Cholecystectomy reduces the risk of myocardial and cerebral infarction in patients with gallstone-related infection

Seon Mee Park  
Chungbuk National University College of Medicine and Chungbuk National University Hospital

Hyun Jung Kim  
Korea University College of Medicine

Tae Uk Kang  
Health & Wellness College, Sungshin Women's University

Heather Swan  
Korea University College of Medicine

Hyeong Sik Ahn  (iebm.ku@gmail.com)  
Korea University College of Medicine

Article

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Abstract

Aim: We compared the risk of myocardial infarction (MI) or cerebral infarction (CI) in patients with or without-gallstone-related infection (GSI) and change in the risk following cholecystectomy.

Methods: GSI (n=84,467) and non-GSI (n=406,800) patients with age- and sex-matched controls (n=4,912,670) were identified from Korean population based data. The adjusted hazard ratios (aHRs) of MI or CI were analyzed in both groups treated with or without cholecystectomy. Subgroup analysis was performed for both sex and different ages.

Results: The risk of MI or CI was higher in the GSI group than in the non-GSI group (aHR for MI; 1.32 vs. 1.07, aHR for CI; 1.24 vs. 1.06, respectively). The risk reduction rate of MI following cholecystectomy was 11.4% in the GSI group, whereas it was 0% in the non-GSI group. The risk of CI after cholecystectomy was more reduced in the GSI group than in the non-GSI group (16.1% and 4.7%, respectively). The original risk of MI or CI in patients with gallstone and risk reduction rates following cholecystectomy were higher in females and younger patients than in males and older patients.

Conclusion: Increased risk of MI or CI and greater risk reduction following cholecystectomy were seen in patients with GSI.

Introduction

Gallstones are one of the leading cause of hospital admissions, with a worldwide prevalence as high as 5−15%. The majority of gallstone carriers remain asymptomatic; however, one in five develop biliary pain or gallstone-related complications. Complicated gallstones developed at a rate of 7.2% during 17.5 year follow up. They developed mostly due to gallstone-related infection (GSI) such as acute cholecystitis or acute cholangitis. Cholecystectomy is usually indicated for symptomatic gallstones, and it is widely indicated in laparoscopic era.

An association between gallstones and cardiovascular disease (CVD) has been reported in several studies, demonstrating up to 1.1–2.0-fold CVD risks in patients with gallstones. Shared cardio-metabolic risk factors have been identified as a cause of this association such as smoking, alcohol drinking, physical inactivity, obesity, and health factors including abnormalities in lipid profile, blood pressure, or glucose level. Shared common pathogenesis of CVD and gallstones has been proposed as another cause of this association. Chronic inflammatory process and oxidative stress are the main causes of vascular atherosclerosis and gallstone formation.

There is solid evidence that chronic infection in humans plays a role in the development of atherogenesis. Recent studies have emphasized the role of bacterial infection in the development of atherosclerosis. Gram-negative bacteria, major pathogens of GSI, produce lipopolysaccharide (LPS) or inflammatory mediators in the serum of patients. Vascular CVD, such as acute coronary syndrome, myocardial infarction (MI), and cerebral infarction (CI) may increase in patients with GSI compared to non-GSI. However, only few studies have been reported with mixed results.

Moreover, existing literature shows conflicting findings regarding the role of cholecystectomy in CVD risk. Several studies have demonstrated equivocal CVD risks after cholecystectomy, while others have reported increased or reduced risks of CVD following cholecystectomy. Cholecystectomy may have a role in eliminating the source of inflammation. Because control of inflammation is considered a promising treatment for CVD, cholecystectomy may reduce the risk of MI or CI in patients with GSI. The apparent increased CVD risk in the cholecystectomy group may not be due to gallbladder removal but by confounding variables such as gallstone-related inflammation. This hypothesis is supported by the findings that CVD risks decreased after cholecystectomy by adjustment of severity of gallstone-related inflammation. However, growing evidences were also reported that cholecystectomy itself induces metabolic syndrome, which is a risk factor for CVD. We suggest that the effects of cholecystectomy on CVD risk may depend on GSI or non-GSI state.

This population-based large cohort study aimed to assess the effects of cholecystectomy on the risk of MI or CI in patients with GSI or non-GSI. This study used the Korean National Health Insurance (NHI) and National Health Screening Program (NHSP) databases, which have reliable data regarding lifestyle factors, gallstone diagnoses, and cholecystectomy, to assess the risk of MI or CI with nearly full population coverage. Additional analyses were performed for both sex and different age groups.

Results
Patient characteristics

Gallstone patients (n = 491,267) and controls (n = 4,912,670) are included in this study (Fig. 1) and their demographics are presented in Table 1. The male-to-female ratio was 51.8/48.2 and mean age was 53 years. There were no differences in clinical characteristics between gallstone patients and controls except for BMI; the gallstone group had a higher rate of obesity than the controls (P = 0.2). Among gallstone patients, the GSI (n = 84,467, 17.2%) and non-GSI (n = 406,800, 82.8%) groups were identified. The GSI group included patients with acute cholecystitis (n = 80,076, 94.8%) or acute cholangitis (n = 4,391, 5.2%). They revealed similar clinical features in terms of age, sex, and other risk factors. However, the cholecystectomy rates were quite different, with 66.0% in the GSI group and 30.4% in the non-GSI group.
Table 1
Demographics of study populations with or without gallstone-related infection and controls

| Characteristics                  | Gallstones (+) | Gallstone-related infection | Gallstone-related infection | Total          |
|----------------------------------|----------------|----------------------------|----------------------------|---------------|
| No. of persons                   | 84,467         | 406,800                    | 491,267                    | 4,912,670     |
| Sex                              |                |                            |                            |               |
| Male                             | 44,369         | 209,954                    | 254,323                    | 2,543,230     |
| Female                           | 40,098         | 196,846                    | 236,944                    | 2,369,440     |
| Ages (years), Mean ± SD          | 54.51          | 54.81                      | 54.61                      | 54.56         |
| Ages stratified, years           |                |                            |                            |               |
| 20 ~ 29                          | 2,212          | 10,163                     | 12,375                     | 123,750       |
| 30 ~ 39                          | 9,503          | 41,398                     | 50,901                     | 509,010       |
| 40 ~ 49                          | 17,917         | 88,919                     | 106,836                    | 1,068,360     |
| 50 ~ 59                          | 22,143         | 117,320                    | 139,463                    | 1,394,630     |
| 60 ~ 69                          | 19,316         | 95,141                     | 114,457                    | 1,144,570     |
| 70+                              | 13,376         | 53,859                     | 67,235                     | 672,350       |
| Cholecystectomy                  |                |                            |                            |               |
| Yes                              | 55729          | 123,592                    | 179,321                    | 1,655,334     |
| No                               | 28738          | 283,208                    | 311,946                    | 3,511,413     |
| SBP / DBP (mmHg)                 |                |                            |                            |               |
| < 120 / <80                      | 28117          | 131,965                    | 160,082                    | 1,655,334     |
| 120–129 / <80                    | 10017          | 49,422                     | 59,439                     | 588,377       |
| 130–139 / 80–89                  | 30663          | 149,700                    | 180,363                    | 1,763,149     |
| 140–179 / 90–119                 | 15263          | 73,840                     | 89,103                     | 881,723       |
| 180+ /120+                      | 390            | 1825                       | 2215                       | 23,587        |
| Pulse Pressure (mmHg)            |                |                            |                            |               |
| < 40                             | 12896          | 60,838                     | 73,734                     | 745,937       |
| 40–59                            | 60214          | 29,1799                    | 35,2013                    | 351,1413      |
| ≥ 60                             | 11340          | 54,115                     | 65,455                     | 654,804       |
| Fasting plasma glucose (mg/dl)   |                |                            |                            |               |
| < 100                            | 51307          | 247,957                    | 299,264                    | 3,154,907     |
| 100–125                          | 24463          | 118,045                    | 142,508                    | 1,346,085     |
| ≥ 126                            | 8668           | 40,682                     | 49,350                     | 410,396       |
| Cholesterol (mg/dl)              |                |                            |                            |               |
| < 200                            | 48468          | 230,295                    | 278,763                    | 2,737,743     |

All data represent number of patients (percent); Standardized mean difference (SD) ≤ 0.10 indicates a negligible difference between the two cohorts. All SD were less than 0.1 except BMI (P = 0.2 for gallstone patients vs. matched controls); SBP/DBP, systolic blood pressure/diastolic blood pressure; body mass index (BMI).
## Characteristics

| Characteristics                        | Gallstones (+) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          | Gallstones (-) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          |
|----------------------------------------|----------------|--------------------------------|--------------------------------|---------------|----------------|--------------------------------|--------------------------------|---------------|
|                                        | 25673          | 30.4                           | 125469                         | 30.8          | 151142         | 30.8                           | 1557014         | 31.7          |
| ≥240                                   | 10287          | 12.2                           | 50885                          | 12.5          | 61172          | 12.5                           | 616144          | 12.5          |

BMI (kg/height, m²)

| BMI (%)                           | Gallstones (+) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          | Gallstones (-) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          |
|-----------------------------------|----------------|--------------------------------|--------------------------------|---------------|----------------|--------------------------------|--------------------------------|---------------|
| < 18.5                            | 1924           | 2.3                            | 9390                           | 2.3           | 11314          | 2.3                            | 138799          | 2.8           |
| 18.5–25.0                         | 45334          | 53.7                           | 222092                         | 54.6          | 267426         | 54.4                           | 3022252         | 61.5          |
| ≥25.0                             | 37209          | 44.1                           | 175318                         | 43.1          | 212527         | 43.3                           | 1751619         | 35.7          |

Smoking (pack/year)

| Smoking (pack/year) | Gallstones (+) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          | Gallstones (-) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          |
|---------------------|----------------|--------------------------------|--------------------------------|---------------|----------------|--------------------------------|--------------------------------|---------------|
| none                | 53249          | 63.0                           | 260221                         | 64.0          | 313470         | 63.8                           | 3174589         | 64.6          |
| 1~9                 | 8734           | 10.3                           | 40231                         | 9.9           | 48965          | 10.0                           | 490480          | 10.0          |
| 10~19               | 8927           | 10.6                           | 42272                         | 10.4          | 51199          | 10.4                           | 513203          | 10.5          |
| 20~29               | 5809           | 6.9                            | 28184                         | 6.9           | 33993          | 6.9                            | 329341          | 6.7           |
| 30~39               | 3488           | 4.1                            | 16613                         | 4.1           | 20101          | 4.1                            | 190061          | 3.9           |
| 40+                 | 3422           | 4.1                            | 15180                         | 3.7           | 18602          | 3.8                            | 166347          | 3.4           |

Alcohol drinking

| Alcohol drinking     | Gallstones (+) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          | Gallstones (-) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          |
|---------------------|----------------|--------------------------------|--------------------------------|---------------|----------------|--------------------------------|--------------------------------|---------------|
| none                | 41635          | 49.3                           | 196675                         | 48.3          | 238310         | 48.5                           | 2333815         | 47.5          |
| < one/month         | 18235          | 21.6                           | 84683                          | 20.8          | 102918         | 20.9                           | 1089546         | 22.2          |
| < one/week          | 2352           | 2.8                            | 12495                         | 3.1           | 14847          | 3.0                            | 153866          | 3.1           |
| ≥ one/week          | 11947          | 14.1                           | 59542                          | 14.6          | 71489          | 14.6                           | 701408          | 14.3          |

Physical activity

| Physical activity   | Gallstones (+) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          | Gallstones (-) | Gallstone-related infection (+) | Gallstone-related infection (-) | Total          |
|---------------------|----------------|--------------------------------|--------------------------------|---------------|----------------|--------------------------------|--------------------------------|---------------|
| none                | 42204          | 50.0                           | 199106                         | 48.9          | 241310         | 49.1                           | 2365622         | 48.2          |
| 1~2/week            | 23866          | 28.3                           | 116096                         | 28.5          | 139962         | 28.5                           | 1414395         | 28.8          |
| 3~4/week            | 9863           | 11.7                           | 49307                          | 12.1          | 59170          | 12.0                           | 603795          | 12.3          |
| 5~6/week            | 3857           | 4.6                            | 19004                          | 4.7           | 22861          | 4.7                            | 242165          | 4.9           |
| every day           | 3268           | 3.9                            | 16226                         | 4.0           | 19494          | 4.0                            | 201111          | 4.1           |

All data represent number of patients (percent); Standardized mean difference (SD) ≤ 0.10 indicates a negligible difference between the two cohorts. All SD were less than 0.1 except BMI (P = 0.2 for gallstone patients vs. matched controls); SBP/DBP, systolic blood pressure/diastolic blood pressure; body mass index (BMI).

### Incidences and risks of MI or CI in GSI or non-GSI groups

The cumulative incidence of MI or CI during the 15-year follow-up (4,403,817 person-years) was observed among gallstone patients without cholecystectomy and controls. The incidence of MI or CI was highest in the GSI group, followed by the non-GSI group and controls. The incidence rate ratios (IRR, 95% confidence intervals [CI]) and adjusted hazard ratio (aHR, 95% CI) of MI and CI are presented (Table 2). Among gallstone patients who did not undergo cholecystectomy, the IRR and aHR of MI were higher in the GSI group (1.40 [1.23–1.60] and 1.32 [1.20–1.44], respectively) than in the non-GSI group (1.10 [1.04–1.15] and 1.07 [1.02–1.12], respectively). The IRR and aHR for CI were also higher in the GSI group (1.32 [1.20–1.44] and 1.24 [1.13–1.36], respectively) than in the non-GSI group (1.09 [1.05–1.13] and 1.06 [1.03–1.10], respectively).
| Gallstones | All | GSI | non-GSI |
|------------|-----|-----|---------|
|            | aHR (95% CI) | Events/ person-time | Rate* (95% CI) | IRR (95% CI) | aHR (95% CI) | Events/ person-time | Rate (95% CI) | IRR (95% CI) | aHR (95% CI) |
| **Myocardial infarction** | | | | | | | | | |
| Matched control | 5,035/ 5,414,099 | 9.30 (9.05– 9.56) | 23,831/26,623,120 | 8.95 (8.84– 9.07) |
| Without cholecystectomy | 1.10 (1.05– 1.15) | 235/180,021 | 13.05 (11.49– 14.83) | 1.40 (1.23– 1.60) | 1.32 (1.15– 1.50) | 767/849,656 | 9.03 (8.41– 9.69) | 1.01 (0.94– 1.08) | 1.07 (1.00– 1.15) |
| With cholecystectomy | 1.10 (1.03– 1.16) | 381/356,528 | 10.69 (9.67– 11.82) | 1.15 (1.03– 1.28) | 1.17 (1.05– 1.29) | 767/849,656 | 9.03 (8.41– 9.69) | 1.01 (0.94– 1.08) | 1.07 (1.00– 1.15) |
| Risk reduction by cholecystectomy(%)# | 0.0 (4.9– 1.9) | | 11.4 (8.7– 14.0) | | | | 0.0 (2.7– 2.0) |
| **Cerebral infarction** | | | | | | | | | |
| Matched control | 10,656/ 5,392,612 | 19.76 (19.39– 20.14) | 48,835/ 26,526,916 | 18.41 (18.25– 18.57) |
| Without cholecystectomy | 1.08 (1.05– 1.12) | 466/179,145 | 26.01 (23.75– 28.48) | 1.32 (1.20– 1.44) | 1.24 (1.13– 1.36) | 3,569/1,778,205 | 20.07 (19.42– 20.74) | 1.09 (1.05– 1.13) | 1.06 (1.03– 1.10) |
| With cholecystectomy | 1.02 (0.98– 1.06) | 708/355,075 | 19.94 (18.52– 21.46) | 1.01 (0.93– 1.09) | 1.04 (0.96– 1.12) | 1,474/ 846,798 | 17.41 (16.54– 18.32) | 0.95 (0.90– 1.00) | 1.01 (0.96– 1.07) |
| Risk reduction by cholecystectomy(%)# | 5.6 (5.4– 6.7) | | 16.1 (15.0– 17.6) | | | | 4.7 (2.7– 6.8) |

* No. of events/10^4 person-time; GSI, gallstone-related inflammation; MI, myocardial infarct; CI, cerebral infarct; IRR, incidence rate ratio; aHR, adjusted hazard ratio; #, HR (C−C+) / C−x100(%)

Effects of cholecystectomy on the incidences and risks of MI or CI in both GSI or non-GSI groups

The cumulative incidence of MI or CI according to cholecystectomy in both the GSI and non-GSI groups was presented (Fig. 2). In both the GSI and non-GSI groups, MI or CI incidences were reduced in patients who had undergone cholecystectomy compared to those who did not. However, the GSI group showed a higher risk reduction after cholecystectomy than the non-GSI group.

The IRR (95% CI) and aHR (95% CI) of MI or CI were analyzed according to cholecystectomy in the GSI and non-GSI groups (Table 2). In the GSI group, the IRRs and aHR of MI were lower in patients who underwent cholecystectomy (1.15 [1.03– 1.28] and 1.17 [1.05– 1.29], respectively) than in those who did not (1.40 [1.23– 1.60] and 1.32 [1.15– 1.50], respectively). However, in the non-GSI group, the IRR and aHR of MI were nearly matched between patients who underwent cholecystectomy (1.01 [0.94– 1.08] and 1.07 [1.00– 1.15], respectively) and those who did not (1.10 [1.04– 1.15] and 1.07 [1.02– 1.12], respectively). Risk reduction rates in the GSI and non-GSI groups were 11% and 0%, respectively.

The IRRs and aHR of CI were lower in patients who underwent cholecystectomy (1.01 [0.93– 1.09] and 1.04 [0.96– 1.12], respectively) than in those who did not (1.32 [1.20– 1.44] and 1.24 [1.13– 1.36], respectively) in the GSI group. Although the IRR and aHR of CI were lower in patients who underwent cholecystectomy (0.95 [0.90– 1.00] and 1.01 [0.96– 1.07], respectively) than in those who did not (1.09
[1.05–1.13] and 1.06 [1.03–1.10], respectively), its effect was minimal in the non-GSI group. Risk reduction rates in the GSI and non-GSI groups were 16% and 5%, respectively.

The aHR of each confounding factor are presented in Table 3. Hypertension, pulse pressure, fasting plasma glucose (FPG), body mass index (BMI), cholesterol, and smoking were dose-responsive risk factors for MI or CI. Cholesterol and smoking were associated with a higher risk of MI than CI, whereas hypertension was associated with a higher risk of CI than MI. Pulse pressure, FPG and BMI revealed similar risks between the MI and CI groups. Physical activity reduced the risk of MI and CI, while alcohol consumption being negatively associated with MI but not CI.
Table 3
Cox proportional hazard analysis of risk factors associated with incidences of myocardial infarction and cerebral infarction

| Parameters          | myocardial infarction | cerebral infarction |
|---------------------|------------------------|---------------------|
|                     | HR | 95% CI | HR | 95% CI |
| SBP / DBP           |    |        |    |        |
| <120 / <80          | 1.00 |       | 1.00 |       |
| 120–129 / <80       | 1.05 | 1.00   | 1.09 | 1.02   | 1.09 |
| 130–139 / 80–89     | 1.16 | 1.12   | 1.19 | 1.21   | 1.18 | 1.24 |
| 140–179 / 90–119    | 1.29 | 1.24   | 1.34 | 1.41   | 1.38 | 1.45 |
| 180+ /120+          | 1.68 | 1.52   | 1.86 | 1.94   | 1.82 | 2.07 |
| Pulse Pressure      |    |        |    |        |
| <40                 | 1.00 |       | 1.00 |       |
| 40–59               | 1.07 | 1.03   | 1.12 | 1.09   | 1.06 | 1.13 |
| ≥60                 | 1.13 | 1.07   | 1.18 | 1.14   | 1.10 | 1.18 |
| Fasting Plasma Glucose |        |        |    |        |
| <100                | 1.00 |       | 1.00 |       |
| 100–125             | 1.07 | 1.05   | 1.10 | 1.06   | 1.04 | 1.08 |
| ≥126                | 1.65 | 1.60   | 1.71 | 1.60   | 1.56 | 1.63 |
| BMI                 |    |        |    |        |
| <18.5               | 1.00 |       | 1.00 |       |
| 18.5–25.0           | 1.04 | 0.96   | 1.13 | 1.09   | 1.04 | 1.15 |
| ≥25.0               | 1.08 | 1.06   | 1.11 | 1.02   | 1.01 | 1.04 |
| Cholesterol (mg/dL) |    |        |    |        |
| <18.5               | 1.00 |       | 1.00 |       |
| 18.5–25.0           | 1.21 | 1.18   | 1.24 | 1.05   | 1.03 | 1.07 |
| ≥25.0               | 1.53 | 1.49   | 1.58 | 1.11   | 1.09 | 1.14 |
| Smoking (pack/year) |    |        |    |        |
| none                | 1.00 |       | 1.00 |       |
| 1 ~ 9               | 1.22 | 1.16   | 1.28 | 1.14   | 1.09 | 1.18 |
| 10 ~ 19             | 1.45 | 1.40   | 1.51 | 1.26   | 1.23 | 1.30 |
| 20 ~ 29             | 1.62 | 1.56   | 1.69 | 1.38   | 1.34 | 1.43 |
| 30 ~ 39             | 1.67 | 1.59   | 1.77 | 1.37   | 1.32 | 1.43 |
| 40+                 | 1.81 | 1.73   | 1.90 | 1.50   | 1.45 | 1.56 |
| Alcohol Drinking    |    |        |    |        |
| none                | 1.00 |       | 1.00 |       |
| < one/month         | 0.75 | 0.73   | 0.78 | 0.97   | 0.95 | 1.00 |

HR, Hazard ratio; CI, confidence interval; †, number in parenthesis means the amount of alcohol consumption in women
Subgroup analysis of MI or CI risks by both sexes and by different ages

A subgroup analysis was performed for both males and females. Females had a higher risk and higher risk reduction rate after cholecystectomy for MI than males, while there were no differences in CI risks between sexes (Fig. 3). Subgroup analysis was performed for different age groups. Risk of MI or CI and risk reduction rates by cholecystectomy were higher in younger patients than in older patients (Fig. 4).

Discussion

The positive association between gallstones and CVD has recently received much attention because of the increasing role of inflammation in the development of CVD and gallstones. In addition to the subclinical inflammatory process, acute bacterial infections associated with gallstones may accelerate atherosclerosis in the vasculature. We carried out a risk analysis to investigate the CVD risk in the GSI or non-GSI groups treated by cholecystectomy. In this study, we demonstrated that CVD risks and risk changes due to treatment are determined by the presence or absence of GSI. The GSI group had greater risks of MI or CI and higher risk reduction by cholecystectomy than the non-GSI group. To the best of our knowledge, this is the first study to demonstrate that CVD risk is strongly associated with GSI and is partially reduced by cholecystectomy in patients with gallstones.

The role of inflammation in CVD risk has been emphasized in recent years. Control of the inflammatory reaction is targeted as a strategy for atheroprotection. We hypothesized that CVD risk among gallstone patients increases under GSI conditions. Gram-negative bacteremia frequently occurs in patients with GSI, which produces LPS or circulating endotoxins. These inflammatory mediators accelerate atherosclerosis or vasculopathy via cytokines from human vascular endothelial and smooth muscle cells. In this study, the risk of MI or CI increased by 32% and 24%, respectively, in the GSI group compared to controls, while they were nearly equal to controls in the non-GSI group. Studies regarding CVD risk in GSI and non-GSI groups have reported mixed results. In one study, risk of ischemic stroke increased by 7% in symptomatic gallstones compared with asymptomatic gallstones, while hemorrhagic stroke showed similar results. On the other hand, CVD risk was similar between severe and non-severe gallstone patients in another study. They defined symptomatic gallstones as acute cholecystitis, acute cholangitis, biliary pancreatitis, or those treated by surgery or endoscopic intervention. Moreover, recent meta-analysis reported that CVD risk was higher in screen-detected gallstones than in symptomatic gallstones with 35% and 21% increased risk, respectively, with reference to controls. These unmatched results may be caused by incomplete adjustment of other risk factors such as obesity, physical inactivity, high blood pressure, high blood glucose level, alcohol drinking or smoking.

In the present study, cholecystectomy had a greater effect on the CVD risk in the GSI group than in the non-GSI group. Cholecystectomy partially reduced the increased risk of CVD in the GSI group. Attenuation of systemic inflammation by cholecystectomy may have a role in reducing CVD risk. Risk reduction by cholecystectomy was greater in CI than in MI in the GSI group, with 16.1% and 11.4%, respectively. However, the original risk of CVD and the risk reduction by cholecystectomy were negligible in the non-GSI group. Studies regarding cholecystectomy and CVD risk factors are rare and have reported mixed results. A population-based study in Taiwan revealed that stroke risk decreased in gallstone patients who underwent cholecystectomy compared with those who did not. Risk reduction rates were 46% and 25% for symptomatic gallstones and asymptomatic gallstones, respectively. However, several studies have reported that...
cholecystectomy for gallstones did not influence CVD risks. Moreover, CVD risk was higher in case of gallstones treated by cholecystectomy compared to screening-detected gallstones or gallstones treated conservatively. However, they did not compare CVD risks separately in GSI and non-GSI groups nor adjustment by severity of inflammation. Cholecystectomy is usually indicated for biliary pain and gallstone-related complications. Therefore, patients who require cholecystectomy may have more complicated gallstones. Therefore, the increased CVD risk in the cholecystectomy group was not due to cholecystectomy itself but due to confounding variables related to high CVD risk.

In the present study, CVD risk among gallstone patients was higher in younger than in older patients. This finding was consistent with a recent meta-analysis. Because younger people had a low prevalence of gallstones and fewer other CVD risks, the effect of gallstones or cholecystectomy seemed to be stronger in the younger group. Theses findings suggested that younger patients with gallstones should be given more attention for the prevention of CVD. In addition, the risk of MI was higher in females than in males, whereas the risk of CI was similar between the sexes. These findings were consistent with those of previous studies, where CVD risks were higher in females than in males among gallstone patients. The explanation for these results is not clear, but we speculate that gallstones or cholecystectomy seemed to have a stronger risk of MI in females because of fewer other risk factors and a lower incidence of MI compared to males. No previous studies have performed subgroup analysis for the effect of cholecystectomy in terms of sex or age. This is the first study to demonstrate that risk reduction by cholecystectomy was higher in younger patients and females compared to older patients and males.

Our data were compatible with previous studies showing that obesity, hyperlipidemia, diabetes mellitus, hypertension, smoking and long sedentary periods are associated with gallstones and CVD. These cardiometabolic factors were revealed as dose-responsive predictors of both MI and CI, with a slight difference between them. As in a previous study, hypertension was associated with a higher risk of CI than MI, whereas cholesterol and smoking showed the opposite effect. In this study, the adjusted risk (aHR) of gallstones for CVD development was lower than crude risk (IRR). CVD risk among gallstone patients was usually lower with complete adjustment of confounding factors, longer follow-up, and a larger study compared to their counterparts. Therefore, adjustment of other risk factors is needed to evaluate the effects of gallstones on CVD development.

Disease patterns of CVD are slightly different in Eastern and Western populations. Coronary heart disease is prevalent in Western people, while stroke is prevalent in Eastern people. This study of Korean people revealed that CI incidence was 2-fold higher than MI and the risk reduction rate by cholecystectomy was higher for CI than MI. These differences between MI and CI could be explained by regional or racial variations with regards to the risk factors of MI or CI. Therefore, our results are limited to Asian populations and further studies are needed including patients with other ethnicities.

We selected controls by matching age, sex, and visit frequency as outpatients. Matched clinic visit frequency is important to reduce selection bias in terms of economic status, interest in health, and detection bias. Using this method, we selected a control group to investigate the real effects of gallstones or cholecystectomy on the risk of MI or CI.

We identified patients diagnosed with MI or CI using the International Classification of Disease (ICD)-10 codes. A recent population-based large cohort study using the KNHI demonstrated that the ICD-10 code for CVD is valid. In this study, we defined GSI group as patients diagnosed with acute cholecystitis or acute cholangitis among gallstones using ICD-10 codes. Because the proportion of acute biliary pancreatitis was less than 1% and was not related to bacterial infection, we excluded acute biliary pancreatitis in the GSI group. The ICD-10 code for gallstones has been validated in our previous study.

This study has several limitations. First, GSI was identified using the ICD-10 code, not by clinical findings or pathology results. Detailed information regarding patient symptoms or pathological findings could not be obtained from the KNHI data. However, our data are consistent with the previous results. The proportion of GSI cases among cholecystectomy cases was 31% in this study, consistent with that of Taiwan's study. In addition, the proportion of GSI among gallstones was 17% in this study, which was compatible with 7%-26% of gallstone-related complications among gallstone patients. Therefore, our study population represents a real clinical setting. Second, there were unadjusted risk factors for CVD and gallstones, such as insulin resistance, lipid-lowering drugs, inflammatory mediators, nonalcoholic fatty liver disease and the gut microbiota. Despite these limitations, this is the first study to extensively evaluate the effects of cholecystectomy on the risk of MI or CI by adjusting for confounding factors in a large population-based cohort.

In conclusion, cholecystectomy for GSI reduces the risk of MI or CI independent of other risk factors, and it was greater in females and younger patients. However, it had minimal effect on CVD in the non-GSI group. Among patients with GSI, younger people and females
who have risk factors for CVD need close monitoring for CVD development. Cholecystectomy should be recommended in patients with prior or current biliary tract infection to reduce the risk of ischemic CVD and recurrence of biliary complications.

Methods

Data sources

The NHI and NHSP databases were used in this study. The NHI is a mandatory health insurance program that covers 97.1% of the Korean population comprising approximately 50 million individuals. Comprehensive information regarding the medical services provided to patients, such as diagnosis, demographics, prescriptions, surgeries, tests, and imaging studies were recorded in the NHI database. Patient diagnoses were documented in accordance with the ICD-10. NHI insurance subscribers are recommended to undergo standardized general health screenings biennially under the NHSP, data of which are recorded in the NHSP database. The NHSP data contain information on patients’ lifestyle and behavioral factors such as physical activity, alcohol consumption, and smoking status obtained during health checkups and questionnaires. It also includes laboratory test results and measurements, including BMI, SBP and DBP, FPG, and cholesterol levels. We used NHSP data to obtain information about the risk factors related to MI or CI.

Study population

We extracted all patients with gallstones (n = 1,269,752) from the NHI data who were registered between January 1, 2005, and December 31, 2017 according to the ICD - 10 code (K80.0 and K80.2). We excluded patients with combined bile duct stones (K80.3–80.5, n = 275,528), who had incomplete health surveillance data (n = 354,752), MI or CI prior to or within 1 year of diagnosis (n = 10,200 or n = 27,477, respectively), who underwent cholecystectomy (Q7370) prior to or within 1 year of diagnosis (n = 56,089), who died within 1 year after diagnosis (n = 23,139), and who were diagnosed with cancer before or within 1 year of diagnosis (n = 31,300). The cholecystectomy date was set as the index date, and the index date for non-cholecystectomy subjects was randomly assigned with the same index month as the matched cholecystectomy cases. Finally, 491, 267 participants were included in this study.

Patients were classified into GSI and non-GSI groups. The GSI group included patients with acute cholecystitis (K81.0, n = 80076) or acute cholangitis (K83.0, n = 4391). The GSI and non-GSI groups were further subdivided into individuals treated with or without cholecystectomy. Controls without gallstones were selected with 1:10 matched age, sex, and visit frequency as outpatients within one year for each of the GSI and non-GSI groups (n = 844,670 and n = 4,068,000, respectively).

Assessment of MI and CI

We identified MI (I21–I23) and CI (I63–I66) patients by searching for their respective ICD-10 codes. Patients were followed up until December 31, 2016, and December 31, 2017, to detect MI or CI and identify their vital status. Information regarding the vital status of each individual was obtained from Statistics Korea. For a given case, the person-year at risk was calculated as the period between the date of enrollment and the date of MI or CI diagnosis or the exit date.

Outcomes and statistical analysis

The characteristics of the GSI and non-GSI groups who did or did not undergo cholecystectomy were compared with their corresponding controls using the standard difference of means. The cumulative incidence curves of MI and CI were prepared according to GSI and non-GSI groups. The incidence of MI or CI with 95% CI was measured as the number of cases per 10^4 person-years. We measured the IRR of MI or CI in each group, using controls as a reference. Cox proportional hazard analysis was performed to examine the relationship between MI or CI incidence and explanatory factors such as age (20–29, 30–39, 40–49, 50–59, 60–69, 70 + years old), sex, systolic and diastolic blood pressure (SBP and DBP) (< 120/<80, 120–129/<80, 130–139/80–89, 140–179/90–119, 180+/120 + mmHg), pulse pressure (< 40, 40–59, 60 + mmHg), FPG (< 100, 100–125, 126 + mg/dl), cholesterol (< 200, 200–239, 240 + mg/dl), BMI (< 18.5, 18.5–25.0, 25.0 + kg/m²), smoking (none, 1–9, 10–19, 20–29, 30–39, 40 + pack/year), alcohol drinking (none, < one/month, < one/week and ≥ one/week) and physical activity (none, 1–2/week, 3–4/week, 5–6/week, every day). We adjusted the visit frequency as an outpatient within one year in patients and matched controls ranging from 0–70 to eliminate detection bias. The results are expressed in terms of the aHR of the incidence with 95% CIs. A subgroup analysis was performed for both sex and age groups. Statistical analyses were performed using the Stata/MP2 software (version 13.1; StataCorp, College Station, TX, USA). Statistical significance was defined as a P-value < 0.05.

Ethical Considerations
The study was reviewed and approved by the Ethics Committee of Korea University (KUIRB-2020-0021-01). All methods were performed in accordance with relevant regulations.

**Declarations**

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All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Author contribution**

A.H.S.: conception and design of the study, critical revision of the manuscript, and study supervision.

P.S.M.: study design, data interpretation, drafting the manuscript, and its finalization.

K.H.J.: analyzed and processed data and revision of the manuscript.

K.T.U.: obtaining the data, checking them, and producing results.

S. H.: production of the results and drafting the manuscript.

All authors read and approved the final manuscript.

**Data accessibility**

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Flow chart of the study

MI, myocardial infarction; CI, cerebral infarction; CST, cholecystectomy
Figure 2
Cumulative incidences of myocardial infarction (MI) and cerebral infarction (CI) according to gallstone-related infection (GSI) and cholecystectomy. (A, B) myocardial infarction, A: gallstone-related infection (GSI), B: non-GSI. (C, D) cerebral infarction, C: GSI, D: non-GSI. op, cholecystectomy

Figure 3
Incidence rate ratios of myocardial infarction and cerebral infarction according to gallstone-related infection (GSI) and cholecystectomy in males and females. (A) GSI, (B) non-GSI. op, cholecystectomy

Figure 4
Incidence rate ratios of myocardial infarction and cerebral infarction according to gallstone-related infection (GSI) and cholecystectomy in age groups. (A) GSI, (B) non-GSI. op, cholecystectomy