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Association of cholecystectomy with short-term and long-term risks of depression and suicide

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In addition to the known link between cholecystectomy and depression, the risk of developing short-term and long-term depression after surgery and whether such mental health issues leads to suicide were not known. Therefore, this study aimed to address these questions. Using data from the National Health Insurance Service of Korea (2002–2019), we conducted a retrospective cohort study including 6,688 cholecystectomy patients matched with 66,880 individuals without a history of cholecystectomy for suicide analysis and 6,694 cholecystectomy patients matched with 66,940 individuals for depression analysis. The non-cholecystectomy group was matched at a 1:10 ratio for sex and age. The incidence of depression and suicide were followed from the day of cholecystectomy to December 31, 2019. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression. Short-term depression risk within three years of cholecystectomy was significantly elevated (aHR 1.38, 95% CI 1.19–1.59), while the long-term depression risk beyond three years was not significantly greater (aHR 1.09, 95% CI 0.98–1.22). Cholecystectomy was not associated with an increased risk of suicide in any period. These findings highlight the importance of monitoring and providing postoperative mental health support for patients at risk of short-term depression after cholecystectomy. However, no association was observed with long-term depression or suicide risk.

Keywords Cholecystectomy, Postoperative depression, Suicide risk, Mental health

Cholecystectomy is one of the most common types of organ removal surgery, and most cholecystectomies are performed for people with symptomatic gallstone disease or sludge, gallbladder polyps, and severe complications of gallbladder disease such as acute and chronic cholecystitis, and acute cholangitis[1,2]. It can also be performed in conjunction with liver transplantation and hepatectomy[3]. According to medical statistics from the Korea Health Insurance Review and Assessment Service, the number of cholecystectomies performed in South Korea increased from 47,601 in 2010 to 83,479 in 2021.

Patients who undergo cholecystectomy often experience postcholecystectomy syndrome (PCS), characterized by symptoms such as flatulent dyspepsia, dull abdominal pain, and diarrhea[4–7]. PCS can be linked to psychological disorders, including depression and anxiety[5,8–11]. A recent study of South Koreans that followed patients for an average of 3.67 years revealed that patients in the cholecystectomy group had a greater risk of developing major depressive disorder than the group that did not have cholecystectomy[8]. A study of a Taiwanese population with a 2-year follow-up also found that patients who had undergone cholecystectomy had an increased risk of developing a depressive disorder compared with those who had not. In particular, the risk of depressive disorders was increased in female patients who underwent cholecystectomy[9]. Patients with suspected sphincter of Oddi dysfunction also reported heightened levels of anxiety and depression postcholecystectomy, correlating with their pain and depression[12]. However, no studies have confirmed the long-term effects of cholecystectomy on depression risk.

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The number of cholecystectomies is increasing in Korea, and a multicenter cohort study revealed that 0.9% of patients reported significant levels of anxiety or depression[9]. However, the specific risk of suicide following cholecystectomy remains poorly understood, despite South Korea's high suicide rate. A report by Statistics Korea indicated that in 2021, 13,352 individuals died of suicide[13]. A previous study in Korean population has linked cholecystectomy to depression, attributed in part to changes in the gut microbiome and metabolic consequences[14–17]. Given the known association between postoperative depression and suicide, further investigation into cholecystectomy's potential role in suicide risk is warranted to further explore the possible etiologies, including the gut microbiome and PCS[18,19]. However, to our knowledge, the association between cholecystectomy and suicide has not been studied. Utilizing the National Health Insurance Service-National Health Screening (NHIS-HEALS) cohort, this study aims to explore both short-term and long-term risks of depression and suicide following cholecystectomy.

Methods

Data source

This study was conducted using the NHIS-HEALS cohort database of South Korea from 2002 to 2019[20]. This database, maintained by the National Health Insurance Service (NHIS), draws from health screening programs accessible to most insured Koreans. Since 1995, the NHIS has conducted standardized general health screenings biennially for Korean adults aged 40 and above. Data encompass key health variables including blood pressure, body mass index, cholesterol levels, smoking and drinking habits, as well as weekly exercise frequency.

Study population and design

Figure 1 provides the process of selecting the study population. Utilizing NHIS-HEALS data from 2002 to 2019, 15,437 patients who underwent cholecystectomy between 2004 and 2019 were included. Exclusions comprised 3,819 patients without health screening data, 14 with a history of liver transplantation, 1,032 with liver cancer or choledochocholecystic tumors, and 2,542 with psychiatric disorders diagnosed pre-cholecystectomy. The psychiatric disorders exclusion group was defined as individuals diagnosed with disorders classified under ICD-10 codes F20–F29, F30–F33, F340–F341, F00–F09, and F40–F48. Ultimately, 6,688 patients were included in the cholecystectomy group for depression outcomes, and 6,694 for suicide outcomes. The individuals in the non-cholecystectomy group were matched for age and sex in a 1:10 ratio.

Key variables

We extracted exposure variables using the procedure registry code Q7380 for cholecystectomy. Depression and suicide were defined using codes from the 10th edition of the International Statistical Classification of Diseases (ICD-10)[21]. Suicide was separately collected by the National Statistical Office of Korea as demographic and sociological statistics, and death could be analyzed by combining it with the death date of the health examination cohort database used in this study. In particular, suicide is defined by using information released as a middle classification unit and is not disclosed as a sub-classification system at the national level because it is sensitive

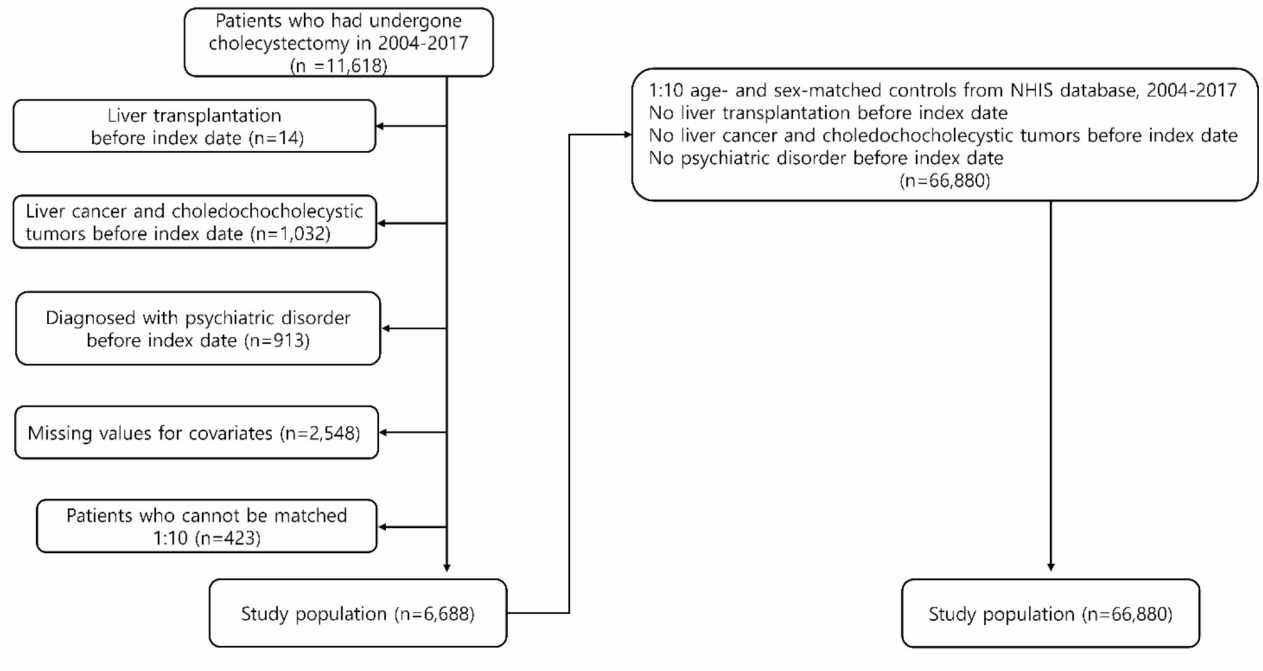

Fig. 1. Title flow diagram of the study subjects.

person information. Suicide mortality was designated by codes X60-X84, while depression was diagnosed as F32-F33. Among the ICD-10 codes that correspond to the operational definition of depression, F33 is the definition of recurrence of depression, but due to the limitations of the database we can access, it is impossible to check the history of depression diagnosis before 2002. Therefore, F33 was included in the definition of depression diagnosis in consideration of the fact that a person with a history of depression diagnosis before 2002 could be defined as a recurrence of depression because he was diagnosed with depression during the follow-up period. Patients with an F32-F33 diagnosis, both outpatient and inpatient records, and at least one antidepressant prescription were considered to have depressive disorder. Follow-up for depression and suicide diagnoses was observed until December 31st, 2019. Variables including sex, age, household income, smoking, exercise frequency, alcohol consumption, blood pressure, fasting serum glucose, body mass index, total cholesterol, and Charlson Comorbidity Index were considered. In the evaluation of the patient's income, the patient's insurance grade was divided into 20 units and grouped into 4 groups based on the data, and then the income was replaced with the corresponding data grouped. The alcohol consumption refers to the frequency of drinking within 1 week. As a limitation in the database of health screening cohort studies used in this study, drinking consumption behavior was replaced by the date of the number of drinking consumption per week. The number of medium-intensity exercises was the sum of strenuous exercise sessions lasting more than 20 min and moderate exercise sessions lasting more than 30 min within one week. Short-term depression risk was defined as diagnosis within 3 years postcholecystectomy, while long-term risk was defined as diagnosis beyond 3 years postcholecystectomy.

Statistical analysis

The characteristics of the participants in this study were stratified by cholecystectomy. Continuous variables were presented as the means and standard deviations, while categorical and dichotomous variables are expressed as percentages and frequencies. We compared the clinical characteristics between cholecystectomy and non-cholecystectomy groups using the chi-squared test and the independent sample t-test. The Cox proportional hazards model was utilized to estimate the association between cholecystectomy and depression, as well as between cholecystectomy and suicide, producing adjusted hazard ratio (aHR) and 95% confidence interval (CI)[22]. The hazard ratio was calculated after adjustments included age, sex, diastolic blood pressure, systolic blood pressure, body mass index, household income, smoking, drinking frequency, physical activity, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index[23]. $P<0.05$ was considered to indicate statistical significance. SAS Enterprise Guide version 8.3 conducted all analyses.

Ethical approval

This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB number: E-2204-038-1314) and adhered to the principles outlined in the Declaration of Helsinki and its subsequent updates. The requirement for informed consent was waived as the NHIS database used for analysis was anonymized according to strict compliance with confidentiality standards prior to analysis.

Results

Baseline characteristics

The baseline characteristics of the population in the study cohort are shown in Table 1. The study cohort comprised 6,688 individuals who underwent cholecystectomy and 66,880 age- and sex-matched controls. Both groups had an average age of 62 years (SD: 9.4). 4,041 males underwent cholecystectomy, alongside 40,410 male controls. For females, 2,647 had cholecystectomy, compared to 26,470 controls. As with several previous studies related to cholecystectomy in Korea, patients with cholelithiasis, one of the subjects of cholecystectomy, seem to dominate in men in Korea. The exposed and control groups were matched at a 1:10 ratio. Median body mass index was 24.5 for cholecystectomy patients and 23.9 for controls. Cholecystectomy patients exhibited higher income, lower alcohol consumption, physical activity, and total cholesterol, along with higher fasting serum glucose, body mass index, and diastolic blood pressure, as well as more comorbidities ($p<0.05$ for all).

Associations of cholecystectomy with depression and suicide outcomes

Table 2 provides the results of the multivariable Cox proportional hazards analysis, indicating the association between cholecystectomy and depression risk after covariate adjustments. This analysis was used to determine the association between cholecystectomy and the risk of developing depression after adjusting for covariates. As shown in the graphical summary (see Fig. 2), patients who underwent cholecystectomy showed an increased risk of depression compared to those who didn't (aHR 1.19 [95% CI, 1.19–1.30]), particularly within 3 years after cholecystectomy (aHR 1.38 [95% CI, 1.19–1.59]). However, no significant long-term risk was observed beyond 3 years postcholecystectomy (aHR 1.09 [95% CI, 0.98–1.22]). Table 3 shows that 229 suicides occurred during the total follow-up period, 22 cases of cholecystectomy and 7 cases of non-operative groups, but there is no association between cholecystectomy and suicide risk (aHR 1.08 [95% CI, 0.69–1.68]). Similarly, there was no significant association observed in the short-term (aHR 0.88 [95% CI, 0.35–2.23]) or long-term (aHR 1.09 [95% CI, 0.68–1.89]) after cholecystectomy.

Subgroup analyses were conducted for age group, sex, comorbidity, and inclusion year to assess study heterogeneity. Among patients with a Charlson Comorbidity Index of less than 2, no significant association was found between cholecystectomy and depression risk, both short-term and long-term. However, those with an index of 2 or more had an elevated risk of short-term depression within 3 years following cholecystectomy (aHR 1.48 [95% CI, 1.24–1.77]) (see Table 4). In the analysis by sex in Table 5, both males and females showed increased depression risk within 3 years of cholecystectomy. Notably, females had a higher risk compared to males (aHR 1.39 [95% CI, 1.13–1.70]). Patients under 65 years old exhibited the highest increase in short-term depression risk after cholecystectomy (aHR 1.48 [95% CI, 1.22–1.80]) (see Supplementary Table S1 online). The

Variables	No cholecystectomy ($n = 66,880$)	Cholecystectomy ($n = 6,688$)	p value
Age (years) *	62(9.4)	62(9.4)	1.000
Sex			1.000
Men	40,410(60.4)	4,041(60.4)	
Women	26,470(39.6)	2,647(39.6)	
Household income[a]			< 0.0001
First (highest)	21,361(31.9)	2,587(38.7)	
Second	17,595(26.3)	1,921(28.7)	
Third	15,227(22.8)	1,243(18.6)	
Fourth (lowest)	12,697(19.0)	937(14.0)	
Body mass index (kg/m^2)*	23.9(2.9)	24.5(3.0)	< 0.0001
Systolic blood pressure (mmHg)*	126.5(15.5)	126.9(15.8)	0.089
Diastolic blood pressure (mmHg)*	78.0(10.0)	78.3(10.2)	0.009
Total cholesterol (mg/dL)*	196.5(37.8)	195.4(39.1)	0.034
Fasting serum glucose (mg/dL)*	101.7(26.7)	104.1(32.5)	< 0.0001
Cigarette smoking status			0.384
Never smoker	42,716(63.9)	4,215(63.0)	
Past smoker	12,944(19.3)	1,329(19.9)	
Current smoker	11,220(16.8)	1,144(17.1)	
Alcohol consumption (times/a week)			< 0.0001
None	35,983(53.8)	3,913(58.5)	
1–2 times/week	21,403(32.0)	1,872(28.0)	
3–4 times/week	6,278(9.4)	568(8.5)	
≥5 times/week	3,216(4.8)	335(5.0)	
Physical activity (times/a week)			< 0.0001
None	25,497(38.1)	2,762(41.3)	
1–2 times/week	17,208(25.7)	1,675(25.1)	
3–4 times/week	9,703(14.5)	919(13.7)	
≥5 times/week	14,472(21.6)	1,332(19.9)	
Charlson comorbidity index			< 0.0001
0	24,557(36.7)	1,532(22.9)	
1	21,282(31.8)	2,026(30.3)	
≥2	21,041(31.5)	3,130(46.8)	

Table 1. Descriptive statistics of the participants in the National Health Insurance Service. Data are presented as n (%), mean (standard deviation)*. [a]Proxy for socioeconomic status based on the insurance premium of the National Health Insurance Service.

association between cholecystectomy and the risk of depression was analyzed based on the year of inclusion. Patients included between 2004 and 2007 (aHR 1.46 [95% CI, 1.05–2.04]) and 2008–2012 (aHR 1.13 [95% CI, 0.89–1.43]) showed a significantly increased risk of depression (see Supplementary Table S2). In contrast, no significant association was found between cholecystectomy and suicide risk when analyzed by sex, age, or comorbidity, both short-term and long-term (see Supplementary Table S3, S4, and S5 online).

Discussion

Our retrospective cohort study is the first to present the results of further studies on whether the previously known association with mental health, such as depression after cholecystectomy, can even affect long-term mental health and suicide. The focus of this study was to examine the associations between cholecystectomy and depression and between cholecystectomy and suicide in Koreans who underwent cholecystectomy. we observed an increased risk of short-term depression postcholecystectomy, particularly among those with more comorbidities and individuals under 65 years old. Additionally, both males and females had a greater risk of short-term depression, and the extent of risk elevation was greater for women. However, we found no association between cholecystectomy and long-term depression risk, nor was there a significant association with suicide risk.

Previous studies have indicated a higher risk of major depressive disorder among those with a history of cholecystectomy, particularly in patients aged 40–49 years[8]. Another study found a greater risk of depressive disorder postcholecystectomy, especially among women[9]. To better understand the mechanisms that explain the association between cholecystectomy and depression and between cholecystectomy and suicide, this study analyzed the risk of depression and suicide after cholecystectomy, dividing patients into short-term and long-

			HR (95% CI)			
	Event, *n*	Per 1,000 PYs	Model 1	Model 2	Model 3	Model 4
Whole period risk						
No Cholecystectomy (*n*=66,880)	4,660	547.222	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy (*n*=6,688)	687	52.298	1.30 (1.20-1.42)***	1.30 (1.19-1.42)***	1.29 (1.18-1.41)***	**1.19 (1.19-1.30)*****
Short-term risk (≤3 years)						
No Cholecystectomy	1,471	524.767	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy	330	49.844	1.58 (1.37-1.82)***	1.58 (1.37-1.82)***	1.56 (1.36-1.80)***	**1.38 (1.19-1.59)*****
Long-term risk (>3 years)						
No Cholecystectomy	3,189	544.989	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy	357	52.419	1.18 (1.06-1.32)**	1.17 (1.05-1.31)**	1.17 (1.05-1.30)**	**1.09 (0.98-1.22)**

Table 2. HRs of short-term and long-term risk of depression by cholecystectomy. Acronyms: HR, hazard ratio; CI, confidence interval. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and household income. Model 3: adjusted for age, sex, household income, smoking status, alcohol consumption, and physical activity. Model 4: adjusted for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. **p<0.01, ***p<0.001.

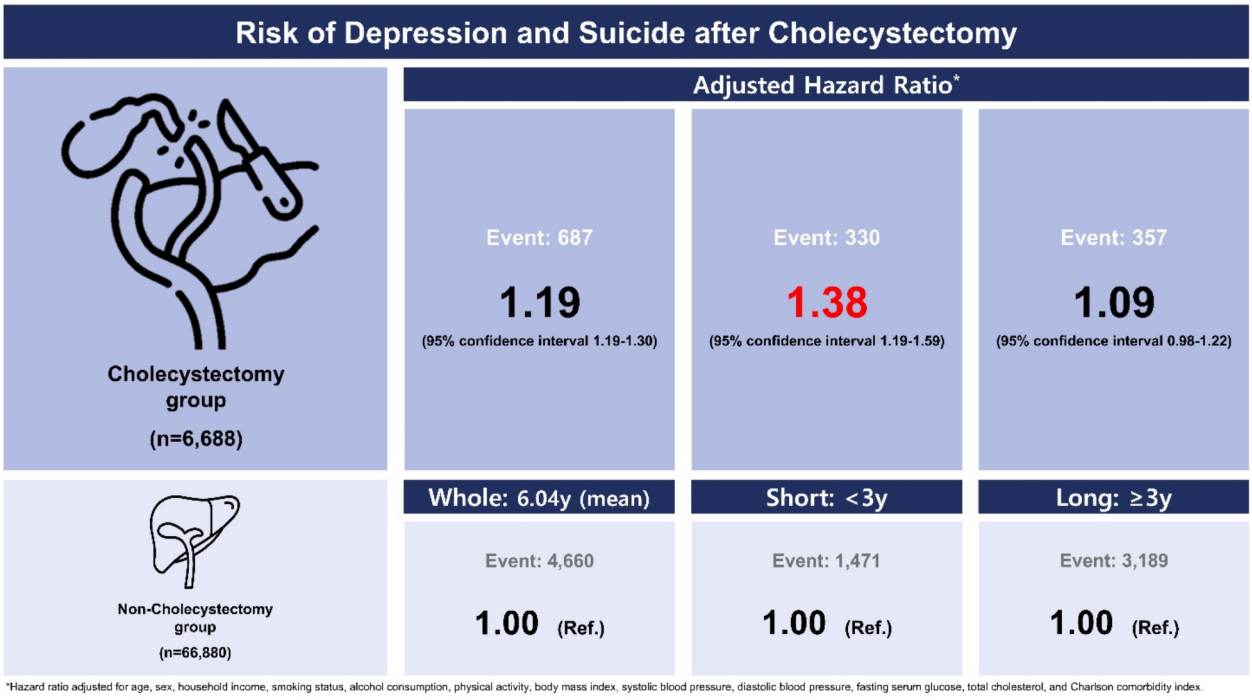

Fig. 2. Graphical abstract illustrating the key findings of the study.

term categories. The findings revealed an increased short-term risk of depression but no long-term association. Additionally, no significant association was found between cholecystectomy and suicide. These results can be analyzed from three viewpoints.

First, in line with previous studies reporting that depression occurred in 1.8–3.5% of patients who underwent cholecystectomy[8,9,24–26], our study showed a 1.3% incidence rate of depression in patients undergoing cholecystectomy. Patients with cholelithiasis have a higher incidence of depression than does the population in general, the relationship between mental health issues and gallbladder disease appears to be bidirectional[27,28]. There may be a risk of developing depression due to symptomatic cholelithiasis in the cholecystectomy group included in our study. Therefore, to minimize this potential bias, we adjusted for potential confounding factors such as sex, age, total cholesterol, body mass index, smoking status, household income, alcohol consumption,

			HR (95% CI)			
	Event, *n*	Per 1,000 PYs	Model 1	Model 2	Model 3	Model 4
Whole period risk						
No Cholecystectomy (*n*=66,880)	207	569.617	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy (*n*=6,688)	22	56.541	1.08 (0.69-1.67)	1.13 (0.73-1.75)	1.13 (0.73-1.75)	1.08 (0.69-1.68)
Short-term risk (≤3 years)						
No Cholecystectomy	54	568.477	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy	5	56.410	0.94 (0.38-2.35)	1.00 (0.40-2.50)	1.01 (0.40-2.52)	0.88 (0.35-2.23)
Long-term risk (>3 years)						
No Cholecystectomy	153	569.537	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Cholecystectomy	17	56.533	1.13 (0.68-1.86)	1.17 (0.71-1.94)	1.17 (0.71-1.93)	1.14 (0.68-1.89)

Table 3. HRs of short-term and long-term risk of suicide mortality by cholecystectomy. Acronyms: HR, hazard ratio; CI, confidence interval. Model 2: adjusted for age, sex, and household income. Model 3: adjusted for age, sex, household income, smoking status, alcohol consumption, and physical activity. Model 4: adjusted for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

	No Cholecystectomy	Cholecystectomy
Charlson comorbidity index<2	45,839	3,558
Events, n	2,590	251
Per 1,000 person-y	390.784	30.310
aHR (95% CI)	**1.00 (Ref.)**	**1.10 (0.96-1.26)**
Short-term risk (≤3 years)	43,977	3,398
Events, n	728	91
Per 1,000 person-y	377.265	29.146
aHR (95% CI)	**1.00 (Ref.)**	**1.18 (0.92-1.52)**
Long-term risk (>3 years)	45,111	3,467
Events, n	1,862	160
Per 1,000 person-y	389.640	30.291
aHR (95% CI)	**1.00 (Ref.)**	**1.07 (0.91-1.26)**
Charlson comorbidity index≥2	21,041	3,130
Events, n	2,070	436
Per 1,000 person-y	156.438	21.988
aHR (95% CI)	**1.00 (Ref.)**	**1.23 (1.10-1.39)*****
Short-term risk (≤3 years)	19,714	2,933
Events, n	743	239
Per 1,000 person-y	147.502	20.697
aHR (95% CI)	**1.00 (Ref.)**	**1.48 (1.24-1.77)*****
Long-term risk (>3 years)	20,298	2,891
Events, n	1,327	197
Per 1,000 person-y	155.348	22.127
aHR (95% CI)	**1.00 (Ref.)**	**1.09 (0.94-1.27)**

Table 4. Sensitivity analysis on the association of cholecystectomy with risk of depression among participants with fewer or more comorbidities. Acronyms: aHR, adjusted hazard ratio; CI, confidence interval. The aHR adjusted for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. ***$p<0.001$.

physical activity, diastolic blood pressure, fasting serum glucose, systolic blood pressure and Charlson Comorbidity Index. We also excluded people who were diagnosed with depression before their cholecystectomy. A total of 913 people with a history of depression were excluded from the study. We used the same exclusion criteria to establish an age- and sex-matched non-cholecystectomy group of people who underwent cholecystectomy. This

	No Cholecystectomy	Cholecystectomy
Male	40,410	4,041
Events, n	2,213	327
Per 1,000 person-y	321.795	31.028
aHR (95% CI)	**1.00 (Ref.)**	**1.17 (1.03-1.33)***
Short-term risk (≤3 years)	38,928	3,872
Events, n	731	158
Per 1,000 person-y	311.378	29.823
aHR (95% CI)	**1.00 (Ref.)**	**1.37 (1.11-1.67)****
Long-term risk (>3 years)	39,679	3,883
Events, n	1,482	169
Per 1,000 person-y	320.687	31.057
aHR (95% CI)	**1.00 (Ref.)**	**1.07 (0.91-1.26)**
Female	26,470	2,647
Events, n	2,447	360
Person-years	225.427	21.270
aHR (95% CI)	**1.00 (Ref.)**	**1.19 (1.06-1.35)****
Short-term risk (≤3 years)	24,763	2,459
Events, n	740	172
Per 1,000 person-y	213.389	20.020
aHR (95% CI)	**1.00 (Ref.)**	**1.39 (1.13-1.70)****
Long-term risk (>3 years)	25,730	2,475
Events, n	1,707	188
Per 1,000 person-y	224.302	21.362
aHR (95% CI)	**1.00 (Ref.)**	**1.10 (0.95-1.29)**

Table 5. Sensitivity analysis on the association of cholecystectomy with risk of depression among male or female. Acronyms: aHR, adjusted hazard ratio; CI, confidence interval. The aHR adjusted for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. *$p<0.05$, **$p<0.01$.

enabled us to eliminate the possibility that the prevalence of depression in the cholecystectomy group may have influenced the risk of depression after cholecystectomy.

Second, the increased short-term risk of depression following cholecystectomy may be attributed to alterations in the gut microbiome, influenced by changes in bile acid flow[29–32]. These alterations can disrupt physiological balance, affecting immunity and causing fatigue[14,15]. Previous studies have linked gut microbiome changes to depression[16,17,33,34], impacting neurotransmitter systems and leading to anxiety and stressful behaviors[17], possibly exacerbated by an increase in harmful bacteria[16,33,35,36]. However, the gut microbiome may adapt in the long-term after cholecystectomy, so the medium- to long-term effects of changes in the gut microbiome remain controversial. Therefore, additional studies are needed to further analyze the relationship between the gut microbiome and depression duration.

Finally, PCS is a heterogeneous group of symptoms consisting of persistent postoperative abdominal pain, gastrointestinal symptoms, and jaundice, and has been posited as a mechanism behind the increased risk of short-term depression following cholecystectomy[37–40]. The incidence of PCS varies from as little as 2 days to as long as 25 years, but late PCS is defined as PCS occurring several months after surgery[1,39–41]. Although there are various causes of PCS, bowel movement disorders, notably irritable bowel syndrome or sphincter of Oddi dysfunction, are proposed as major causes[39,42]. PCS is linked to depression and anxiety[10,38,43], correlating with decreased quality of life[42,44]. Patients with symptoms of gallstone disease achieved higher long-term quality of life after cholecystectomy[45]. Therefore, the increased risk of short-term depression after cholecystectomy in our study may be explained by the early PCS experienced by cholecystectomy patients. There was no association between cholecystectomy and the risk of long-term depression, probably because symptoms, such as pain after cholecystectomy, appear early after surgery[46] and gradually improve over time after cholecystectomy, as does quality of life[24]. Previous studies have reported that more than 90% of patients experience an improvement in symptoms after cholecystectomy 1 year after cholecystectomy[47]. Further studies on the mechanism of PCS occurrence could be beneficial for understanding the health outcomes of patients who have undergone cholecystectomy. Although PCS may explain the increased risk of short-term depression after cholecystectomy, the underlying mechanism is likely complex, as changes in the gut microbiome may also play a role.

The mechanism behind the highest increase in short-term depression risk in women in the subgroup analysis can be explained as follows. Previous studies have reported that PCS is common in women with a high incidence of gallstones[37]. Additionally, a negative association between women and health-related quality of life after cholecystectomy has been noted[48]. Furthermore, our findings indicate a greater risk of short-term depression

postcholecystectomy in patients with a higher Charlson Comorbidity Index, which aligns with previous studies showing a higher incidence of major depressive disorder in patients with hypertension, diabetes, or dyslipidemia[8]. Patients with hypertension, diabetes, or dyslipidemia, in general, were found to have a higher incidence of depression[49,50]. Changes in bile acids due to cholecystectomy may influence lipid metabolism, potentially contributing to the development of metabolic diseases, which could explain our results[15,31].

This study has several strengths. First, the study analyzed data from a large population cohort. Data from the entire period established from 2002 to 2019 were used. Second, our study is the first to analyze the association between cholecystectomy and suicide risk in Korean adults. The limitation of this study is that it is not a total inspection database because it is a retrospective cohort study. Since the study was not conducted for the entire population, there are limitations in applying the study results to the entire population. Additionally, as the study population is limited to Korea, the findings may not be broadly applicable to a global context. Second, patients who underwent cholecystectomy may have underlying diseases such as gallbladder cancer, bile duct cancer, or liver cancer, and their gallbladder may have been removed during liver transplantation; Therefore, they could be affected by any of these conditions or surgeries, potentially influencing their outcomes. Third, cholecystectomy, depression, and suicide were identified using ICD-10 codes, which have the potential for misclassification because they may not be accurately recorded. Fourth, inaccuracies in suicide coding within claims databases may have occurred[51]. Fifth, one limitation of this study is the absence of data on complications following cholecystectomy, specifically PCS, which is often considered a potential mechanism linking cholecystectomy to depression. While we attempted to identify PCS using the ICD-10 code K91.5 in the cholecystectomy group, no cases were recorded in our dataset. This limitation prevents us from analyzing the potential correlation between PCS and outcome parameters, including depression. In addition, there is a limitation that it is not possible to confirm in the database used in our study, but PCS may at least partially include patients with genetic diseases such as ABCB4/LPAC syndrome. Note that these patients may be included, it would be good if a follow-up study on PCS considered genetic diseases. Additionally, this study suggests an association only, and further research is needed to explain the causal relationship between cholecystectomy and depression and suicide.

In conclusion, the results of this study suggest that cholecystectomy is associated with an increased risk of short-term depression within 3 years postoperatively, whereas its association with long-term depression and suicide risk appears to be negligible. These findings emphasize the importance of monitoring and supporting patients' mental health during the immediate postoperative period. Clinicians should carefully consider the risk of depression in patients undergoing cholecystectomy. Additionally, further research is needed to explore the underlying mechanisms and to validate these findings in diverse populations.

Data availability

The dataset generated in the NHIS repository (https://nhiss.nhis.or.kr/). Data are available from permitted rese archers and are not publicly available.

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Author contributions

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intellectual content: All the authorsStatistical analysis: J.Y. and S.P.Administrative, technical, or material support: All authors.Proofreading the article: S.H.Study supervision: S.M.P.

Declarations

Competing interests
The authors declare no competing interests.

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