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# Are there modifiable risk factors affecting the prevalence of gallbladder polyps or those 5 mm or larger? A retrospective cross-sectional study

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**Abstract**

Gallbladder polyps (GBPs), especially GBPs ≥5 mm in diameter, are clinically important because they can progress to gallbladder cancer. The known modifiable risk factors for GBP are obesity, metabolic syndrome, and dyslipidemia; however, there is limited evidence regarding specific modifiable risk factors for GBPs ≥5 mm in diameter. Therefore, this study is aimed to investigate the existence of modifiable risk factors affecting the prevalence of GBPs and GBPs ≥5 mm in diameter in a Korean population.

A total of 10,119 subjects who visited a single health-screening center at Jeju National University Hospital between January 2009 and December 2019 was included in this study. Binary logistic analyses were performed to identify risk factors affecting the prevalence of GBPs and GBPs ≥5 mm in diameter.

The overall prevalence of GBPs and GBPs ≥5 mm in diameter were 9.0% and 4.1%, respectively. Multivariable analysis identified male gender as an independent risk factor affecting the prevalence of GBPs. Moreover, multivariable analysis revealed age and high-density lipoprotein cholesterol levels as independent risk factors for GBPs ≥5 mm in diameter.

This study showed that gender was a risk factor affecting the prevalence of GBPs and that age and high-density lipoprotein-cholesterol levels were risk factors for the presence of GBPs ≥5 mm in diameter. High-density lipoprotein cholesterol levels could be a modifiable risk factor affecting the prevalence of large-diameter GBPs.

**Abbreviations:** ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GBP = gallbladder polyp, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

**Keywords:** dyslipidemia, gallbladder polyps, modifiable risk factor

## 1. Introduction

Gallbladder polyps (GBPs) are mucosal lesions protruding into the gallbladder lumen. GBP diagnoses have been increasing in frequency due to recent advances in medical imaging technology, such as abdominal computed tomography and ultrasonography, and due to increasing awareness of the need for regular medical evaluations.[1] The general rule for gallstone disease is that treatment is only necessary if there are associated symptoms. When a small polypoid lesion is discovered in the gallbladder, treatment decisions often become a dilemma due to the possibility of malignancy.[1] GBPs are commonly categorized into neoplastic polyps (true polyps) and non-neoplastic polyps (pseudopolyps). Neoplastic polyps include adenomas and adenocarcinomas, whereas pseudopolyps include cholesterol polyps, inflammatory polyps, and hyperplastic polyps. The prevalence of GBPs in South Korea is reported to be 1.3% to 9.5%.[2] Surgical resection is recommended for GBPs ≥10 mm in diameter because the probability of malignancy is approximately 3% to 8% for such polyps[3]; ultrasound cannot differentiate between benign and malignant tumors. Gallbladder cancer has a poor prognosis, with a survival rate of only 28.3%. Additionally, gallbladder cancer remains fatal despite advancements in imaging equipment and treatment methods.[4]

For most adenomatous gallbladder lesions, similar to other neoplastic polyps, the adenoma–carcinoma sequence is a known cause of transformation of adenoma to adenocarcinoma[5]; thus, adenomas should be regarded as precancerous lesions, and all neoplastic polyps should be surgically removed. However, preoperative collection of a polyp tissue sample is challenging; no method exists for accurately differentiating neoplastic polyps from non-neoplastic polyps; thus, doctors and patients alike are not free from concerns about malignancy. It may be challenging to differentiate GBPs <5 mm in diameter from gallstone disease, but most such GBPs are not neoplastic.[6] However, malignancy cannot be ruled out for GBPs ≥5 mm in diameter, necessitating

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periodic abdominal ultrasonography. Cholecystectomy is recommended for polyps ≥10 mm wide due to their malignant potential.[1]

Known risk factors for GBP include male gender, obesity, hepatitis B surface antigen positivity, metabolic syndrome, and dyslipidemia.[2,6] However, the risk factors for clinically meaningful GBPs ≥5 mm wide are not well known. An understanding of the factors affecting the prevalence of GBPs and the modifiable risk factors for GBPs could reduce the development of polyps and prevent progression to clinically significant disease. Namely, if modifiable risk factors influencing the prevalence of GBPs or GBPs ≥5 mm in diameter can be identified, patient education for high-risk groups and advertisements for the general public can help reduce the rates of polyp development and progression to clinically significant polyps, reducing the associated public health burden and socioeconomic costs.

The primary aim of this study was to determine if the known modifiable risk factors for GBPs, such as obesity, dyslipidemia, and metabolic syndrome, affect the prevalence of GBPs.[2,6] The second objective was to identify modifiable risk factors affecting clinically significant GBPs ≥5 mm in diameter. When risk factors were found, we performed subgroup analyses to determine the differences that were attributable to these variables.

## 2. Methods

### 2.1. Subjects

For this study, we screened 11,242 participants visited a single health-screening center at Jeju National University Hospital between January 2009 and December 2019. Among these, 1,123 participants were excluded because they underwent cholecystectomy (n = 370) or hepatectomy (n = 12), or because they refused consent or returned incomplete questionnaires (n = 741). Twelve participants who underwent hepatectomy also had their gallbladders removed because of hepatocellular carcinoma (n = 7), gallbladder cancer (n = 3), and cholangiocarcinoma (n = 2) during hepatectomy. Among the 370 participants who underwent cholecystectomy, 314 cholecystectomies were performed due to acute or chronic cholecystitis, and 56 cholecystectomies were performed to treat GBPs. Among 741 participants who refused consent or returned incomplete questionnaires, 543 participants refused when they were asked to complete the questionnaire after being informed about the collection of clinical information. There were 146 participants who initially consented but did not complete the questionnaire because of a lack of time or unwillingness to answer certain questions; 52 participants lost the parts of questionnaires. If a subject underwent more than 1 medical checkup during the study period, their initial data were used. Finally, 10,119 subjects were included in this study (Fig. 1). This study was reviewed and approved by the hospital's institutional review board (IRB number. JNUH 2020-10-011).

### 2.2. Questionnaire

Participants were asked to complete a questionnaire and to declare clinical indicators and demographic data. The questionnaire was included the following items and categories: address, telephone number, history of medical diseases (including, specifically, hyperlipidemia, diabetes mellitus and related medication history, hypertension, stroke, heart disease, and tuberculosis), smoking history, familial causes of death, alcohol consumption, and other medications. We minimized self-report bias by using objective and graded questions and questionnaire items. We also provided no information about the study to the person who distributed the questionnaires or the study participants while they responded to the questionnaire. We minimized recall bias by providing no information about the study to the individuals who were asked to complete the questionnaire, and we provided information only when they could not understand the items or questions.

### 2.3. Diagnosis of gallbladder polyps

Ultrasound examinations using IU22 (Koninklijke Philips Electronics N.V., Amsterdam, the Netherlands) high-resolution ultrasound equipment were performed by special radiologists. The abdominal scans were performed after subjects had fasted for at least eight hours. GBPs were identified on abdominal sonograms as fixed, hyperechoic material protruding from the gallbladder wall into the lumen without an acoustic shadow, characterized by the absence of shift with positional changes. For each patient, the number of polyps and the diameter of the largest polypoid lesion were recorded.[7]

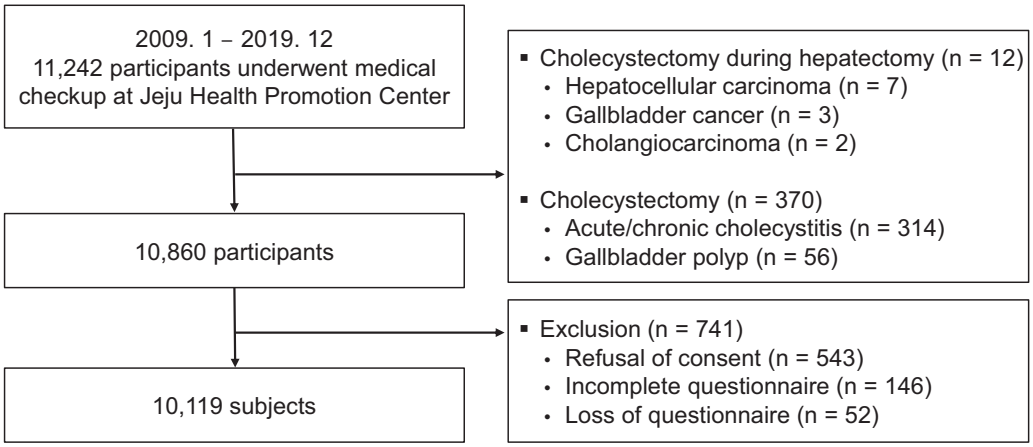


**Figure 1.** Flow diagram of included study subjects who underwent medical checkups.

### 2.4. Definition of physical activity

Participants were asked to complete a questionnaire evaluating physical activity levels according to the World Health Organization's Global Recommendations on Physical Activity for Health 2010.[8] Participants were defined as physically active if they performed moderate-intensity aerobic physical activity for at least 150 min or vigorous activity for at least 75 min per week with aerobic activity comprising at least 10 min duration in each exercise session.

### 2.5. Definitions of alcohol consumption and metabolic syndrome

Alcohol consumption data were collected using the healthcare questionnaire. For men, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses in female) and drinking 2 or more times per week irrespective of the glass size.[9]

Metabolic syndrome was defined according to the revised National Cholesterol Education Program criteria. Subjects were diagnosed as having metabolic syndrome if they fulfilled 3 or more of the following criteria: waist circumference ≥90 cm for men or ≥80 cm for women using the International Obesity Task Force criteria for the Asian–Pacific population to determine waist circumference,[10] triglycerides ≥150 mg/dL, antidyslipidemic medication use, high-density lipoprotein (HDL) cholesterol <40 mg/dL for men or <50 mg/dL for women, high blood pressure ≥130/85 mmHg or antihypertensive medication use, high fasting blood glucose ≥100 mg/dL or diabetes medication use (insulin or oral hypoglycemic agents).

### 2.6. Physical examination

Height and weight were measured using an electronic combined scale and stadiometer (GL-150R, G-Tech International Co., Gyeong-gido, Korea) without shoes and with light clothing for each participant. Participants age and gender were extracted from medical records. Venous blood samples were taken after 8 h of fasting. Fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total cholesterol, triglycerides, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol levels were measured using venous blood samples.

GBP prevalence was calculated according to gender and age. The participants were divided into 4 groups according to age: the 20–49-, 50–59-, and ≥60-year age groups. Body mass index (BMI) was calculated by dividing weight by the square of height and classified into 4 groups, according to the World Health Organization's BMI categories for Asian populations[11]: underweight, <18.5 kg/m$^2$; normal weight, 18.5–22.9 kg/m$^2$; overweight, 23.0–24.9 kg/m$^2$; and obese, ≥25.0 kg/m$^2$. Fasting blood glucose levels were classified into 3 groups based on the standard proposed by the American Diabetes Association in 2015: normoglycemia, <100 mg/dL; impaired fasting glucose, 100–125 mg/dL; and diabetes, ≥126 mg/dL. Fasting was defined as the absence of caloric intake for at least eight hours. Total cholesterol levels were classified into 3 groups: <200 mg/dL, 200–239 mg/dL, and ≥240 mg/dL. Serum LDL cholesterol levels were classified into 5 groups: <100 mg/dL, 100–129 mg/dL, 130–159 mg/dL, 160–189 mg/dL, and ≥190 mg/dL. Serum HDL cholesterol levels were classified into 3 groups: <40 mg/dL, 40–60 mg/dL, and ≥60 mg/dL. Serum triglyceride levels were classified into 4 groups: <150 mg/dL, 150–199 mg/dL, 200–499 mg/dL, and ≥500 mg/dL. Each lipid level was classified according to the 2015 Korean Guidelines for the Management of Dyslipidemia. AST levels were considered elevated if they were over 32 IU/L for men and over 26 IU/L for women. ALT levels were considered elevated if they were over 34 IU/L for men and over 24 IU/L for women. ALP and GGT levels were considered high if they were greater than 130 IU/L and 71 IU/L, respectively.

### 2.7. Statistical analysis

We compared clinical variables using Student's *t*-test for continuous variables and the chi-square test for categorical variables, depending on the presence of GBP. We performed binary logistic regression analysis, including gender; age; metabolic syndrome status; BMI; fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, ALT, AST, GGT, and ALP levels; hepatitis B antigen status; as well as alcohol consumption. Binary logistic regression with backward selection was used to identify independent risk factors for prevalence of GBPs or GBPs ≥5 mm in diameter when the factors were less than 0.1 on the univariable analysis. One-way analysis of variance was used for the 3 aforementioned age categories. We considered *P* values <.05 as statistically significant. All statistical analyses were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Prevalence of GBPs and GBPs ≥5 mm in diameter

A total of 10,119 subjects was included in the final analysis, including 909 subjects with GBPs and 9,210 subjects without GBPs. Fig. 1 shows the enrollment flow chart. Of the 10,119 subjects, 5,779 (57.1%) were men, and 4,340 (42.9%) were females. The overall prevalences of GBPs and GBPs ≥5 mm in diameter were 9.0% (n = 909) and 4.1% (n = 416), respectively. The annual prevalence of GBPs or GBPs ≥5 mm in diameter was not correlated with the study period.

### 3.2. Comparisons of clinical variables among subjects with and without GBPs

Subjects were classified into 2 groups according to the presence or absence of GBPs. The proportion of men and the mean LDL cholesterol level were significantly higher among subjects with GBPs. The proportion of women, subjects who had metabolic syndrome, and the mean age were significantly lower among subjects with GBPs (Table 1).

### 3.3. Univariable analysis of risk factors affecting GBPs and GBPs ≥5 mm in diameter

Factors for the presence of GBPs are summarized in Table 2. The prevalence of GBPs was 9.5% in the 20–49-year age group, 9.8% in the 50–59-year age group, and 7.6% in the ≥60-year age group (*P* = .004). Male gender, metabolic syndrome status, BMI, LDL cholesterol level, and HDL cholesterol level were risk factors for the presence of GBPs (Table 2). The factors affecting the prevalence of GBPs ≥5 mm in diameter are summarized in Table 3. Male gender, age, and HDL cholesterol levels were risk factors affecting the prevalence of GBPs ≥5 mm wide.

**Table 1**

**Comparisons of the variables between 2 groups according to the presence or absence of gallbladder polyps among subjects who underwent medical checkups.**

| Variable | Subjects with GBPs (n = 909) | Subjects without GBPs (n = 9210) | *P* value |
|---|---|---|---|
| Gender (%) | | | .009 |
| Male | 557 (61.3) | 5222 (56.7) | |
| Female | 352 (38.7) | 3988 (43.3) | |
| Metabolic syndrome | | | .013 |
| Yes | 188 (24.6) | 2185 (28.8) | |
| No | 577 (75.4) | 5395 (71.2) | |
| Age (years) | 52.8 ± 10.5 | 53.9 ± 11.9 | .010 |
| Body mass index (kg/m$^2$) | 24.6 ± 3.0 | 24.7 ± 3.3 | .696 |
| Fasting blood glucose (mg/dL) | 98.7 ± 27.8 | 99.4 ± 27.0 | .487 |
| Total cholesterol (mg/dL) | 201.6 ± 36.1 | 199.9 ± 37.3 | .192 |
| LDL cholesterol (mg/dL) | 124.2 ± 33.0 | 121.5 ± 34.6 | .024 |
| HDL cholesterol (mg/dL) | 53.8 ± 14.4 | 54.2 ± 13.9 | .459 |
| Triglycerides (mg/dL) | 118.2 ± 86.7 | 121.7 ± 96.4 | .294 |
| AST (IU/L) | 26.2 ± 24.5 | 28.4 ± 85.0 | .422 |
| ALT (IU/L) | 30.2 ± 81.1 | 31.0 ± 99.1 | .815 |
| GGT (IU/L) | 44.6 ± 58.4 | 47.9 ± 80.5 | .238 |
| ALP (IU/L) | 209.6 ± 97.2 | 207.2 ± 78.5 | .418 |
| HBsAg | | | .854 |
| Positive | 35 (4.8) | 349 (4.7) | |
| Negative | 690 (95.2) | 7107 (95.3) | |
| Physical activity | | | .535 |
| Yes | 148 (16.3) | 1428 (15.5) | |
| No | 761 (83.7) | 7782 (84.5) | |
| High-risk alcohol drinker* | | | .275 |
| Yes | 335 (36.9) | 3223 (35.0) | |
| No | 574 (63.1) | 5987 (65.0) | |

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyltransferase, HBsAg = hepatitis B surface antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* For male, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses for female) and drinking 2 or more times per week irrespective of the glass size.

### 3.4. Multivariable analysis of risk factors for GBPs and GBPs ≥5 mm in diameter

Binary logistic regression analyses were performed for clinical variables, including gender, age, metabolic syndrome status, BMI, LDL cholesterol and HDL cholesterol levels, and AST levels among subjects with GBPs. Gender, age, and HDL cholesterol levels were risk factors affecting the presence of GBPs or GBPs ≥5 mm in diameter in the univariable analysis (Table 4). Male gender was an independent risk factor among subjects with GBPs, whereas age and HDL cholesterol levels were independent risk factors among subjects with GBPs ≥5 mm in diameter. The prevalence of GBPs ≥5 mm wide was significantly higher in the 50–59-year age group than in the ≥60-year age group (odds ratio [OR], 1.026 in the 50–59-year age group; OR, 0.722 in the ≥60-year age group; $P = .013$; GBPs ≥5 mm in diameter).

### 3.5. Comparisons of clinical variables according to gender and age

Male gender was an independent risk factor for the presence of GBPs. To investigate whether there was a difference in the prevalence of GBPs between the genders, we compared clinical variables according to gender. Men had significantly higher rates of metabolic syndrome, medication use for diabetes, hypertension, hepatitis B surface antigen positivity, physical activity, and high-risk alcohol consumption. Men also had a higher mean BMI as well as higher mean fasting blood glucose, total cholesterol, LDL cholesterol, triglyceride, AST, ALT, GGT, and ALP levels than women. However, the mean age and HDL cholesterol levels were significantly higher among female subjects (Table 5).

Because age was a risk factor for GBPs ≥5 mm in diameter, we divided subjects into 3 age groups (age 20–49 years, age 50–59 years, and age ≥60 years). Compared with the other age groups, the 50–59-year age group had a significantly higher proportion of GBPs and GBPs ≥5 mm in diameter as well as higher mean levels of total cholesterol and LDL cholesterol (Table 6).

## 4. Discussion

The presence of GBPs is a well-known risk factor for gallbladder cancer. GBPs are asymptomatic, and most are discovered by chance during medical evaluations. Reported GBP prevalence vary by geographic location. In Western countries, reported GBP prevalences range from 1.0%–6.9%,[12–14] compared with 2.2% to 9.5% in Asia.[2,6,13,15] The prevalence in South Korea varies widely, from 2.9% to 9.9%, by region and population.[2,16] Notably, the prevalence in South Korea has shown a gradually increasing trend.[6] Recent advances in diagnostic imaging technology, such as abdominal ultrasonography and computed tomography, as well as improved awareness of the need for regular medical evaluations, are the leading causes of the increased rate of GBP identification.[2,15] However, this study could not confirm an increase in the prevalence of GBPs. We speculate that this may be because our study only covered 10 years from 2009 to 2019, which may not have been long enough to detect any observable changes in the prevalence of GBPs.

Many studies have reported that the prevalence of GBPs is higher among men than among women.[17–22] This study also showed that male gender was an independent risk factor for GBPs. To determine why male gender independently influences the prevalence of GBPs, we conducted an analysis for each gender and found that, compared with their female counterparts, male subjects had higher rates of metabolic syndrome, hepatitis B surface antigen positivity, and alcohol consumption, as well as a higher mean BMI and higher fasting blood glucose, total cholesterol, LDL cholesterol, triglyceride, AST, ALT, GGT, and ALP levels. In contrast, women were older and had higher HDL cholesterol levels than men. Therefore, male gender could be an independent risk factor for GBPs because, out of the known risk factors for GBPs, dyslipidemia, obesity, and metabolic syndrome tended to occur more frequently in men than women.

There are minor discrepancies between published studies in terms of risk factors for GBPs; however, in many studies, a specific age group (< 60 years) has been observed as an independent risk factor.[12,15,22–25] Although age <60 years was not an independent risk factor for the prevalence of GBPs in this study, it was a risk factor for the prevalence of GBPs ≥5 mm wide. The prevalence of GBPs ≥5 mm wide was significantly lower among subjects ≥60 years of age. Although the reason that GBPs are less prevalent among older adults is unknown, many previous studies have suggested a decreased incidence of cholesterol polyps due to lipid metabolism changes.[26] A recent study reported that the cause of the lower prevalence of GBPs among older persons might be associated with dyslipidemia. From birth to adulthood, blood cholesterol and triglyceride levels

**Table 2**

**Univariable analysis of risk factors affecting for GBPs in subjects who underwent medical checkups.**

| GBPs | | | | |
|---|---|---|---|---|
| **Factor** | **Number of subjects** | **Number of gallbladder polyps, n (%)** | **Odds ratio (95% Confidence interval)** | ***P value** |
| Gender | | | | <.001 |
| Male | 5779 | 557 (9.6) | 1.000 | |
| Female | 4340 | 352 (8.1) | 0.107 (0.720–0.952) | |
| Age (years) | | | | .004 |
| 20–49 | 3605 | 341 (9.5) | 1.000 | |
| 50–59 | 3265 | 320 (9.8) | 1.040 (0.886–1.221) | .631 |
| ≥60 | 3249 | 248 (7.6) | 0.791 (0.667–0.938) | .007 |
| Metabolic syndrome | | | | .013 |
| Yes | 2373 | 188 (7.9) | 1.243 (1.047–1.476) | |
| No | 5972 | 577 (9.7) | 1.000 | |
| BMI (kg/m$^2$) | | | | .028 |
| <18.5 | 178 | 12 (6.7) | 1.000 | |
| 18.5–22.9 | 2568 | 225 (8.8) | 1.328 (0.728–2.425) | .355 |
| 23–24.9 | 2366 | 251 (10.6) | 1.642 (0.901–2.992) | .106 |
| ≥25 | 4094 | 353 (8.6) | 1.305 (0.719–2.369) | .381 |
| Fasting blood glucose (mg/dL) | | | | |
| <100 | 6816 | 624 (9.2) | 1.000 | .400 |
| 100–125 | 2403 | 198 (8.2) | 0.891 (0.754–1.053) | .176 |
| ≥126 | 833 | 74 (8.9) | 0.967 (0.752–1.245) | .797 |
| Total cholesterol (mg/dL) | | | | |
| <200 | 5144 | 446 (8.7) | 1.000 | .306 |
| 200-239 | 3391 | 327 (9.6) | 1.124 (0.968–1.306) | .126 |
| ≥240 | 1398 | 125 (8.9) | 1.034 (0.840–1.273) | .750 |
| LDL cholesterol (mg/dL) | | | | .076 |
| <100 | 2522 | 197 (7.8) | 1.000 | |
| 100–129 | 3394 | 304 (9.0) | 1.161 (0.963–1.400) | .118 |
| 130–159 | 2504 | 254 (10.1) | 1.332 (1.096–1.619) | .004 |
| 160–189 | 964 | 90 (9.3) | 1.215 (0.936–1.578) | .143 |
| ≥190 | 302 | 28 (9.3) | 1.206 (0.796–1.827) | .376 |
| HDL cholesterol (mg/dL) | | | | .049 |
| <40 | 1271 | 130 (10.2) | 1.000 | |
| 40-60 | 5526 | 515 (9.3) | 0.902 (0.736–1.105) | .319 |
| ≥60 | 3124 | 253 (8.1) | 0.773 (0.619–0.966) | .024 |
| Triglycerides (mg/dL) | | | | |
| <150 | 7480 | 688 (9.2) | 1.000 | .546 |
| 150–199 | 1195 | 111 (9.3) | 1.011 (0.819–1.248) | .920 |
| 200–499 | 1168 | 93 (8.0) | 0.854 (0.681–1.071) | .171 |
| ≥500 | 78 | 6 (7.7) | 0.823 (0.356–1.899) | .647 |
| AST (IU/L) | | | | .032 |
| ≤32 for men | 8378 | 776 (9.3) | 1.000 | |
| >32 for men | 1740 | 133 (7.6) | 0.811 (0.669–0.982) | |
| ALT (IU/L) | | | | |
| ≤34 for men | 7842 | 712 (9.1) | 1.000 | .530 |
| >34 for men | 2277 | 197 (8.7) | 0.948 (0.804–1.119) | |
| GGT (IU/L) | | | | |
| ≤71 | 8551 | 776 (9.1) | 1.000 | .459 |
| >71 | 1566 | 133 (8.5) | 0.930 (0.767–1.127) | |
| ALP (IU/L) | | | | |
| ≤130 | 641 | 53 (8.3) | 1.000 | .608 |
| >130 | 8416 | 746 (8.9) | 1.079 (0.807–1.443) | |
| HBsAg | | | | |
| Positive | 384 | 35 (9.1) | 0.968 (0.678–1.382) | .858 |
| Negative | 7797 | 690 (8.8) | 1.000 | |
| Physical activity | | | | |
| Yes | 1576 | 148 (9.4) | 0.944 (0.784–1.135) | .538 |
| No | 8543 | 761 (8.9) | 1.000 | |
| High-risk alcohol drinker† | | | | |
| Yes | 3558 | 335 (9.4) | 0.922 (0.801–1.062) | .263 |
| No | 6561 | 574 (8.7) | 1.000 | |

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyltransferase, HBsAg = hepatitis B surface antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* This value was obtained using the binary regression test.

† For male, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses for female) and drinking 2 or more times per week irrespective of the glass size.

**Table 3**

**Univariable analysis of risk factors for GBPs ≥5 mm in diameter among subjects who underwent medical checkup.**

| GBPs ≥5 mm in diameter | | | | |
|---|---|---|---|---|
| **Factor** | **Number of subjects** | **Number of gallbladder polyps, n (%)** | **Odds ratio (95% Confidence interval)** | *** *P* value** |
| Gender | | | | <.001 |
| Male | 5779 | 263 (4.6) | 1.000 | |
| Female | 4340 | 153 (3.5) | 0.048 (0.625–0.939) | |
| Age (years) | | | | .024 |
| 20–49 | 3605 | 159 (4.4) | 1.000 | |
| 50–59 | 3265 | 149 (4.6) | 1.036 (0.825–1.303) | .760 |
| ≥60 | 3249 | 108 (3.3) | 0.745 (0.581–0.956) | .021 |
| Metabolic syndrome | | | | |
| Yes | 2373 | 87 (3.7) | 1.191 (0.930–1.526) | .166 |
| No | 5972 | 259 (4.3) | 1.000 | |
| BMI (kg/m$^2$) | | | | |
| <18.5 | 178 | 6 (3.4) | 1.000 | .437 |
| 18.5–22.9 | 2568 | 99 (3.9) | 1.149 (0.497–2.658) | .745 |
| 23–24.9 | 2366 | 111 (4.7) | 1.411 (0.612–3.256) | .419 |
| ≥25 | 4094 | 165 (4.0) | 1.204 (0.526–2.757) | .661 |
| Fasting blood glucose (mg/dL) | | | | |
| <100 | 6816 | 290 (4.3) | 1.000 | .493 |
| 100–125 | 2403 | 89 (3.7) | 0.866 (0.679–1.103) | .242 |
| ≥126 | 833 | 33 (4.0) | 0.928 (0.643–1.341) | .691 |
| Total cholesterol (mg/dL) | | | | |
| <200 | 5144 | 210 (4.1) | 1.000 | .843 |
| 200–239 | 3391 | 141 (4.2) | 1.019 (0.820–1.268) | .863 |
| ≥240 | 1398 | 62 (4.4) | 1.090 (0.816–1.457) | .558 |
| LDL cholesterol (mg/dL) | | | | |
| <100 | 2522 | 93 (3.7) | 1.000 | .467 |
| 100–129 | 3394 | 136 (4.0) | 1.090 (0.833–1.427) | .529 |
| 130–159 | 2504 | 116 (4.6) | 1.269 (0.960–1.676) | .094 |
| 160–189 | 964 | 44 (4.6) | 1.249 (0.866–1.802) | .234 |
| ≥190 | 302 | 14 (4.6) | 1.270 (0.714–2.256) | .416 |
| HDL cholesterol (mg/dL) | | | | .014 |
| <40 | 1271 | 60 (4.7) | 1.000 | |
| 40–60 | 5526 | 250 (4.5) | 0.956 (0.717–1.276) | .762 |
| ≥60 | 3124 | 103 (3.3) | 0.688 (0.497–0.953) | .024 |
| Triglyceride (mg/dL) | | | | |
| <150 | 7480 | 308 (4.1) | 1.000 | .561 |
| 150–199 | 1195 | 55 (4.6) | 1.123 (0.838–1.507) | .437 |
| 200–499 | 1168 | 49 (4.2) | 1.020 (0.749–1.387) | .901 |
| ≥500 | 78 | 1 (1.3) | 0.302 (0.042–2.181) | .236 |
| AST (IU/L) | | | | |
| ≤32 for men | 8378 | 349 (4.2) | 1.000 | .547 |
| >32 for men | 1740 | 67 (3.9) | 0.921 (0.706–1.203) | |
| ALT (IU/L) | | | | |
| ≤34 for men | 7842 | 321 (4.1) | 1.000 | .868 |
| >34 for men | 2277 | 95 (4.2) | 1.020 (0.807–1.289) | |
| GGT (IU/L) | | | | |
| ≤71 | 8551 | 354 (4.1) | 1.000 | .955 |
| >71 | 1566 | 62 (4.0) | 0.955 (0.725–1.257) | |
| ALP (IU/L) | | | | |
| ≤130 | 641 | 26 (4.1) | 1.000 | .972 |
| >130 | 8416 | 339 (4.0) | 0.993 (0.661–1.492) | |
| Hepatitis B surface antigen | | | | |
| Positive | 384 | 17 (4.4) | 0.909 (0.552–1.497) | .708 |
| Negative | 7797 | 315 (4.0) | 1.000 | |
| Physical activity | | | | |
| Yes | 1576 | 69 (4.4) | 0.925 (0.710–1.204) | .561 |
| No | 8543 | 347 (4.1) | 1.000 | |
| High-risk alcohol drinker† | | | | |
| Yes | 3558 | 142 (4.0) | 1.048 (0.852–1.289) | .654 |
| No | 6561 | 274 (4.2) | 1.000 | |

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyltransferase, HBsAg = hepatitis B surface antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* This value was obtained using binary regression analysis.

† For male, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses for female) and drinking 2 or more times per week irrespective of the glass size.

**Table 4**

**Multivariable analysis of risk factors for gallbladder polyps among subjects who underwent medical checkups.**

| GBPs | | | |
|---|---|---|---|
| **Factor** | **Odds ratio** | **95% Confidence interval** | ***P* value** |
| Gender (%) | | | <.001 |
| Male | 1.000 | | |
| Female | 0.073 | 0.756–1.867 | |
| **GBPs ≥5 mm in diameter** | | | |
| **Factors** | **Odds ratio** | **95% Confidence interval** | ***P* value** |
| Age (years) | | | .013 |
| 20–49 | 1.000 | | |
| 50–59 | 1.026 | 0.815–1.291 | .828 |
| ≥60 | 0.722 | 0.562–0.928 | .011 |
| HDL cholesterol (mg/dL) | | | .011 |
| <40 | 1.000 | | |
| 40-60 | 0.946 | 0.709–1.263 | .706 |
| ≥60 | 0.676 | 0.488–0.936 | .018 |

HDL = high-density lipoprotein.

**Table 5**

**Comparisons of the variables between men and women who underwent medical checkups.**

| Factor | Men (n = 5779) | Women (n = 4340) | *P* value |
|---|---|---|---|
| GBPs (%) | | | .009 |
| Yes | 352 (8.1) | 557 (9.6) | |
| No | 3988 (91.9) | 5222 (90.4) | |
| GBPs ≥5 mm in diameter (%) | | | .010 |
| Yes | 153 (3.5) | 263 (4.6) | |
| No | 4187 (96.5) | 5516 (95.4) | |
| Metabolic syndrome | | | <.001 |
| Yes | 1562 (32.5) | 811 (22.9) | |
| No | 3246 (67.5) | 2726 (77.1) | |
| Age (years) | 53.54 ± 11.6 | 54.2 ± 12.1 | .002 |
| Body mass index (kg/m$^2$) | 25.5 ± 3.1 | 22.6 ± 3.3 | <.001 |
| Fasting blood glucose (mg/dL) | 102.3 ± 29.7 | 95.4 ± 22.6 | <.001 |
| Total cholesterol (mg/dL) | 201.2 ± 37.5 | 198.4 ± 36.8 | <.001 |
| LDL cholesterol (mg/dL) | 122.5 ± 34.9 | 120.7 ± 33.9 | .009 |
| HDL cholesterol (mg/dL) | 49.9 ± 12.2 | 59.8 ± 14.0 | <.001 |
| Triglycerides (mg/dL) | 144.9 ± 110.7 | 89.6 ± 56.3 | <.001 |
| AST (IU/L) | 31.2 ± 99.2 | 24.2 ± 48.3 | <.001 |
| ALT (IU/L) | 37.0 ± 117.5 | 22.8 ± 61.2 | <.001 |
| GGT (IU/L) | 64.6 ± 95.8 | 24.8 ± 36.8 | <.001 |
| ALP (IU/L) | 213.0 ± 74.4 | 199.7 ± 87.1 | <.001 |
| Medication use for diabetes | | | <.001 |
| Yes | 356 (6.2) | 139 (3.2) | |
| No | 5423 (93.8) | 4201 (96.8) | |
| Medication use for dyslipidemia | | | .012 |
| Yes | 313 (5.4) | 287 (6.6) | |
| No | 5466 (94.6) | 4053 (93.4) | |
| Medication use for hypertension | | | <.001 |
| Yes | 952 (16.5) | 529 (12.2) | |
| No | 4827 (83.5) | 3811 (87.8) | |
| HBsAg | | | .039 |
| Positive | 241 (5.1) | 143 (4.1) | |
| Negative | 4472 (94.9) | 3325 (95.9) | |
| Physical activity | | | <.001 |
| Yes | 976 (16.9) | 600 (13.8) | |
| No | 4803 (83.1) | 3740 (86.2) | |
| High-risk alcohol drinker* | | | <.001 |
| Yes | 2951 (51.1) | 607 (14.0) | |
| No | 2828 (48.9) | 3733 (86.0) | |

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyltransferase, HBsAg = hepatitis B surface antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* For male, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses for female) and drinking 2 or more times per week irrespective of the glass size.

increase 3–4-fold, with a continued increase from 20–50 years of age, followed by a natural decrease once people reach their sixties when dietary fat consumption decreases due to dental or digestive problems.[27] This may explain the improvement in blood lipid profiles and subsequent decreases in the prevalence of GBPs among individuals >60 years of age. In our study, the 50–59-year age group had the highest mean levels of total cholesterol and LDL cholesterol. These results support the hypothesis of improved dyslipidemia in old age proposed by Yamin et al.[26] Most GBPs are cholesterol polyps. Although the pathogenetic mechanism of GBPs remains unknown, a common hypothesis is that cholesterol deposition in the blood or bile combined with gallbladder dysmotility directly affects the development and growth of GBPs. Thus, improvements in blood lipid profiles decrease the cholesterol concentration of bile, leading to the formation of unsaturated bile. Additionally, an increase in gallbladder sensitivity to cholecystokinin due to decreased LDL cholesterol levels might increase gallbladder motility, preventing the growth of cholesterol polyps. Younger age (<60 years) might have become a risk factor for GBPs ≥5 mm in diameter through such a process.

Many studies have reported that dyslipidemia is a risk factor for GBPs. Furthermore, a recent meta-analysis of an East Asian population showed that HDL cholesterol and LDL cholesterol are also risk factors for GBPs.[26] In our study, HDL cholesterol level was not an independent risk factor for GBPs, but it was a modifiable risk factor for GBPs ≥5 mm in diameter. This may be because GBP growth might have been prevented by increased HDL cholesterol levels reducing the cholesterol levels in blood or bile. However, the question remains as to whether younger age or lower HDL cholesterol levels might have affected only the growth of GBPs without independently contributing to the prevalence of GBPs. Both younger age and decreased HDL cholesterol levels were statistically significant factors in the univariate analysis, but this was not the case in the multivariable analysis. Although younger age and lower HDL cholesterol levels exerted influences, sex is a strongly unamendable decisive factor and ultimately might not have remained an independent factor in the multivariable analysis. Thus, further research analyzing each gender separately is needed.

Clinically significant GBPs ≥5 mm in diameter are associated with increased morbidity, mortality, and economic losses due to the need for additional periodical ultrasound exams or progression to gallbladder cancer requiring surgery or other treatment. These burdens could be mitigated if modifiable risk factors for GBPs ≥5 mm in diameter are identified and addressed. In this study, age < 60 years and HDL cholesterol level ≥60 mg/dL were independent factors affecting the presence of GBPs ≥5 mm in diameter. Frequent ultrasonographic evaluations (and their accompanying costs) can be avoided as GBPs <5 mm wide in patients >60 years are not likely to progress to clinically significant GBPs. Additionally, this information can be used for patient education or in advertisements for the general public to improve HDL cholesterol levels to prevent the development of

**Table 6**

**Comparisons of the variables associated with the presence of gallbladder polyps among 3 age groups in subjects who underwent medical checkups.**

| Factor | Age <50 years (n = 3605) | Age 50–59 years (n = 3265) | Age ≥60 years (n = 3249) | *P* value |
|---|---|---|---|---|
| Gender (%) | | | | <.001 |
| Male | 2153 (59.7) | 1866 (57.2) | 1760 (54.2) | |
| Female | 1452 (40.3) | 1399 (42.8) | 1489 (45.8) | |
| GBPs (%) | | | | .004 |
| Yes | 341 (9.5) | 320 (9.8) | 248 (7.6) | |
| No | 3264 (90.5) | 2945 (90.2) | 3001 (92.4) | |
| **GBPs ≥5 mm in diameter** | | | | .022 |
| Yes | 159 (4.4) | 149 (4.6) | 108 (3.3) | |
| No | 3446 (95.6) | 3116 (32.1) | 3141 (96.7) | |
| Metabolic syndrome | | | | <.001 |
| Yes | 523 (19.9) | 777 (26.9) | 1073 (38.0) | |
| No | 2109 (80.1) | 2113 (73.1) | 1750 (62.0) | |
| Body mass index (kg/m$^2$) | 24.5 ± 3.8 | 24.7 ± 3.1 | 24.8 ± 3.0 | <.001 |
| Fasting blood glucose (mg/dL) | 94.4 ± 20.3 | 99.7 ± 27.7 | 104.5 ± 31.7 | <.001 |
| Total cholesterol (mg/dL) | 195.4 ± 36.2 | 204.6 ± 36.3 | 200.6 ± 38.5 | <.001 |
| LDL cholesterol (mg/dL) | 116.3 ± 33.0 | 125.9 ± 34.1 | 123.5 ± 35.8 | <.001 |
| HDL cholesterol (mg/dL) | 54.7 ± 14.3 | 54.3 ± 13.7 | 53.4 ± 13.7 | .001 |
| Triglycerides (mg/dL) | 123.0 ± 109.2 | 122.4 ± 94.8 | 118.6 ± 79.1 | .127 |
| AST (IU/L) | 29.1 ± 128.7 | 27.2 ± 30.0 | 28.4 ± 37.3 | .643 |
| ALT (IU/L) | 34.0 ± 138.0 | 30.3 ± 80.3 | 28.2 ± 45.7 | .044 |
| GGT (IU/L) | 47.1 ± 83.7 | 50.9 ± 81.1 | 44.7 ± 70.3 | .006 |
| ALP (IU/L) | 198.9 ± 84.5 | 203.7 ± 66.4 | 220.5 ± 85.9 | <.001 |
| Medication use for diabetes | | | | <.001 |
| Yes | 45 (1.2) | 136 (4.2) | 314 (9.7) | |
| No | 3560 (98.8) | 3129 (95.8) | 2935 (90.3) | |
| Medication use for dyslipidemia | | | | <.001 |
| Yes | 59 (1.6) | 164 (5.0) | 377 (11.6) | |
| No | 3546 (98.4) | 3101 (95.0) | 2872 (88.4) | |
| Medication use for hypertension | | | | <.001 |
| Yes | 122 (3.4) | 397 (12.2) | 962 (29.6) | |
| No | 3483 (96.6) | 2868 (87.8) | 2287 (70.4) | |
| Hepatitis B surface antigen | | | | .004 |
| Positive | 120 (3.8) | 143 (5.7) | 121 (4.9) | |
| Negative | 3049 (96.2) | 2382 (94.3) | 2366 (95.1) | |
| Physical activity | | | | <.001 |
| Yes | 473 (13.1) | 497 (15.2) | 606 (18.7) | |
| No | 3132 (86.9) | 2768 (84.8) | 2643 (81.3) | |
| High-risk alcohol drinker* | | | | <.001 |
| Yes | 1447 (40.1) | 1265 (38.7) | 846 (26.0) | |
| No | 2158 (59.9) | 2000 (61.3) | 2403 (74.0) | |

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyltransferase, HBsAg = hepatitis B surface antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* For male, a high-risk alcohol drinker was defined as a subject consuming 7 or more glasses of alcohol (5 or more glasses for female) and drinking 2 or more times per week irrespective of the glass size.

significant polyps. Prospective multicenter studies are warranted to investigate the clinical implications of these results.

There were several limitations to this study. First, the participants were from Jeju Island, South Korea, which is isolated from mainland Korea. Thus, the results from mainland Korea might have been different. Future studies should include participants from mainland Korea. Second, this study did not collect or analyze data, such as a history of smoking, nonalcoholic fatty liver disease, and body weight changes, but these factors are likely associated with GBPs. Third, risk factors could not be compared in terms of GBP components because ultrasonography cannot be used to perform GBP component analysis. Fourth, this was a retrospective study wherein participants had to complete a questionnaire. Consequently, self-report bias was inherent despite our best efforts to minimize it.

Despite the above-mentioned limitations, this study was the first analysis to emphasize clinically significant GBPs ≥5 mm in diameter. A prospective, long-term, multicenter observational study is required to validate the findings of this study for clinical applicability.

This study showed that gender was a risk factor affecting the prevalence of GBPs and that age and high-density lipoprotein-cholesterol levels were risk factors for the presence of GBPs ≥5 mm in diameter. HDL cholesterol levels could be a modifiable risk factor affecting the presence of GBPs ≥5 mm wide.

## Author contributions

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