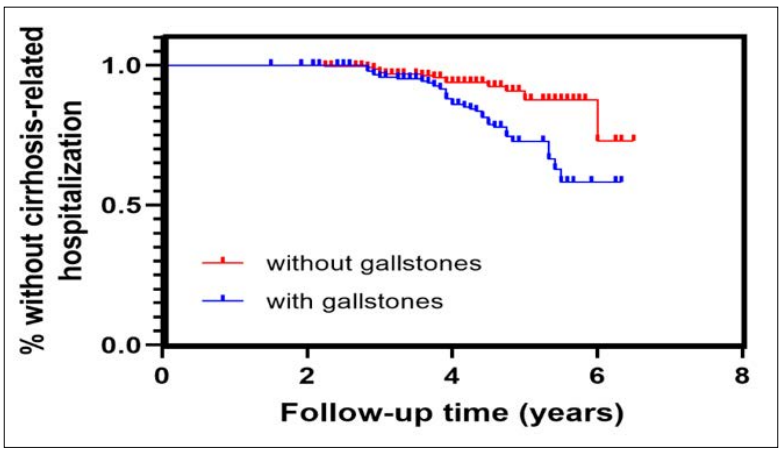
Variables	General model (n=619)			PSM model (n=492)		
	With gallstones (n=252)	Without gallstones (n=367)	p	With gallstones (n=246)	Without gallstones (n=246)	p
Male, n (%)	173 (68.6%)	265 (72.2%)	0.339	168 (68.3%)	178 (72.4%)	0.324
Age, years	47 (40, 55)	46 (38, 53)	0.044	47 (40, 55)	48 (39, 55)	0.931
ALT, U/L	36 (20, 74)	46 (25, 76)	0.043	36 (20, 74)	40 (23, 75)	0.237
AST, U/L	41 (25, 75)	49 (29, 95)	0.005	41 (25, 74)	44 (26, 79)	0.393
TBIL, umol/L	18 (12, 32)	20 (13, 33)	0.302	18 (12, 32)	18 (13, 28)	0.669
ALB, g/L	38 (30, 43)	37 (31, 42)	0.476	38 (31, 43)	38 (31, 42)	0.948
HBeAg-positive	57 (22.6%)	102 (27.8%)	0.148	56 (22.8%)	68 (27.6%)	0.213
HBV DNA≥2000 IU/mL	148 (58.7%)	233 (63.5%)	0.232	145 (58.9%)	150 (61.0%)	0.645
No antiviral medication	148 (58.7%)	210 (57.2%)	0.709	144 (58.5%)	136 (55.3%)	0.466

PSM, propensity score matching; Continuous variables are expressed as the median (25th and 75th percentiles). Categorical variables are displayed as numbers and percentages. ALT, alanine aminotransferase; AST, aspertate aminotransferase; TBIL, total bilirubin; ALB, albumin.

A total of 492 patients were finally analyzed, the median age of the patients was 48 years, 70% were male, 18.2% HBeAg positive rate, 60% of patients were HBV DNA levels above 2000IU/L, the mean ALT was 68 U/L and 56.9% were treat-naïve.

Liver Cirrhosis Incidence for CHB Patients with Gallstones vs. without Gallstones

In this study, 60 (12.2%) participants were hospitalized due to cirrhosis during 3.99 years of mean follow-up, including 45 with gallstones and 15 without gallstones at baseline. The annual cirrhosis incidence rates were 4.46 cases per 100 person-years (95% CI, 3.16-5.77) for CHB patients with gallstone and 1.57 cases per 100 person-years (95% CI, 0.78-2.37) among those without gallstones, respectively, the difference between the two has statistical significance (p= 0.001). In addition, the 5-year estimated cumulative incidence of cirrhosis were significantly higher among CHB patients with gallstones than those without gallstones (16.7% vs. 5.7% p<0.001) (Figure 2).



Groups	Person-years	Events (n)	Incidence per 100 P-Y	5-year incidence (%)	P
Without gallstones	954	15	1.57 (0.78-2.37)	16.7%	<0.001
With gallstones	1008	45	4.46(3.16-5.77)	5.7%	

Figure 2: Cirrhosis Incidence in CHB Patients with Gallstones vs Patients without Gallstones

In univariate analysis, age, HBV DNA levels above 2,000 IU/ml, no antiviral medication and CHB patients with gallstone were risk factors for liver cirrhosis. In the multivariate analysis, CHB patients with gallstones were 2.69 times more likely to develop cirrhosis (95% CI, 1.49-4.84, P= 0.001) than persons without gallstones. In addition, the age (HR 1.06, 95% CI, 1.04-1.09, P<0.001) and HBV DNA levels above 2,000 IU/ml (HR 2.33, 95% CI, 1.11-4.89, P=0.025) were also the risk factors of cirrhosis (Table 2).

Table 2: Factor predictive of liver cirrhosis for CHB patients

Variables	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Male sex	0.633 (0.348-1.153)	0.135	0.742 (0.398-1.385)	0.348
Age, years	1.058 (1.031-1.085)	<0.001	1.062 (1.035-1.090)	<0.001
ALT, U/L	1.002 (1.000-1.005)	0.100	1.001 (0.998-1.005)	0.334
TBIL, umol/L	1.001 (0.997-1.004)	0.731	1.000 (0.996-1.004)	0.995
HBV DNA≥2000 IU/mL	2.570 (1.390-4.752)	0.003	2.333 (1.112-4.894)	0.025
No antiviral medication	1.846 (1.062-3.209)	0.030	1.203 (0.625-2.315)	0.580
With gallstones at baseline	2.494 (1.388-4.481)	0.002	2.685 (1.489-4.840)	0.001

A Cox proportional hazards model with a enter approach was used for multivariable analysis. HR, hazard ratio; CI, confidence interval;

Discussion

Gallstone disease is a widespread common digestive disorder that has comprised 13% to 50% of digestive diseases in the United States and Europe [12]. According to estimates, approximately 4.6% of the Chinese (both adults and elder) population is affected by gallstone [13]. Although multiple previous studies had reported that patients with cirrhosis have a higher incidence of gallstone disease, we aimed to investigate the reverse association, that is, whether CHB patients with gallstones are more likely to develop liver cirrhosis.

Nevertheless, those CHB patients with gallstones were significantly elder compared with those without gallstones at baseline in general model. Previous studies had shown that older age increased the risk of liver cirrhosis [14]. To reduce the effect of confounders between the groups, we employed PSM, and the results showed both the annual rates and the 5-year estimated cumulative incidence of cirrhosis were significantly higher among CHB patients with gallstones versus those without gallstones. Meanwhile, Cox proportional hazards regression model analyses showed that CHB patients with gallstones were 2.69 times more likely to develop cirrhosis than persons without gallstones. The median age of the patients was 48 years in our study, which may accelerate liver cirrhosis development combined with gallstone.

Whether early cholecystectomy is more likely to decline the incidence of cirrhosis? George N et al. found that cholecystectomy is a predictor of the development of cirrhosis because it damages the mechanism of eliminating excess cholesterol formed in the gall bladder, increases intestinal cholesterol reabsorption and the proportion delivered to the liver, and result in benefit cirrhosis development [6]. In our study, patients who underwent cholecystectomy were excluded during follow-up. Therefore, we could not identify the association between cholecystectomy and the incidence of cirrhosis in CHB patients.

This study has several limitations. First, as a single-center study, the findings were potentially subject to selection bias and confounding. Second, this study used clinical and ultrasonic criteria for diagnosing cirrhosis. Thus, there is a possibility that some patients with advanced fibrosis may be included. Third, no data were available on the family history of cirrhosis. Finally, a newly emerging method (transient elastography) in the diagnosis of cirrhosis could not be incorporated because most of our study patients were recruited before the availability of transient elastography.

In conclusion, the present cohort study showed that gallstone disease is a predictor of the development of cirrhosis in patients with CHB; whether early cholecystectomy is associated with cirrhosis remains to be determined.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Xueshan Xia designed the research and supervised the whole process. Min Liu and Jiawei Geng performed study. LiYue Zheng and JinYang Zhang completed data analysis and interpretation. Min Liu wrote initial draft of manuscript. All authors were agreed to publish, and agree to be accountable for all aspects of the work.

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