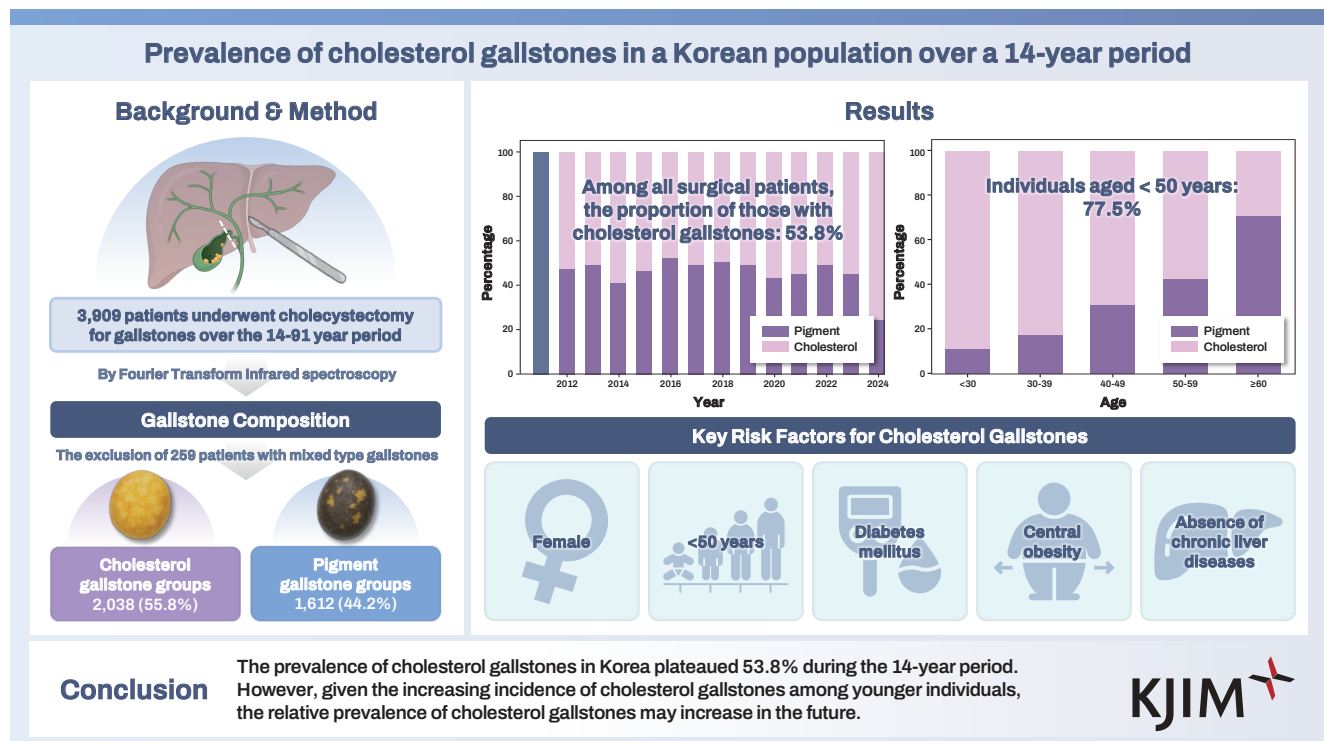


Prevalence of cholesterol gallstones in a Korean population over a 14-year period

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Background/Aims: The incidence of cholesterol gallstones has increased in the last few decades. This study aimed to evaluate the prevalence of cholesterol gallstones in Korea over a 14-year period, analyze any changes, and identify the predisposing factors.

Methods: A total of 3,909 patients underwent cholecystectomy for gallstones over the 14-year period and were considered for inclusion in this study. Patients were divided into cholesterol and pigment gallstone groups based on gallstone composition, as determined by Fourier Transform Infrared spectroscopy. Patient characteristics were compared between the two groups.

Results: After the exclusion of 259 patients with mixed type gallstones, 3,650 patients were finally included in this study; 2,038 (55.8%) with cholesterol gallstones and 1,612 (44.2%) with pigment gallstones. The proportion of cholesterol gallstones over the 14-year period was 53.8% of the study population as a whole and 77.5% of individuals aged < 50 years. The multivariate analysis revealed that cholesterol gallstones were associated with an age < 50 years, female sex, central obesity, absence of chronic liver diseases, and diabetes mellitus. High density lipoprotein-cholesterol levels showed a tendency toward an association with cholesterol gallstones.

Conclusions: The prevalence of cholesterol gallstones in Korea plateaued 53.8% during the 14-year period. However, given the increasing incidence of cholesterol gallstones among younger individuals, the relative prevalence of cholesterol gallstones may increase in the future.

Keywords: Cholecystolithiasis; Cholesterol; Prevalence; Korea

INTRODUCTION

Gallstone disease, or cholecystolithiasis, is one of the most common gastrointestinal disorders and is characterized by the formation of solid deposits in the gallbladder. Gallstones develop because of an imbalance in the composition of bile, a digestive fluid produced by the liver and stored in the gallbladder, leading to the crystallization and aggregation of bile components. While some individuals remain asymptomatic, others experience significant discomfort with abdominal pain, nausea, vomiting, and indigestion. In severe cases, gallstones can obstruct bile ducts, leading to cholecystitis, cholangitis, or pancreatitis [1,2].

In addition to its clinical impact, gallstones impose a significant economic burden. Each year, more than one million people are newly diagnosed with gallstones, and approximately 700,000 cholecystectomies are performed in the United States alone, at an estimated annual economic cost of \$6.5 billion [3,4]. The number of cholecystectomies performed in Europe and Asia is also increasing, reflecting an increasing prevalence of gallstone disease [5-7].

Gallstones are composed of cholesterol crystals, calcium bilirubinate, calcium carbonate, bile salts, mucin, and proteins [1]. Based on their composition, gallstones can be classified into three primary types: cholesterol, pigment, and mixed stones.

The development of cholesterol gallstone is primarily due to increased cholesterol synthesis and secretion, and predisposing factors include genetic predisposition, lifestyle factors, and characteristics such as age, female sex, pregnancy, obesity, rapid weight reduction, diabetes mellitus, and dyslipidemia. In contrast, pigment stones are primarily associ-

ated with conditions such as hemolysis, biliary infections, chronic liver diseases (such as cirrhosis), alcoholism, pancreatitis, and prolonged use of total parenteral nutrition [8].

In Western countries, cholesterol gallstones account for 75–80% of cases, whereas historically pigment gallstones have been more prevalent in Asia [2,8,9]. However, since the 1960s, cholesterol gallstones in East Asia have been increasing in prevalence, and now account for 50–80% of cases in countries such as Japan, Korea, and Taiwan. This increase is largely attributed to changes in diet and lifestyle, including increased calorie and fat intake, reduced fiber consumption, a more sedentary lifestyle, and a decline in chronic biliary infections [5,8,10].

A preliminary report of 365 Korean patients showed that the prevalence of pigment gallstones increased over time, whereas that of cholesterol gallstones decreased with age. The main predisposing factors included younger age, female sex, obesity, and the absence of chronic liver disease [11]. Despite the increasing prevalence of cholesterol gallstones in Asia, studies examining recent changes in gallstone composition and the associated predisposing factors remain limited, particularly in Korea. The present study therefore aimed to evaluate changes in gallstone composition over a 14-year period, and investigate the association between gallstone types and potential predisposing factors.

METHODS

Study design

The study protocol was approved by the Institutional Review Board of Chung-Ang University Hospital (No. 2501-

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006-19557). This study was conducted in compliance with the ethical principles for medical research involving human subjects outlined in the 1975 Helsinki Declaration. The requirement for written informed consent was waived due to the retrospective nature of the study.

Data from 3,909 patients who underwent cholecystectomy for gallstones and/or calculous cholecystitis at Chung-Ang University Hospital (Seoul, Korea) between May 2011 and December 2024 were retrospectively analyzed, including 73 patients reported in the preliminary study of 2013 [11].

The chemical composition of the gallstones was determined by their infrared absorption spectrum using Fourier Transform Infrared (FT-IR) spectroscopy (PerkinElmer, Waltham, MA, USA) [12]. Gallstones were categorized as cholesterol, calcium bilirubinate, calcium carbonate, calcium phosphate, or mixed stones, and the patients were divided into cholesterol and pigment stone groups accordingly.

Data collection

Data on patient characteristics including age, sex, and history of diabetes mellitus, hypertension, and chronic liver diseases such as cirrhosis and chronic hepatitis B and C, and physical and laboratory findings including body mass index (BMI), waist circumference, fasting blood glucose and serum cholesterol profiles, were prospectively collected and compared between the two groups. Obesity was defined as a BMI ≥ 25 kg/m² and central obesity was defined as a

waist circumference ≥ 90 cm in men and ≥ 85 cm in women [13,14]. Metabolic syndrome was diagnosed when three or more of the following five criteria were met: central obesity, blood pressure $\geq 130/80$ mmHg, fasting triglyceride levels ≥ 150 mg/dL, fasting high-density lipoprotein (HDL) cholesterol levels ≤ 40 mg/dL, and fasting blood glucose levels ≥ 100 mg/dL [14].

Statistical analysis

For continuous variables, the normality of data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables are reported as the mean $\pm$ standard deviation and were compared between groups using Student's t-test. Non-normally distributed variables are presented as the median (P_{25} – P_{75}) and were analyzed using the Mann–Whitney U test. Categorical variables were evaluated using the chi-square (χ^2) or Fisher's exact tests, as appropriate.

To identify significant risk factors associated with cholesterol stone, multiple logistic regression analysis was conducted to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI). Enter and backward selection methods were applied. To address potential multi-collinearity, central obesity was selected as the representative variable among the obesity-related factors (obesity and central obesity), and HDL was selected from the lipid profile variables (total cholesterol, HDL, triglycerides, and low-density lipoprotein [LDL]) for inclusion in the regression model. Multi-collinearity diagnostics confirmed the absence of sig-

Table 1. Patient characteristics

Characteristic	Cholesterol gallstones (N=2,038)	Pigment gallstones (N=1,612)	<i>p</i> value
Age (yr)	46.5 $\pm$ 14.3	61.5 $\pm$ 14.6	< 0.001
Sex, male:female	820:1,218	876:736	< 0.001
Body mass index (kg/m ²)	25.5 (23.0–28.3)	24.5 (22.0–26.8)	< 0.001
Waist circumference (cm)	91.1 (83.8–97.9)	89.8 (82.9–96.3)	< 0.001
Serum cholesterol (mg/dL)	189.0 (163.0–215.0)	167.0 (136.0–197.8)	< 0.001
Serum fasting glucose (mg/dL)	104.0 (94.0–120.0)	109.0 (96.0–133.8)	< 0.001
High-density lipoprotein (mg/dL)	51.0 (41.0–62.0)	45.2 (35.0–56.8)	< 0.001
Diabetes mellitus	145 (7.1)	394 (24.4)	< 0.001
Chronic liver diseases	73 (3.6)	136 (8.4)	< 0.001
Liver cirrhosis	7 (0.3)	51 (3.2)	< 0.001
Metabolic syndrome	187 (33.7)	323 (59.9)	< 0.001

Values are presented as mean $\pm$ standard deviation, number only, median (quartile 1–quartile 3), or number (%).

Chronic liver diseases include liver cirrhosis and chronic hepatitis B and C.

nificant multi-collinearity among the selected independent variables (condition indices < 30 ; variance inflation factor < 10). Variables with a univariate p value < 0.1 were included in the multivariate analysis. All statistical analyses were performed using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Of the 3,909 patients considered for inclusion in the study, 259 patients had mixed stones based on FT-IR spectroscopy and were excluded from the study. Finally, data from 3,650 patients were included in the analysis (Table 1).

Of the 3,650 patients, 2,038 (55.8%) had cholesterol gallstones and the remaining 1,612 (44.2%) had pigment gallstones. Patients in the cholesterol gallstone group were younger than those in the pigment gallstone group, with mean age of 46.5 years and 61.5 years, respectively ($p < 0.001$). Gallstones were slightly more common in female than in male (53.5% vs 46.5%); however, cholesterol gallstones were more prevalent in female than pigment gallstones (62.3% vs 37.7%, $p < 0.001$). Chronic liver disease, including liver cirrhosis and chronic hepatitis B and C, was significantly more prevalent in the pigment gallstone group than in the cholesterol gallstone group ($p < 0.001$). Patients in the cholesterol gallstone group had a significantly higher median BMI (median 25.5 kg/m² vs. 24.5 kg/m², $p < 0.001$), waist circumference (91.1 cm vs. 89.8 cm, $p < 0.001$) and serum cholesterol level (median 189.0 mg/dL vs. 167.0 mg/dL, $p <$

0.001) than those of patients in the pigment gallstone group.

Cholesterol gallstone prevalence in Korea

Between 2011 and 2023, the prevalence of cholesterol gallstones remained between 47.8% and 58.8%, with a slight deviation in 2024, suggesting that a plateau has been reached (Fig. 1).

Decreased prevalence of cholesterol gallstones with age

Of the 3,650 patients, There were 247, 632, 701, 729, and 1,341 patients were aged < 30 , 30–39, 40–49, 50–59, and ≥ 60 years, respectively, with the number of patients with gallstones increasing with age (Fig. 2). The proportion of the patients with cholesterol gallstones was highest in those aged ≤ 30 years (88.7%), and gradually decreased with age (82.4%, 69.0%, 57.3%, and 29.5% in patients aged 30–39, 40–49, 50–59, and ≥ 60 years, respectively).

Predisposing factors for cholesterol gallstones

Univariate analysis revealed that, compared with patients with pigment gallstones, those with cholesterol gallstones were more likely to be younger ($p < 0.001$) and female ($p < 0.001$); have obesity ($p < 0.001$), central obesity ($p < 0.001$), high levels of serum cholesterol ($p < 0.001$), lower HDL level ($p < 0.001$), and higher LDL levels ($p = 0.005$); have no chronic liver diseases ($p < 0.001$), or liver cirrhosis ($p < 0.001$); and have diabetes mellitus ($p < 0.001$). Multivariate analysis revealed that cholesterol gallstone group were associated with an age < 50 years (OR 4.975, 95%

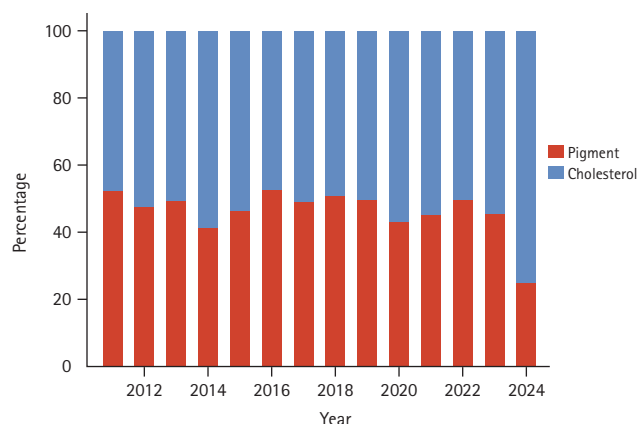


Figure 1. Proportion of patients with cholesterol and pigment gallstones over the 14-year study period.

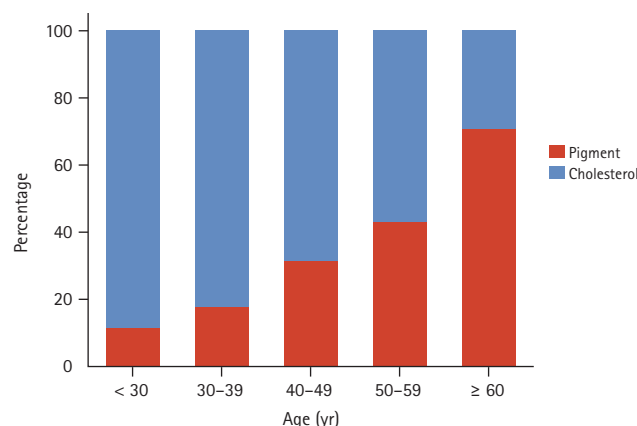


Figure 2. Proportion of patients with cholesterol and pigment gallstones according to age.

CI 4.184–5.917; $p < 0.001$), female sex (OR 1.870, 95% CI 1.583–2.209; $p < 0.001$), central obesity (OR 1.576, 95% CI 1.328–1.870; $p < 0.001$), the absence of chronic liver diseases (OR 1.838, 95% CI 1.269–2.667; $p = 0.001$), and diabetes mellitus (OR 2.655, 95% CI 2.092–3.370; $p < 0.001$). HDL levels < 40 mg/dL showed a tendency toward an association (OR 1.190, 95% CI 0.991–1.433; $p = 0.063$) (Table 2).

DISCUSSION

This study analyzed a large cohort of patients treated during a 14-year period and found no significant change in the prevalence of cholesterol and pigment gallstones over this period, suggesting that a plateau has been reached following previous increases in the proportion of patients with cholesterol gallstones. The prevalence of cholesterol gall-

Table 2. Univariate and multivariate analysis of predisposing factors for cholesterol gallstones

	Cholesterol stones (n)	Pigment stones (n)	Univariate		Multivariate backward conditional	
			OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (yr)						
≥ 50	814	1,256	1	< 0.001	1	< 0.001
< 50	1,224	356	5.319 (4.587–6.135)		4.975 (4.184–5.917)	
Sex						
Male	820	876	1	< 0.001	1	< 0.001
Female	1,218	736	1.768 (1.549–2.018)		1.870 (1.583–2.209)	
Obesity						
Yes	1,104	692	1.571 (1.378–1.792)	< 0.001		
No	934	920	1			
Central obesity						
Yes	1,308	941	1.278 (1.117–1.461)	< 0.001	1.576 (1.328–1.870)	< 0.001
No	730	671	1		1	
Total cholesterol (mg/dL)						
≥ 240	201	99	1.672 (1.302–2.147)	< 0.001		
< 240	1,828	1,505	1			
HDL-cholesterol (mg/dL)						
< 40	416	412	1	< 0.001	1	0.063
≥ 40	1,265	878	0.701 (0.597–0.823)		0.840 (0.698–1.009)	
TG (mg/dL)						
> 150	382	302	0.984 (0.829–1.167)	0.849		
≤ 150	1,362	1,059	1			
LDL-cholesterol (mg/dL)						
≥ 160	64	32	1.801 (1.165–2.783)	0.005		
< 160	854	769	1			
Chronic liver disease						
Yes	73	136	0.404 (0.302–0.542)	< 0.001	0.544 (0.375–0.788)	0.001
No	1,959	1,476	1		1	
Diabetes mellitus						
Yes	145	394	4.210 (3.434–5.160)	< 0.001	2.655 (2.092–3.370)	< 0.001
No	1,887	1,218	1		1	

OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; TG, triglyceride; LDL, low-density lipoprotein.

stones was significantly higher in younger individuals and gradually decreased with age. In the univariate analysis, young age, female sex, obesity, central obesity, high serum cholesterol levels, low HDL levels, high LDL levels, absence of chronic liver disease, absence of liver cirrhosis, and diabetes mellitus were associated with cholesterol gallstones. Multivariate analysis identified an age < 50 years, female sex, central obesity, the absence of chronic liver diseases, and diabetes mellitus as significant predisposing factors for cholesterol gallstones.

The proportion of patients with cholesterol gallstones remained stable between 47.8% and 58.8% from 2011 to 2023, but showed a slight increase to 75.4% in 2024. This may be due to the higher proportion of younger patients treated in 2024; 107 of 187 patients (58.2%) with cholesterol gallstones were < 50 years.

Low HDL-cholesterol levels showed only a tendency toward an association with cholesterol gallstone formation. A recent study reported a significant association between a higher triglyceride-glucose index and an increased risk of cholesterol gallstones. This association was particularly prominent in individuals < 50 years, women, those with total cholesterol levels > 200 mg/dL, individuals with a BMI > 25 kg/m², and those without diabetes. Therefore, the triglyceride-glucose index may serve as a more effective predictor of cholesterol gallstone risk than single lipid marker such as HDL [15].

Obesity promotes the development of lithogenic bile. Studies have shown that patients with obesity tend to have bile that is supersaturated with cholesterol and a larger gallbladder volume, which increases with obesity severity [16-18]. In Korea, the prevalence of obesity has risen steadily from 29.7% in 2009 to 36.3% by 2019 [19]. The prevalence of obesity in the present study was 49.2%; it was notably higher in the cholesterol gallstone group than in the pigment gallstone group (61.5% vs. 38.5%).

Although obesity as measured by BMI is commonly used in studies of gallstone disease, increasing evidence suggests that central obesity may be a more significant risk factor for gallstone formation [20,21]. Central obesity, a key component of metabolic syndrome, was therefore included in the multivariate analysis performed in the present study instead of BMI. Recent studies has also reported that the waist-to-height ratio is a more reliable predictor of metabolic risk than waist circumferences or BMI [22,23].

Cholesterol gallstone disease is a multifactorial disorder

influenced by genetic and environmental factors [2]. Among these factors, hepatic cholesterol metabolism, encompassing cholesterol biosynthesis, uptake, export, and esterification, plays a crucial role [24]. While LDL cholesterol has traditionally been associated with cholesterol transport and metabolism, recent studies suggest that HDL may play a more significant role in the pathogenesis of cholesterol gallstone disease. Studies on the molecular expression of gene related to hepatic cholesterol metabolism in patients with gallstones have shown that cholesterol gallstone formation is associated with the upregulation of scavenger receptor class B type I. This upregulation enhances HDL-derived cholesteryl ester uptake, leading to cholesterol accumulation and bile saturation [25-27]. The role of HDL in hepatic cholesterol influx and bile phospholipid content makes it a critical factor in cholesterol gallstone pathogenesis. Thus, in the present study, HDL rather than LDL was included in the multivariate analysis.

The current study has several limitations. First, lifestyle factors, such as diet and physical activity, were not investigated. Questionnaires assessing these factors at a single time point may not capture their long-term effects on gallstone formation, and it is therefore essential to track lifestyle habits over the course of a patient's life and correlate these data with gallstone development. Second, the current study was conducted at a single center. Despite the large cohort involved, a future multicenter or general population based study is necessary to better understand the epidemiology of gallstones in the Korean population.

In conclusions, the result of the present study demonstrated that cholesterol gallstones occurred in 53.8% of the total patient population over a 14-year period among individuals aged ≤ 50 years, this proportion increased to 77.5%. Key independent predisposing factors for cholesterol gallstones included younger age, female sex, central obesity, and the absence of chronic liver diseases. Furthermore, two components of metabolic syndrome; central obesity and elevated fasting blood glucose levels, were associated with cholesterol gallstones, whereas low HDL-cholesterol levels showed a tendency toward an association and triglyceride levels showed no significant association. Although the prevalence of cholesterol gallstones in Korea has remained relatively stable over the past 14 years, this trend may shift as cholesterol gallstones become more prevalent among in younger individuals.

KEY MESSAGE

1. The proportion of cholesterol gallstones was 53.8% in the study population over 14-years period and 77.5% among individuals under the age of 50.
2. Central obesity and elevated fasting blood glucose were associated with an increased risk of cholesterol gallstones as well as the established predisposing factors of younger age, female sex, and the absence of chronic liver disease.

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Conflict of interest

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