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Increased risk of gallstones after appendectomy

A longitudinal follow-up study using a national sample cohort

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Abstract

To evaluate the association between appendectomy and the occurrence of gallstones using a national sample cohort from Korea.

The Korean National Health Insurance Service-National Sample Cohort was collected from 2002 to 2013. We extracted data for patients who had undergone appendectomy (n = 14,955) and a 1:4 matched control group (n = 59,820) and then analyzed the occurrence of gallstones. The patients were matched according to age, sex, income, region of residence, hypertension, diabetes mellitus, and history of dyslipidemia. Appendectomies were identified using operation codes (Q2860-Q2863) for appendicitis alone (International Classification of Disease-10: K35). Gallstones were diagnosed if the corresponding International Classification of Disease-10 code (K80) was reported ≥2 times. Crude (simple) and adjusted hazard ratios (HRs) were analyzed using stratified Cox proportional hazard models, and 95% confidence intervals were calculated. Subgroup analyses were performed based on age, sex, and time period after appendectomy.

The adjusted HR for gallstones was 1.78 (95% confidence interval = 1.51–2.09, $P < .001$) in the appendectomy group. Consistent HRs were found in the analyses of all the subgroups determined using age and sex, with the exception of men ≥60 years of age. The risk of gallstones was increased during the first year after appendectomy.

The occurrence of gallstones was increased in the patients who had undergone appendectomy.

Abbreviations: CIs = confidence intervals, HRs = hazard ratios, ICD-10 = International Classification of Disease-10, NHIS = National Health Insurance Service, NHISS = National health Insurance Sharing Service, SD = standard deviation.

Keywords: appendectomy, appendicitis, appendix, cholelithiasis, gallstones, nested case-control studies

1. Introduction

The vermiform appendix is considered a component of gut-associated lymphoid tissue and a safe house for normal gut bacteria.[1,2] Acute appendicitis is one of the most common abdominal emergencies in the world.[3] The annual incidences (per 100,000) of appendicitis or appendectomy were reported to be 100 in North America, 151 in Western Europe, and 206 in Korea.[4] Another study indicated that the incidences of appendicitis and appendectomy were 227.1 and 135.6 (per 100,000), respectively, in Korea.[5] Direct luminal obstruction, infectious agents (adenoviruses, cytomegalovirus, and fusobac-

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SYK and HL contributed equally to this study.

Releasing of the data by the researcher is not allowed legally. All of data are available from the database of the National health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/).

NHISS allows all of this data for the any researcher who promises to follow the research ethics with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics.

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teria), genetic factors (family history), and environmental factors (seasonal presentation and ozone exposure) have been suggested as causes of appendicitis.[6]

Gallstones are crystalline deposits in the gallbladder.[7] In the USA, the prevalence of gallstones was reported to be 5.5% in men and 8.6% in women,[8] whereas in Korea, reported prevalences range from 4.2% to 5.3%.[9,10] Gallstones are categorized as cholesterol stones, pigment stones, or mixed stones based on their composition.[7] In Korea, prevalences of 58.1%, 25.2%, and 12.1% have been reported for the presence of cholesterol, black pigment, and brown pigment, respectively, in gallstones.[11] Aging, female sex, ethnicity, estrogen treatment, obesity, Westernized diet, low physical activity, liver cirrhosis, diabetes mellitus, and dyslipidemia are known to be risk factors for gallstones.[12]

A previous study reported that appendectomy increases the risk of gallstones.[13] That study also indicated that appendectomy was independently associated with gallstones in women. When we searched the PubMed and EMBASE databases using the keywords "([appendix] OR [appendectomy] OR [appendicitis]) AND ([cholelithiasis] OR [gallstones])" and limited the results to English-language, human-based studies published until December 2017, we found only 1 study that addressed this association.[13] The previous study reported the 1.79 times higher risk of gallstone following appendectomy (95% confidence intervals [95% CI]=1.29–2.48).[13] Therefore, we sought to verify this association.

The purpose of this study is to evaluate the association between appendectomy and gallstones in the Korean population using a national sample cohort.

2. Materials and methods

2.1. Study population and data collection

The ethics committee of the Hallym University approved the use of the study data (2014-I148). The requirement for written informed consent was waived by the university's institutional review board.

This national cohort study relies on data from the Korean National Health Insurance Service (NHIS)-National Sample Cohort. The Korean NHIS selects samples directly from a database that includes the entire population to prevent non-sampling errors. Approximately 2% of samples (representing 1 million individuals) were selected from the entire Korean population (50 million individuals). The selected data can be classified in 1476 ways (based on age [18 categories], sex [2 categories], and income level [41 categories]), with randomized stratified systematic sampling methods involving proportional allocation used to ensure representation of the entire population. The appropriateness of the sample after data selection was verified by a prior study.[14] Details regarding the methods used to perform these procedures are provided by the National Health Insurance Sharing Service.[15] This cohort database included

(1) personal information,
(2) health insurance claim codes (procedures and prescriptions),
(3) diagnostic codes determined using the International Classification of Disease-10 (ICD-10),
(4) death records from the Korean National Statistical Office (that use the Korean Standard Classification of Diseases),
(5) socio-economic data (regarding residence and income), and
(6) medical examination data for each participant from 2002 to 2013.

Because a 13-digit resident registration number is used to identify all Korean citizens from birth to death, exact population statistics can be determined using this database. Enrollment in the NHIS is mandatory for all Koreans. All Korean hospitals and clinics use this 13-digit number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one location to another. Moreover, without exception, all medical treatments in Korea can be tracked using the Health Insurance Review & Assessment system. In Korea, submission of a notice of death to an administrative entity is legally required before a funeral can be held. Cause(s) of death and date of death are recorded by medical doctors on a death certificate.

2.2. Participant selection

Among 1,125,691 patients with 114,369,638 medical claim codes, we included individuals who were treated with appendectomy. Appendectomies were identified based on operation codes (Q2860-Q2863); only appendectomies for appendicitis alone (ICD-10: K35) were included (n=22,047). Gallstones were defined using the ICD-10 code K80 (cholelithiasis). From the NHIS- National Sample Cohort, we selected patients who were treated ≥2 times for gallstones (n=21,501). We extracted data for patients who underwent appendectomy and a 1:4 matched control group and then analyzed the occurrence of gallstones.

In the cohort, the participants treated with appendectomy were matched 1:4 with participants (control subjects) who never underwent appendectomy between 2002 and 2013. The control group was selected from the mother population (n=1,103,644). The participants were matched based on age group, sex, income group, region of residence, and prior medical history (hypertension, diabetes, and/or dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order and were then selected from top to bottom. It was assumed that each appendectomy patient and the matching control participants were receiving any needed medical treatment during concurrent time periods (based on the relevant index date). Therefore, the patients in the control group who died before the index date were excluded. In both the appendectomy and control groups, the participants with a history of gallstones before the index date were excluded. In the appendectomy group, 133 participants were excluded. The appendectomy patients for whom we could not identify enough matching participants were also excluded (n=16). We excluded the participants under 20 years old (n=6943). Finally, 1:4 matching resulted in the inclusion of 14,955 appendectomy recipients and 59,820 control participants (Fig. 1). However, the participants were not matched with respect to ischemic heart disease, cerebral stroke, and history of depression because strict matching based on these characteristics increased the drop-out rate for subjects due to a lack of control participants.

2.3. Variables

The following age groups were defined using 5-year intervals: 20 to 24, 25 to 29, 30 to 34 . . . , and 85+ years. A total of 14 age groups were designated. The income groups were initially divided

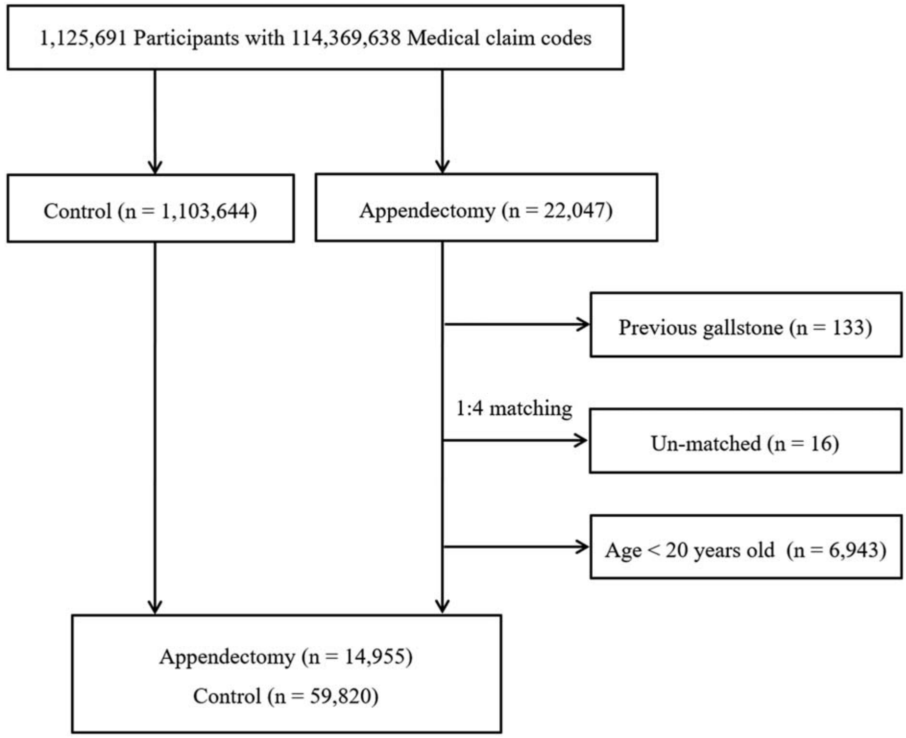

Figure 1. A schematic illustration of the participant selection process used in the present study. Among a total of 1,125,691 individuals, 14,955 appendectomy patients were matched with 59,820 control participants based on age, group, sex, income group, region of residence, and prior medical history.

into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 5 classes (class 1 [lowest income]-class 5 [highest income]). Region of residence was initially divided into 16 areas based on administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants' prior medical histories were evaluated using ICD-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were regarded as present if a participant was treated ≥1 time. Depression was defined based on ICD-10 codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist from 2002 to 2013. Among patients with such codes, we selected the participants who were treated ≥2 times.

2.4. Statistical analyses

Chi-square tests or Wilcoxon rank-sum test were used to compare the general characteristics between the appendectomy and control groups.

Stratified Cox-proportional hazard models were used to assess hazard ratios (HRs) for appendectomy with respect to gallstones. In this analysis, crude (simple) and adjusted (for ischemic heart disease, cerebral stroke, and depression) models were used, and 95% CIs were calculated. Both crude and adjusted model were stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

For the subgroup analyses, we divided the participants by age (20–39, 40–59, and 60+ years) and sex (men and women). In another subgroup analysis, we calculated HRs for follow-up periods of <1 year, 2 to 3 years, and ≥4 years after the index date.

Two-tailed analyses were conducted, and *P*-values less than .05 were regarded as indicative of significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

The mean follow-up was 68.1 months (standard deviation [SD] = 40.7) in the appendectomy group and 68.4 months (SD = 40.6) in the control group. The time interval between the index date and the occurrence of gallstones was 34.1 months (SD = 35.2) in the appendectomy group and 47.1 months (SD = 32.7) in the control group. The rate of gallstones was higher in the appendectomy group (1.4% [214/14,955]) than that in the control group (0.8% [485/59,820], $P < .001$, Table 1). The 2 groups of participants were identical with respect to the general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) due to the matching ($P = 1.000$). The rates of ischemic heart disease, cerebral stroke, and a history of depression were higher in the appendectomy group than those in the control group ($P < .05$ for each comparison).

Crude and adjusted HRs for gallstones were 1.78 (95% CI = 1.51–2.09) and 1.77 (95% CI = 1.51–2.08) in the appendectomy group, respectively ($P < .001$ for both comparisons, Table 2 and Supplemental Fig S1, http://links.lww.com/MD/E245).

Table 1

General characteristics of participants.

Characteristics	Total participants: Appendectomy (n, %)	Control group (n, %)	*P*-value
Age (yr old)			1.000
20–24	1813 (12.1)	7252 (12.1)	
25–29	2016 (13.5)	8064 (13.5)	
30–34	2047 (13.7)	8188 (13.7)	
35–39	1820 (12.2)	7280 (12.2)	
40–44	1613 (10.8)	6452 (10.8)	
45–49	1318 (8.8)	5272 (8.8)	
50–54	1173 (7.8)	4692 (7.8)	
55–59	895 (6.0)	3580 (6.0)	
60–64	693 (4.6)	2772 (4.6)	
65–69	597 (4.0)	2388 (4.0)	
70–74	455 (3.0)	1820 (3.0)	
75–79	282 (1.9)	1128 (1.9)	
80–84	171 (1.1)	684 (1.1)	
85+	62 (0.4)	248 (0.4)	
Sex			1.000
Male	7560 (50.6)	30,240 (50.6)	
Female	7395 (49.4)	29,580 (49.4)	
Income			1.000
1 (lowest)	2184 (14.6)	8736 (14.6)	
2	2521 (16.9)	10,084 (16.9)	
3	3030 (20.3)	12,120 (20.3)	
4	3408 (22.8)	13,632 (22.8)	
5 (highest)	3812 (25.5)	15,248 (25.5)	
Region of residence			1.000
Urban	6719 (44.9)	26,876 (44.9)	
Rural	8236 (55.1)	32,944 (55.1)	
Hypertension			1.000
Yes	3213 (21.5)	12,852 (21.5)	
No	11,742 (78.5)	46,968 (78.5)	
Diabetes			1.000
Yes	1637 (10.9)	6548 (10.9)	
No	13,318 (89.1)	53,272 (89.1)	
Dyslipidemia			1.000
Yes	2771 (18.5)	11,084 (18.5)	
No	12,184 (81.5)	48,736 (81.5)	
Ischemic heart disease			<.001*
Yes	610 (4.1)	2023 (3.4)	
No	14,345 (95.9)	57,797 (96.6)	
Cerebral stroke			.001*
Yes	908 (6.1)	3231 (5.4)	
No	14,047 (93.9)	56,589 (94.6)	
Depression			<.001*
Yes	1250 (8.4)	4282 (7.2)	
No	13,705 (91.6)	55,538 (92.8)	
Gallstone			<.001*
Yes	214 (1.4)	485 (0.8)	
No	14,741 (98.6)	59,335 (99.2)	

* Chi-square or Wilcoxon rank-sum test. Significance at $P < .05$.

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of appendectomy for gall stone.

Characteristics	Gallstone: Crude†	*P*-value	Adjusted†,‡	*P*-value
Appendectomy	1.78 (1.51–2.09)	<.001*	1.77 (1.51–2.08)	<.001*
Control	1.00		1.00	

* Stratified Cox-proportional hazard regression model, Significance at $P < .05$.
† A model stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.
‡ Adjusted for ischemic heart disease, cerebral stroke, and depression.

In the subgroup analyses according to age and sex, crude and adjusted HRs for gallstones were higher in the appendectomy group than those in the control group for all age categories except for men ≥60 years. The adjusted HRs were 2.03 (95% CI=1.31–3.16) in men <40 years of age, 1.86 (95% CI=1.24–2.78) in women <40 years of age, 1.64 (95% CI=1.13–2.39) in men between 40 and 59 years of age, 1.88 (95% CI=1.32–2.67) in women between 40 and 59 years of age, and 2.25 (95% CI= 1.54–3.30) in women ≥ 60 years of age ($P < 0.05$ for each comparison, Table 3). In another subgroup analysis based on follow-up period, the adjusted HR for gallstones was 4.31 (95% CI=3.16–5.87, $P < 0.001$) for a period < 1 year. However, differences were not significant for the periods of 2 to 3 years and ≥4 years (Table 4).

4. Discussion

The present study demonstrated that appendectomy increased the risk of gallstones (adjusted HR=1.78. 95% CI=1.51–2.09). This finding is consistent with the results of a previous study (adjusted HR=1.79, 95% CI=1.29–2.48).[13] We found this association in both women and men, whereas the previous study identified this association only in women. This difference may be attributable to greater statistical power in our investigation due to the larger number of participants in our study (n=74,775) than that in the aforementioned study (n=9832). Moreover, we consistently found this association between appendectomy and gallstones in all the subgroups stratified based on age and sex except for men ≥60 years of age. We found that this association was also significant for the time period of ≤1 year after appendectomy, although the HRs for the time periods of 2 to 3 years and ≥4 years did not reach significance.

It is not evident why appendectomy might increase the risk of gallstones. Inflammation and ulceration of the appendix mucosa could accelerate bacterial translocation from the appendix to the hepatic portal system,[16] which could result in damage to liver cells and the excretion of bile acid.[17]*Escherichia coli* in serum can destroy red blood cells, causing hemolysis.[18] Thus, hemolysis and chronic bacterial infections could lead to the formation of pigment stones in the gallbladder.[19] The appendix is regarded as the immunologic barrier to bacterial translocation from the colon to the small bowel.[20] Thus, appendectomy could decrease intestinal immunity and increase the risk of bacterial infection.[21] A recent study demonstrated an increased risk of antibiotic-resistant bacteria from a biliary tract infection among appendectomy patients (OR of appendectomy for antibiotic-resistant bacteria=3.02, 95% CI=1.26–7.64),[21] implying that participants who have undergone appendectomy might have a higher chance of suffering from an obstinate infection.

We used a very large, representative, nationwide population. Because NHIS data include all Korean citizens, with no exceptions, none of the participants were lost during follow-up. The control group was randomly selected with matching by age, sex, income, region of residence, and prior medical history to avoid confounding effects. An adjusted hazard model was used to further minimize the impact of confounders. We evaluated this study using competing risks model (Fine-Gray model, Supple-

Table 3

Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval) of appendectomy for gall stone according to age and sex.

	Gallstone			
Characteristics	Crude	*P*-value	Adjusted†	*P*-value
Age <40 yr old, men (n=19,845)				
Appendectomy	2.07 (1.33–3.21)	.001*	2.03 (1.31–3.16)	.002*
Control	1.00		1.00	
Age <40 yr old, women (n=18,635)				
Appendectomy	1.90 (1.27–2.83)	.002*	1.86 (1.24–2.78)	.003*
Control	1.00		1.00	
Age 40–59 yr old, men (n=12,790)				
Appendectomy	1.64 (1.13–2.38)	.010*	1.64 (1.13–2.39)	.009*
Control	1.00		1.00	
Age 40–59 yr old, women (n=12,205)				
Appendectomy	1.90 (1.34–2.70)	<.001*	1.88 (1.32–2.67)	<.001*
Control	1.00		1.00	
Age ≥60 yr old, men (n=5165)				
Appendectomy	1.05 (0.65–1.68)	.853	1.04 (0.64–1.67)	.883
Control	1.00		1.00	
Age ≥60 yr old, women (n=6135)				
Appendectomy	2.28 (1.56–3.34)	<.001*	2.25 (1.54–3.30)	<.001*
Control	1.00		1.00	

* Stratified Cox-proportional hazard regression model, Significance at $P<.05$.
† A model stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.
‡ Adjusted for ischemic heart disease, cerebral stroke, and depression.

Table 4

Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval) of appendectomy for gallstone according to follow up periods after index dates.

	Gallstone			
Characteristics	Crude	*P*-value	Adjusted†	*P*-value
Periods ≤1 yr				
Appendectomy	4.29 (3.15–5.84)	<.001*	4.31 (3.16–5.87)	<.001*
Control	1.00		1.00	
Periods 2–3 yr				
Appendectomy	1.36 (0.97–1.91)	.073	1.35 (0.97–1.90)	.080
Control	1.00		1.00	
Periods ≥4 yr				
Appendectomy	1.27 (1.00–1.62)	.054	1.26 (0.99–1.61)	.060
Control	1.00		1.00	

* Stratified Cox-proportional hazard regression model, Significance at $P<.05$.
† A model stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.
‡ Adjusted for ischemic heart disease, cerebral stroke, and depression.

mental Tables S2, http://links.lww.com/MD/E246 and S3, http://links.lww.com/MD/E247). The results were in line with the results of Cox model.

Our study has certain limitations. Because many patients with gallstones are asymptomatic or experience mild or vague symptoms,[7] it is possible that preexisting gallstones may have been readily found after appendectomy. Visits to medical institutions for appendectomy may have increased the probability of detecting such gallstones. Therefore, we analyzed the HR for gallstones detected >3 months after appendectomy (Supplemental Table S4, http://links.lww.com/MD/E248), and the results were consistent with those described above (adjusted HR=1.36, 95% CI=1.13–1.63, $P=.001$). It is also possible that gallstone ileus might have presented as appendicitis,[22] although this phenomenon is extremely unusual. Participants who did not visit a medical institution for gallstones may have been underestimated. Obesity, smoking, alcohol, and dietary habits could affect the development of both appendicitis and gallstones.[6,12] However, we did not have data regarding these factors and therefore could not adjust for them.

In conclusion, the occurrence of gallstones was increased in the participants who underwent appendectomy compared with the matched control participants.

Author contributions

Formal analysis: Hyun Lim, Miyoung Kim, Il Gyu Kong.
Writing – original draft: So Young Kim, Hyoseob Lim, Hyun Lim.
Writing – review & editing: So Young Kim, Hyoseob Lim, Hyun Lim, Miyoung Kim, Il Gyu Kong.

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