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# Fatty liver increases gallstone disease risk in younger Chinese patients

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**Abstract**

We investigated possible associations between fatty liver and gallstone disease (GD) in a Chinese population.

This cross-sectional study included 897 people who visited the clinical center and underwent ultrasonography at The First Hospital of Jilin University between January 2018 and June 2018.

The overall prevalence of GD was 8.8%; the between-sex difference (9.3% in men, 8.4% in women) was not statistically significant. The risk of GD was similar for men and women across all age groups. GD prevalence increased steadily with increasing age, from 2.1% in patients ≤30 years of age to 15.4% in those >70 years of age. Older age (≥50 years) and fatty liver were associated with GD development. Diabetes mellitus (adjusted odds ratio [AOR]: 3.066; 95% confidence interval [CI]: 1.563–6.013) was associated with GD in female but not in male subjects. In younger patients (<50 years), fatty liver (AOR: 5.268; 95% CI: 1.832–15.147) was associated with GD development.

The factors older age and fatty liver predicted GD risk in Chinese individuals. Further studies are required to explore differences in lithogenesis according to sex.

**Abbreviations:** ALP = alkaline phosphatase, AOR = adjusted odds ratios, CI = confidence intervals, DM = diabetes mellitus, GD = gallstone disease, GGT = gamma-glutamyl transpeptidase, HBV = hepatitis B virus, HCV = hepatitis C virus, NAFLD = nonalcoholic fatty liver disease.

**Keywords:** fatty liver, gallstones, insulin resistance

## 1. Introduction

Gallstone disease (GD) and its associated complications (eg, cholecystitis, pancreatitis, and cholangitis) have major public health significance worldwide.[1–3] Since 2010, 20% to 30% of adults in developed countries have had a diagnosis of GD. The prevalence of GD has also been increasing in China in recent years.[4] The main risk factors associated with gallstone formation are sex, advanced age, obesity, alcohol consumption, diabetes mellitus (DM), hypertriglyceridemia, and metabolic syndrome.[5,6]

Fatty liver and gallstones have common risk factors (eg, obesity, DM, dyslipidemia, and hyperinsulinemia).[7–9] Patients with gallstones may be susceptible to developing fatty liver as a result of impaired gallbladder motility and increased bile lysogenicity.[10] GD may represent another component of metabolic syndrome, as defined by the National Cholesterol Education Program's Adult Treatment Panel III report.[11–14]

The association between fatty liver and gallstones has been evaluated in populations in the United States, Italy, Pakistan, Korea, and Taiwan.[15–17,4,18,9,19] No association has been found between fatty liver and GD in US or Korean populations.[15,9] Fatty liver is associated with increased gallstone risk in Pakistani and Taiwanese individuals.[16,20,19] Few studies have investigated whether fatty liver is associated with the risk of gallstone development in a Chinese population.[21,22]

The objective of this study was to identify risk factors for gallstone development and the association between fatty liver and GD in Chinese patients. Adjustment for age and gender was included in the analysis.

## 2. Patients and methods

### 2.1. Sample collection

This cross-sectional study included subjects who visited the clinical center and underwent ultrasonography at The First Hospital of Jilin University between January 2018 and June 2018. All methods were performed in accordance with approved guidelines.

The independent Institutional Review Board of The First Hospital of Jilin University approved the study protocol and the recruitment of human participants. Written informed consent was obtained from each participant before enrollment in the study.

### 2.2. Diagnosis of gallbladder disease and fatty liver

A confirmed GD diagnosis was defined as ultrasonographic detection of an echogenic area within the gallbladder lumen that produced a posterior acoustic shadow[23] or a history of cholecystectomy for GD, or both.

Fatty liver was diagnosed by first excluding other etiologies of chronic liver disease (eg, positive for hepatitis C virus antibody or hepatitis B antigen, autoimmune hepatitis). Abdominal ultraso-

Editor: Lei Huang.

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Medicine (2019) 98:22(e15940)

Received: 8 January 2019 / Received in final form: 18 April 2019 / Accepted: 13 May 2019

http://dx.doi.org/10.1097/MD.0000000000015940

**Table 1**

**Demographic and clinical characteristics of cases and controls.**

| Variable | No gallstones (N = 818) | Gallstones (N = 79) | *P* value |
|---|---|---|---|
| Male, N (%) | 340 (41.6) | 35 (44.3) | .637 |
| Age, yr | 53.0 (42.0, 63.0) | 59.0 (50.0, 67.0) | <.001 |
| GGT, IU/L | 26.6 (17.7, 48.1) | 32.5 (21.9, 62.7) | .019 |
| ALP, IU/L | 74.5 (59.7, 93.1) | 80.0 (67.5, 99.1) | .017 |
| Excessive alcohol consumption, N (%) | 15 (1.8) | 0 (0.0) | .225 |
| Diabetes, N (%) | 147 (18.0) | 24 (30.4) | .007 |
| Hypertension, N (%) | 189 (23.1) | 27 (34.2) | .028 |
| Fatty liver, N (%) | 324 (39.6) | 43 (54.4) | .011 |

Results for continuous variables are expressed as median (25th, 75th percentiles) values. Results for categorical variables are presented as numbers and percentage values.
ALP = alkaline phosphatase, GGT = glutamyl transpeptidase.

nographic evidence of brightness of the liver and of the presence of diffuse echogenicity in the liver parenchyma was then used to identify fatty liver.[24]

### 2.3. Diagnosis of DM

A diagnosis of DM was defined as a history of diabetes treated using an antidiabetic therapy, or the presence of at least one of the following:

(1) fasting glucose concentration ≥7.0 mmol/L,
(2) randomly-measured glucose concentration ≥11.1 mmol/L, or
(3) 2-hour postprandial plasma glucose concentration ≥11.1 mmol/L.[25]

### 2.4. Study variables

Demographic (ie, sex, age) and clinical presentation variables (ie, history of excessive alcohol consumption, the presence of DM, fatty liver, or hypertension) were evaluated in this study. Biochemical parameters (ie, glutamyl transpeptidase [GGT] and alkaline phosphatase [ALP]) were also analyzed and abdominal ultrasonography results were reviewed to detect the presence of gallstones or fatty liver.

### 2.5. Statistical analysis

Two-tailed, independent sample *t* tests and Chi-square analyses were used to evaluate continuous and categorical variables, respectively. The results for continuous variables were presented as median (25th and 75th percentile) values. The results for categorical variables were presented as numbers and percentages. Multivariate logistic regression analysis was used to adjust for potential confounding effects among variables. The results were reported as adjusted odds ratios (AORs) and 95% confidence intervals (CIs). *P* values < .05 were considered to indicate statistically significant results. SPSS software (version 13.0; SPSS Inc, Chicago, IL) was used for the data analysis.

## 3. Results

### 3.1. Demographic and clinical characteristics

The results for baseline demographic and clinical characteristics of the study population (N = 897) are presented in Table 1. The case group consisted of 79 patients with gallstones. There were 35 (44.3%) male and 44 female patients in this group. The median age was 59.0 years. In this group, 24 (30.4%) patients had DM, 27 (34.2%) had hypertension, and 43 (54.4%) had fatty liver. There were 818 patients in the control group (ie, patients without gallstones). The median age of this group was 53.0 years ($P < .001$ vs the case group); 41.6% were male. A total of 147 (18.0%) patients in this group had DM, 189 (23.1%) had hypertension, and 324 (39.6%) had fatty liver. Compared with the case group, the percentages for all 3 diseases were significantly lower in the control group. GGT and ALP levels were significantly higher in the case group compared with the control group.

The results for the analysis of GD prevalence rates in different age groups, according to sex, are presented in Table 2. The overall prevalence of GD was 8.8% and was similar in men and women (9.3% vs 8.4%, $P = .637$). For the entire study population, the rate of GD increased with age. It was 2.1% for the ≤30 years group and 15.4% for the >70 years group (Fig. 1). This trend was present in both sexes. Prevalence was 2.3% in the group of men ≤30 years of age and increased to 15.1% in the group of men >70 years of age. It was 2.0% in the group of women ≤30 years of age and increased to 15.7% in the group of women >70 years of age.

### 3.2. Univariate and multivariate analyses of variables associated with the presence of gallstones

The univariate analysis revealed statistically significant differences between the case and control groups for the distributions for age, DM, fatty liver, and hypertension (Table 3). Sex, age, excessive alcohol consumption, and the presence of DM, fatty liver, or hypertension were thus considered for multivariate analysis. The AOR for the comparison between the group of patients without fatty liver and the group of patients with fatty liver was 1.714 (95% CI: 1.074–2.736; $P = .024$) (Table 3). The AOR for the group of patients ≥50 years of age, compared with

**Table 2**

**Prevalence of gallstone disease in different age groups, by sex.**

| Age, yr | Males (N [%]) | Females (N [%]) | *P* value |
|---|---|---|---|
| ≤30 | 1 (2.3) | 1 (2.0) | .916 |
| 31–40 | 4 (9.1) | 4 (6.5) | .612 |
| 41–50 | 4 (7.0) | 7 (6.0) | .803 |
| 51–60 | 11 (12.5) | 9 (7.1) | .179 |
| 61–70 | 7 (7.9) | 15 (13.0) | .237 |
| >70 | 8 (15.1) | 8 (15.7) | .933 |
| Overall | 35 (9.3) | 44 (8.4) | .637 |

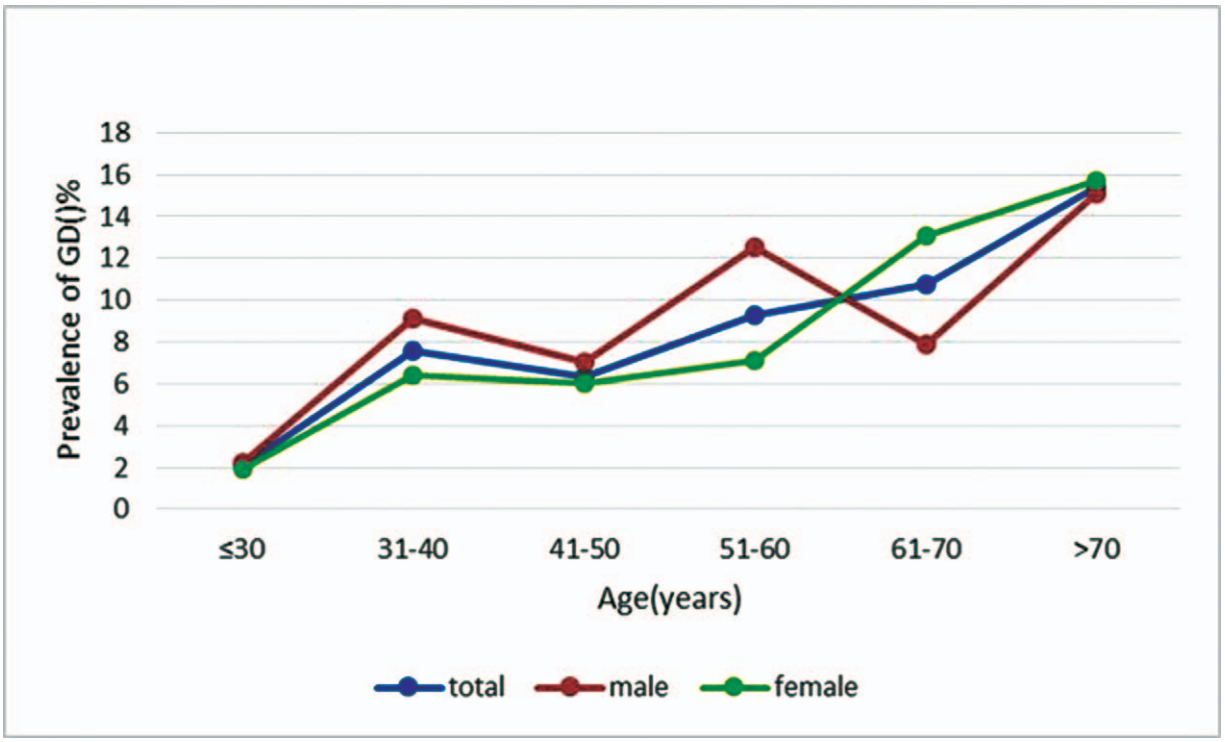


**Figure 1.** Gallstone prevalence for the entire population, and by sex. For all participants, the rate of GD increased with age, from 2.1% for those ≤30 yr to 15.4% for those >70 yr. This trend was observed in both sexes; prevalence increased from 2.3% in men ≤30 yr to 15.1% in men >70 yr and from 2.0% in women ≤30 yr to 15.7% in women >70 yr. GD = gallstone disease.

younger patients (<50 years), was 2.070 (95% CI: 1.209–3.541; $P = .008$). Sex, excessive alcohol consumption, hypertension, and DM were not significantly associated with gallstone formation.

### *3.3. Effects of sex and age on risk factors associated with the presence of gallstones*

The sex-adjusted logistic regression analysis found that older age (AOR: 2.476, 95% CI: 1.051–5.832) was associated with GD in

**Table 3**

**Results for univariate and multivariate analyses of variables associated with gallstone disease.**

| Variable | No gallstones (N = 818) | Gallstones (N = 79) | *P* value* | AOR (95% CI)† | *P* value‡ |
|---|---|---|---|---|---|
| Sex | | | .637 | – | – |
| Female, N (%) | 478 (58.4) | 44 (55.7) | | | |
| Male, N (%) | 340 (41.6) | 35 (44.3) | | | |
| Age | | | .004 | 2.070 (1.209–3.542) | .008 |
| <50 years, N (%) | 334 (40.8) | 19 (24.1) | | | |
| ≥50 yr, N (%) | 484 (59.2) | 60 (75.9) | | | |
| Excessive alcohol consumption | | | .225 | – | – |
| <20 g/d, N (%) | 803 (98.2) | 79 (100.0) | | | |
| ≥20 g/d, N (%) | 15 (1.8) | 0 (0.0) | | | |
| Diabetes mellitus | | | .007 | – | – |
| No, N (%) | 671 (82.0) | 55 (69.6) | | | |
| Yes, N (%) | 147 (18.0) | 24 (30.4) | | | |
| Fatty liver | | | .011 | 1.714 (1.074–2.736) | .024 |
| No, N (%) | 494 (60.4) | 36 (45.6) | | | |
| Yes, N (%) | 324 (39.6) | 43 (54.4) | | | |
| Hypertension | | | .028 | – | – |
| No, N (%) | 629 (76.9) | 52 (65.8) | | | |
| Yes, N (%) | 189 (23.1) | 27 (34.2) | | | |

AOR = adjusted odds ratio, CI = confidence interval.

* *P* value for univariate analysis.

† Adjusted for sex, age, diabetes mellitus, excessive alcohol consumption, fatty liver, and hypertension.

‡ *P* value for multivariate analysis.

**Table 4**

**Risk factors for gallbladder disease in males and females.**

| Variable | Males | | Females | |
|---|---|---|---|---|
| | AOR (95% CI)* | *P* value† | AOR (95% CI)* | *P* value† |
| Age | | .038 | – | – |
| <50 yr, N (%) | 1 | | | |
| ≥50 yr, N (%) | 2.476 (1.051–5.832) | | | |
| Diabetes mellitus | – | – | | .001 |
| No, N (%) | | | 1 | |
| Yes, N (%) | | | 3.066 (1.563–6.013) | |

AOR = adjusted odds ratio, CI = confidence interval.

* Adjusted for age, diabetes mellitus, excessive alcohol consumption, fatty liver, and hypertension.

† *P* value for multivariate analysis.

men. The clinical characteristics DM, fatty liver, and hypertension were not associated with GD in males. In females, DM was significantly associated with the risk of gallstone development (AOR: 3.066, 95% CI: 1.563–6.013) (Table 4). Age, excessive alcohol consumption, fatty liver, and hypertension were not significantly associated with gallstone formation in females.

The results for the analysis of associations between gallstone risk and sex, DM, excessive alcohol consumption, fatty liver, and hypertension in patients of different ages are presented in Table 5. In younger patients (<50 years), the AOR for developing GD was 5.268 (95% CI: 1.832–15.147; $P = .002$) in patients with fatty liver, compared with patients without fatty liver. The association between fatty liver and gallstone formation in patients ≥50 years of age was not statistically significant. Sex, DM, excessive alcohol consumption, and hypertension were not associated with GD in younger or older subjects.

## 4. Discussion

We found that Chinese people with gallstones were more likely to have a fatty liver; this association occurred mainly in patients <50 years of age. This finding is consistent with the findings of other studies.[26,7–9,22] Lee et al[20] assessed the relationship between GD and severity of fatty liver. They found that moderate to severe nonalcoholic fatty liver disease (NAFLD) is associated with an elevated risk of GD. In a prospective observational study, Qiao et al[22] found that gallstones were strongly associated with NAFLD in a Chinese population. However, other studies found no statistically significant associations between NAFLD and GD.[27–29] The discrepant results between studies may be due to differences between study populations, such as differences in income or eating habits.[22]

The results of previous studies suggest there is an association between GD and fatty liver.[8,30,31] The risk of both disorders is especially high in patients with obesity, hyperlipidemia, type 2 DM, and hypertension.[7,32,33] Therefore, this association may reflect that gallstones and fatty liver are caused by common pathogenic factors. Obesity, hyperlipidemia, type 2 DM, and hypertension are all components of metabolic syndrome, and the presence of fatty liver significantly increases the risk of development of metabolic syndrome.[34–36] After we adjusted for metabolic factors, the association between fatty liver and GD remained statistically significant.

Insulin resistance may contribute to the association between fatty liver and GD.[37,38] Sekine et al[39] found that accumulation of abdominal visceral fat has an important role in the development of GD, and that visceral adiposity can promote insulin resistance and hyperinsulinemia. Hyperinsulinemia reduces the gallbladder's response to cholecystokinin, the hormone responsible for effective gallbladder contraction.[39] Therefore, fatty liver may lead to the formation of gallstones through gallbladder dysmotility induced by insulin resistance and high insulin levels. Insulin resistance also promotes gallstone formation via activation of hydroxymethylglutaryl CoA reductase. This enzyme increases bile secretion and cholesterol content.[40] Insulin resistance stimulates the lipolysis in adipose tissue and influx of free fatty acids into the liver that potentially aggravates hepatic insulin resistance. Thus, systemic and hepatic insulin resistance are interrelated. An animal model found that hepatic insulin resistance increased bile cholesterol secretion by stimulating the expression of biliary cholesterol transporter proteins, reduced bile acid synthesis by suppressing bile acid synthetic enzymes, and impaired gallbladder motility.[41]

In Taiwan, a community-based study examined associations between GD and hyperinsulinemia, insulin resistance, and pancreatic beta-cell function in subjects with type 2 DM.[42] Compared with females without GD, females with GD had significantly higher serum insulin and HOMA–insulin resistance values, and worse beta-cell function.[42] None of these 3 variables differed between males with or without GD.[42] Our study also found that females with DM have a 3-fold higher likelihood of gallstones than females without DM, but there was no similar association for males. Taken together, these results suggest that there are sex-based differences in lithogenesis that may be related to the effects of estrogen on glucose metabolism in females.[4,22] More research to investigate this hypothesis and the underlying molecular mechanisms.

We found that older age was a significant risk factor for GD; this result is consistent with the results of previous studies.[43,44] The prevalence of gallstones and fatty liver increases with age.[7,4] The possible explanations for the higher prevalence of GD with increasing age include that the prevalence of metabolic syndrome rises with increasing age, and the risk of GD is associated with metabolic syndrome.[45] Another possibility is that older people are often exposed to sedentary lifestyles and other risk factors for GD for longer periods than younger individuals. These exposures may increase the risk of gallstone development.[46,47] GD is a chronic disorder, so prevalence increases as age increases.[48]

This study had some limitations. The retrospective design prevented us from obtaining detailed information about triglyceride and cholesterol levels or the results of other investigations useful for exploring associations between metabolic factors and GD. The case and control subjects were selected from patients seeking medical care at our hospital, which permitted us to obtain a sufficient number of subjects. However, this study population did not necessarily reflect the general

**Table 5**

**Logistic regression analysis, adjusted odds of gallbladder disease in different age groups.**

| Variable | Age ≥50 years | | Age <50 years | |
|---|---|---|---|---|
| | AOR (95% CI)* | *P* value† | AOR (95% CI)* | *P* value† |
| Fatty liver | – | – | | .001 |
| No, N (%) | | | 1 | |
| Yes, N (%) | | | 5.780 (2.030–16.458) | |

* Adjusted for sex, diabetes mellitus, excessive alcohol consumption, fatty liver, and hypertension.

† *P* value for multivariate analysis.

Chinese population (eg, incidence of fatty liver in both case group and control group are higher than in general Chinese population). We also did not examine the type of GD or fatty liver (eg, nonalcoholic vs alcoholic fatty liver disease). Consequently, we were unable to examine risk factors for the different types of GD or the effect of alcohol on the development of GD.

In conclusion, we found that fatty liver was an independent risk factor for the presence of gallstones in our study population of Chinese patients, particularly for the group of subjects <50 years of age. Future studies that examine the relationships between metabolic factors and the risk of developing GD should include adjustment for sex.

## Author contributions

**Conceptualization:** Pujun Gao.
**Data curation:** Xu Li, Pujun Gao.
**Formal analysis:** Xu Li.
**Investigation:** Xu Li.
**Project administration:** Xu Li, Pujun Gao.
**Writing – original draft:** Xu Li.
**Writing – review and editing:** Pujun Gao.

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