

# Relationship Between Gallstone Disease and Cardiometabolic Risk Factors in Elderly People with Non-Alcoholic Fatty Liver Disease

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Man-Chen Hung <sup>1</sup>  
Chuen-Fei Chen<sup>1</sup>  
Meng-Ting Tsou <sup>2</sup>  
Hsin-Hui Lin <sup>2</sup>  
Lee-Ching Hwang <sup>1,2</sup>  
Ching-Ping Hsu<sup>2</sup>

<sup>1</sup>Department of Medicine, Mackay Medical College, New Taipei City, Taiwan;  
<sup>2</sup>Department of Family Medicine, Mackay Memorial Hospital, Taipei, Taiwan

**Background:** The prevalence of gallstone disease (GSD) increases with age, and the elderly have a much higher mortality risk and incidence of surgical comorbidities. The aim of this study was to explore the relationship between GSD and cardiometabolic risk factors in elderly people with non-alcoholic fatty liver disease (NAFLD).

**Methods:** In this cross-sectional study, we analyzed the data of elderly people who underwent annual health check-ups at a Northern Taiwan health examination center. These data were collected from physical examination, blood tests, abdominal ultrasonography, and medical histories. We excluded those with hepatitis B or C infections, heavy alcohol consumption, or cholecystectomy.

**Results:** The analysis included 3,037 participants with a mean age of 73.6±6.0 years. Over 70% were overweight or obese, and the overall prevalence of GSD was 17.7%. In our univariate analysis, GSD was positively correlated with age, body mass index, metabolic syndrome, diabetes mellitus (DM), hypertension (HTN), and various metabolic factors (fasting plasma glucose [FPG], triglyceride, uric acid, and high-density lipoprotein cholesterol [HDL-C] levels). After adjustment for age, gender, and body mass index, metabolic syndrome showed a positive association with GSD (odds ratio [OR] 1.31 [95% confidence interval [CI], 1.05–1.64];  $P=0.020$ ). Specific components of metabolic syndrome that increased the risk for GSD in NAFLD elderly include lower levels of HDL-C (OR 1.35 [95% CI, 1.10–1.66];  $P<0.001$ ) and elevated FPG (OR 1.36 [95% CI, 1.10–1.69];  $P<0.001$ ).

**Conclusion:** Our study concluded that GSD is significantly associated with metabolic syndrome in elderly people with NAFLD. Reduced HDL-C and elevated FPG both heighten the risk of developing GSD. Therefore, to lower the risk of GSD in NAFLD patients, their FPG levels and HDL-C levels must be regularly followed-up, and these patients should be educated about the symptoms of GSD if they meet the criteria for metabolic syndrome.

**Keywords:** gallstone disease, cardiometabolic risk factors, metabolic syndrome

## Introduction

The prevalence of gallstone disease (GSD) in Taiwan varies from 4.3% to 10.7% and rapidly increases in individuals aged over 40 years.<sup>1–5</sup> Although GSD is asymptomatic in two-thirds of cases, the medical burden related to GSD should not be neglected. Previous studies suggested that the cumulative probability of developing biliary colic among asymptomatic patients after 10 years ranges between 15% and 25%, and the mortality rate increases once severe complications occur.<sup>6,7</sup>

Correspondence: Ching-Ping Hsu  
Department of Family Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Road, Zhongshan District, Taipei City 104, Taiwan  
Tel +886-2-25433535  
Fax +886-2-25213847  
Email drhsuinfo@gmail.com

Taiwan is predicted to become a super-aged society in 2026. Older patients with GSD are expected to require surgical treatment for GSD-related conditions.<sup>8,9</sup> In addition, elderly patients had a higher risk of mortality after a cholecystectomy and a higher incidence of peri-operative complications than younger ones.<sup>9–11</sup>

Previous studies demonstrated that GSD is strongly associated with female gender, advanced age, race, obesity, hyperlipidemia, alcohol consumption, liver cirrhosis, diabetes mellitus (DM), and metabolic syndrome (MetS).<sup>1,4,12–16</sup> In particular, obesity, hyperlipidemia, DM, and MetS are notorious cardiometabolic risk factors. The risk factors of non-alcoholic fatty liver disease (NAFLD) and GSD are highly overlapped but the sequential relationship of NAFLD and GSD remains controversial.<sup>17</sup> As predisposing factors are metabolic abnormalities, NAFLD is also regarded as the liver manifestation of the metabolic syndrome.<sup>18–20</sup>

NAFLD in the elderly is more severe and carries worse prognosis and more comorbidities such as cirrhosis and hepatocellular carcinoma than younger age groups.<sup>21</sup> Age-related alterations in hepatic cholesterol homeostasis cannot be defined yet; however, some studies support that a decline of liver function by aging may result in abnormal cholesterol metabolism, including a decrease in low-density lipoprotein cholesterol (LDL-C) turnover and an increase in biliary cholesterol output. This is possibly associated with a reduction in cholesterol degradation to bile acid which creates a suitable environment for cholesterol gallstone to generate.<sup>22</sup>

It is expected that Taiwan will become a super-aged society in 2026 and the increase in geriatric population raises concern for even more NAFLD elderly at risk for MetS and GSD. Therefore, our current study aims to explore the relationship between GSD and cardiometabolic risk factors in this high-risk population.

## Materials and Methods

### Study Population

This study examined 3,233 people aged  $\geq 65$  who underwent annual health checkups at a health examination center in Northern Taiwan. Fatty liver was diagnosed by abdominal ultrasound. We collected data including physical examination, blood tests, abdominal ultrasonography, health-related behavior, and medical histories. After we excluded those who had a history of hepatitis B or C infection, consumed alcohol regularly, or had received

a cholecystectomy, the final sample for analyses consisted of 3,037 elderly people.

### Study Design and Variables

This cross-sectional study collected data regarding age, sex, height, weight, waist circumference, body mass index (BMI), blood pressure, and medical history of DM and hypertension (HTN). Blood biochemical data included fasting plasma glucose (FPG), lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, and triglyceride), uric acid, and liver function tests (aspartate transaminase [AST] and alanine transaminase [ALT]).

### Diagnostic Criteria

According to the Taiwan National Health Department, those who met at least three of the following criteria were considered to have MetS: 1) abdominal obesity (waist circumference  $\geq 90$  cm in men and  $\geq 80$  cm in women); 2) elevated triglyceride levels ( $\geq 150$  mg/dL); 3) reduced serum HDL-C levels ( $< 40$  mg/dL in men and  $< 50$  mg/dL in women); 4) elevated blood pressure (systolic blood pressure  $\geq 130$  mmHg, diastolic blood pressure  $\geq 85$  mmHg, or a history of HTN based on self-reports or medical records); and 5) elevated FPG levels ( $\geq 100$  mg/dL) or a history of DM (based on self-reports or medical records).

Although the gold standard for the diagnosis of NAFLD is percutaneous liver biopsy, our study chose to use abdominal sonography as the diagnostic method for the following reasons. First, there are certain complications of liver biopsy, including haemorrhage and pneumothorax.<sup>23</sup> Second, none of our subjects met the indications for a biopsy, which includes 1) to diagnose patients a high risk for nonalcoholic steatohepatitis (NASH) or advanced fibrosis; 2) to determine the extent of liver damage for treatment and prognosis.<sup>24,25</sup> Lastly, using sonography as the first imaging procedure by a well-trained gastrologist is a reliable way for diagnosing fatty liver.<sup>26</sup>

Diagnosis of NAFLD by ultrasonography was according to the following criteria: 1) increased echogenicity of liver parenchyma in contrast to the kidney; 2) decreased clarity of the borders of intrahepatic vessels; and 3) decreased penetration of ultrasound signal and visibility of the diaphragm.<sup>26</sup>

GSD was diagnosed based on at least one of the following criteria: 1) visible gallbladder lumen presenting one or more echogenic movable structures with an

acoustic shadow. 2) non-visualization of the gallbladder lumen and high-density echogenic material with acoustic shadow in the gallbladder fossa.<sup>27,28</sup>

## Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 software (IBM Corp.). The participants were classified into two groups based on the presence or absence of GSD. Continuous variables are expressed as means with standard deviations while categorical variables are expressed in the form of frequencies and percentages.

The two groups were compared using the Student's *t*-test (continuous variables) and the  $\chi^2$  test (categorical variables). Variables in the univariate analyses that showed significant association with GSD were included in a binary logistic regression model. In model 1, we controlled potential confounders including age, gender, BMI, DM, and HTN to compare if MetS increased the risk of GSD. In model 2, we added the five components of MetS to determine the specific factors associated with risk of GSD. The odds ratios (ORs) and 95% confidence intervals (CIs) were presented, and any *P*-value <0.05 was considered statistically significant.

## Results

The final sample for analyses included 3,037 eligible participants, including 886 (29.2%) men and 2,151 (70.8%) women, with a mean age of 73.6±6.0 years. The overall prevalence of participants with GSD was 17.7% (18.4% in men vs 17.4% in women).

Over 70% of all participants were either overweight or obese (40.7% having a BMI of 24.0–26.9 kg/m<sup>2</sup> and 32.4% having a BMI ≥27 kg/m<sup>2</sup>) with a mean FPG of 110.3±23.7 mg/dL. Participants with MetS, DM, and HTN accounted for 63.2%, 18.2%, and 56.9% of the total population, respectively.

The differences in age, gender, and individual metabolic components between the GSD and non-GSD groups are shown in Table 1. Compared to the non-GSD group, the GSD group were of older age, had a higher BMI, and a larger waist circumference. In addition, they had a higher prevalence of MetS, DM, and HTN (*P*<0.05). In respect to the metabolic parameters, the GSD group had higher levels of FPG, triglyceride, uric acid, but lower levels of HDL-C than the non-GSD group (*P*<0.05).

The binary logistic regression models in Table 2 show the associations between clinical factors and the risk of

GSD. After adjustment for age, gender, and BMI, MetS was positively associated with GSD (OR 1.31 [95% CI, 1.05–1.64]; *P*=0.02). Among the components of MetS, reduced HDL-C (OR 1.35 [95% CI, 1.10–1.66]; *P*<0.001) and elevated FPG (OR 1.36 [95% CI, 1.10–1.69]; *P*<0.001) were associated with a higher risk for GBD.

## Discussion

Gallstones can be distinguished into cholesterol stone, black pigment stones, and brown pigment stones.<sup>29</sup> Cholesterol stones result from supersaturated cholesterol in the bile, which associated with abnormal cholesterol metabolism. On the other hand, black pigment stones form in sterile bile and are primarily related to chronic hemolysis or cirrhosis while brown pigment stones are relevant to bacterial infection.<sup>30,31</sup>

One Taiwanese study revealed that the percentage of cholesterol and pigment stones had been roughly 40% and 60%, respectively.<sup>32</sup> Due to the improvement of living standards and Westernization of diet, the proportion of cholesterol stones is increasing. Metabolic risk factors are considered determinants of cholesterol gallstone formation.

## GSD and Sex

In our study, prevalence of GSD in elderly men with NAFLD was 18.4%, compared to 17.4% in their female counterparts, indicating no significant association between GSD and sex. However, the role of sex in the development of GSD is inconsistent across studies. Unlike studies in Asian countries, most of those conducted in Western countries showed that female sex is a risk factor for GSD.<sup>4,5,33</sup> Besides, the composition of gallstones varies across races. Cholesterol gallstones are more prevalent in Western populations (70~80%) while pigment gallstones, which are related to bacterial infection, liver disease, or other medical conditions, are predominant in Asian populations.<sup>34,35</sup> Female sex is reported to be highly associated with GSD in Western studies possibly because estrogen increases the concentration of cholesterol in bile, leading to the formation of cholesterol gallstones.<sup>36,37</sup> Like some Taiwanese studies, our study demonstrated that sex distribution was not an influential factor for GSD development in Taiwanese people.<sup>1,16</sup> Some studies suggest that GSD was closely associated with the use of oral contraceptives but not with female sex, which indicates that estrogen may be

**Table 1** Elderly People's Demographic Characteristics, Biochemical Variables and Metabolic Components, by the Presence of Gallstone Disease

Characteristics	Total n=3,037	Presence of Gallstone Disease		p-value <sup>a</sup>
		No n=2,500 (82.3%)	Yes n=537 (17.7%)	
Sex				0.507
Male	886 (29.2%)	723 (28.9%)	163 (30.4%)	
Female	2,151 (70.8%)	1,777 (71.1%)	374 (69.6%)	
Age (years)	73.6±6.0	73.4±6.0	74.5±6.0	<0.001
BMI <sup>b</sup> (kg/m <sup>2</sup> )	26.0±3.1	25.8±3.1	26.7±3.2	<0.001
18.5-<24	817 (26.9%)	716 (28.6%)	101 (18.8%)	<0.001
24-<27	1,235 (40.7%)	1,002 (40.1%)	233 (43.4%)	<0.001
≥ 27	985 (32.4%)	782 (31.3%)	203 (37.8%)	<0.001
NAFLD <sup>c</sup>				0.077
Mild	2,309 (76.0%)	1,921 (76.8%)	388 (72.3%)	
Moderate	649 (21.4%)	516 (20.6%)	133 (24.8%)	
Severe	79 (2.6%)	63 (2.5%)	16 (3.0%)	
MetS <sup>d</sup>	1,920 (63.2%)	1,535 (61.4%)	385 (71.4%)	<0.001
Elevated blood pressure <sup>e</sup>	2,522 (83.0%)	2,065 (82.6%)	457 (85.1%)	0.161
Fasting Plasma Glucose >100 mg/dL	1,989 (65.5%)	1,598 (63.9%)	391 (72.8%)	<0.001
Triglyceride >150 mg/dL	1,363 (44.9%)	1,094 (43.8%)	269 (50.1%)	0.007
Reduced HDL-C <sup>f</sup>	851 (28.0%)	667 (26.7%)	184 (34.3%)	<0.001
Abdominal obesity <sup>g</sup>	2,056 (67.7%)	1,673 (66.9%)	383 (71.3%)	0.048
Diabetes mellitus	554 (18.2%)	422 (16.9%)	132 (24.6%)	<0.001
Hypertension	1,727 (56.9%)	1,400 (56.0%)	327 (60.9%)	0.038
Fasting Plasma Glucose (mg/dL)	110.3±23.7	109.8±23.9	112.9±22.5	0.006
Triglyceride (mg/dL)	125.4±62.6	124.0±62.8	132.2±61.4	0.006
HDL <sup>h</sup> (mg/dL)	55.0±14.1	55.5±14.2	52.7±13.7	<0.001
Waist circumference (cm)	87±8.9	86.7±8.8	88.7±9	<0.001

**Notes:** Data are presented as numbers and percentages, or mean values and standard deviations. <sup>a</sup>The Student's *t*-test was used to analyze continuous variables while the  $\chi^2$  test was applied for categorical variables. <sup>b</sup>BMI, body mass index. <sup>c</sup>NAFLD, non-alcoholic fatty liver disease. <sup>d</sup>MetS, metabolic syndrome. <sup>e</sup>Elevated blood pressure is defined when a patient has a systolic blood pressure  $\geq 130$  mmHg, or a diastolic blood pressure  $\geq 85$  mmHg, or a history of hypertension (according to the patient's self-report or medical record). <sup>f</sup>A reduced HDL-C (High-density lipoprotein cholesterol) level is defined as a serum HDL-C level <40 mg/dL in men and <50 mg/dL in women. <sup>g</sup>Abdominal obesity is defined as a waist circumference  $\geq 90$  cm in men and in  $\geq 80$  cm women. <sup>h</sup>HDL, high-density lipoprotein.

**Table 2** Binary Logistic Regression Models for Predicting Factors Associated with the Development of Gallstone Disease

Model I <sup>i</sup>	OR <sup>j</sup>	95% CI <sup>k</sup>	p-value
MetS <sup>l</sup>	1.31	1.05–1.64	0.02
Model 2 <sup>m</sup>			
Elevated blood pressure	0.97	0.74–1.27	0.82
Fasting Plasma Glucose >100 mg/dL	1.36	1.10–1.69	<0.001
Triglyceride >150 mg/dL	1.17	0.96–1.42	0.11
Reduced HDL-C <sup>n</sup>	1.35	1.09–1.66	<0.001
Abdominal obesity	0.86	0.67–1.10	0.23

**Notes:** <sup>i</sup>Model 1 was adjusted for age, sex, BMI and the presence of hypertension and diabetes; <sup>j</sup>OR, odds ratios; <sup>k</sup>CI, confidence interval; <sup>l</sup>MetS, metabolic syndrome; <sup>n</sup>HDL-C, High-density lipoprotein cholesterol; <sup>m</sup>Model 2 was adjusted for age, sex, and BMI.

more predominant than sex alone.<sup>16</sup> However, as our study only focused on elderly participants with NAFLD, this hormone played a relatively minor role in their metabolic systems. Thus, sex distribution was not a crucial contributor to the development of GSD in our study population.

## GSD and Cardiometabolic Risk Factors

Cardiometabolic risk factors consist of obesity, insulin resistance, and hyperlipidemia. The relationship between GSD with these risk factors will be explained separately in the following paragraphs.

## Obesity

The overall GSD prevalence in the elderly people with NAFLD in our current study was 17.7%, higher than that in other Asian studies (3–15%).<sup>38</sup> This high prevalence may result from the characteristics of our study participants aged  $\geq 65$  years who were also diagnosed with NAFLD.<sup>1,16</sup> Besides, obesity is characteristic of our study population because over 70% of the elderly people in our study were overweight or obese (40.7% and 32.4% having a BMI of 24.0–26.9 kg/m<sup>2</sup> and  $\geq 27$  kg/m<sup>2</sup>, respectively). Obesity is an important risk factor for GSD possibly attributed to hepatic lipid accumulation, leading to the dysfunction of gallbladder contraction.<sup>19,28,39,40</sup>

## Insulin Resistance

One pathophysiological hypothesis of metabolic syndrome is insulin resistance.<sup>41</sup> Some studies supported that an increase in insulin concentration was associated with an increased relative risk of developing GSD.<sup>42</sup>

The mechanism is that hyperinsulinemia stimulates the activity of hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and increases bile cholesterol saturation.<sup>34,39,43</sup> In addition, according to an animal study, hepatic insulin resistance markedly prompted cholesterol gallstone formation. This may result from the changes in specific transcription factors that cause biliary cholesterol secretion and bile acid reduction.<sup>44</sup> On the other hand, in the elderly, decreased liver function and blood perfusion result in abnormal cholesterol metabolism. Moreover, dyslipidemia is another precipitating factor for gallstone generation.<sup>21</sup>

Our study showed that in elderly people with NAFLD, reduced serum HDL-C levels and elevated FPG levels ( $\geq 100$  mg/dL) increased the risk of GSD by 35% and 36%, respectively. Hyperglycemia has been recognized as an important risk factor for GSD, which is possibly attributed to insulin resistance.<sup>34,43</sup> These results were consistent with some previous studies.<sup>39</sup>

## Hyperlipidemia

High triglycerides and low HDL-C have strong association with GSD.<sup>45,46</sup> Hyperlipidemia results in supersaturated cholesterol in bile, which may stimulate the formation of gallstones. For NAFLD patients, both serum and hepatic cholesterol levels are higher. Thus, HDL-C, which enhances cholesterol excretion, may play a decisive role for the development of GSD in this high-risk group.

## Limitations

Our study had several limitations that need to be addressed in the future research. First, the participants in our study lived in the urban area of the capital city of Taiwan, affecting the generalization of the study results to other areas nationwide. Furthermore, because this is a cross-sectional study, we did not document their current medication when conducting elderly annual health check-ups. As a result, subjects taking lipid-lowering drugs and medications for the treatment of cardiovascular diseases may interfere with the result for patient selection. Last but not the least, due to the lack of data on the continuous change in GSD, we could not further clarify the role of MetS in the development of GSD. However, to our best knowledge, this study is the first to elaborate the relationship between MetS and GSD in elderly NAFLD patients.

## Conclusion

Our study concluded that GSD is significantly associated with MetS in elderly patients with NAFLD. In this population, reduced HDL-C and elevated FPG levels increased the risk of developing GSD. Therefore, to lower the risk of GSD in these patients, their FPG levels and HDL-C levels must be regularly followed-up. If they meet the criteria for MetS, patient education about symptoms of GSD is essential, and possible treatment options for GSD-related conditions should also be discussed in advance with these patients.

## Abbreviations

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; GSD, gallstone disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

## Data Sharing Statement

The data supporting the results are from the Health Evaluation Center of MacKay Memorial Hospital.

## Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki, and that verbal informed consent from the patients was approved by the Mackay Memorial

Hospital, Taipei, Taiwan (approval ID: 18MMHIS137). Consent for publication: Verbal consent was witnessed and formally recorded.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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