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Increased risk of *de novo* inflammatory bowel disease following cholecystectomy: a population-based analysis

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Abstract

Background Cholecystectomy (CCY) may alter bile acid flow and gut microbiota, increasing the risk of gastrointestinal disease. Prior studies have suggested that CCY may be associated with bile acid diarrhea and microscopic colitis; however, the association with the new diagnosis of inflammatory bowel disease (IBD) remains unstudied. In this study, we evaluated whether CCY was associated with a greater risk of *de novo* IBD.

Methods We conducted a retrospective cohort study, analyzing data from the TriNetX network (2010-2024), using 1:1 propensity score matching between adult patients undergoing CCY and controls, based on variables that included demographics, comorbidities and medication use. The primary outcome was risk of *de novo* IBD. Secondary outcomes included the risk of developing ulcerative colitis (UC) or Crohn's disease (CD). Kaplan-Meier analysis with hazard ratios (HRs) and 95% confidence intervals (CIs) was used to compare time-to-event rates.

Results Among 570,317 matched pairs, CCY was associated with a greater risk of IBD (adjusted HR [aHR] 1.29, 95%CI 1.22-1.35; P<0.001), and specifically CD (aHR 1.83, 95%CI 1.69-1.99; P<0.001), but not the risk of UC. This elevated risk persisted across both sexes and all age groups. Among patient characteristics, tobacco use was associated with the greatest additional risk of IBD post-CCY (aHR 1.43, 95%CI 1.19-1.76; P<0.001).

Conclusions Prior CCY is associated with a greater risk of CD but not UC. These findings support the need for a low threshold to think about CD in patients with gastrointestinal symptoms after CCY.

Keywords Inflammatory bowel disease, cholecystectomy, bile acids, diarrhea

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Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder of the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis (UC) [1]. The incidence of IBD increased significantly during the second half of the 20th century, and it has recently become one of the most prevalent gastrointestinal diseases [2-4]. The exact pathogenesis of IBD is unknown, but it is thought that the disease develops in patients with a genetic predisposition who get exposed to an environmental trigger [1,5]. In an effort to understand the pathogenesis of IBD, different modifiable risk factors have been studied that might increase the risk of developing IBD [6].

Cholecystectomy (CCY) is one of the most commonly performed procedures in the United States, with more than 1.2 million surgeries performed annually [7]. For this reason, it has become a research focus, with many studies

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Conflict of Interest: FAF: Consulting Fee: Astellas, Avalo Therapeutics, Bausch, BMS, Braintree Labs, Fresenius Kabi, GI Reviewers, GSK, IBD Educational Group, Iterative Health, Janssen, Pharmacosmos, Pfizer, Sandoz Immunology, Viatris. DSMB: Eli Lilly. JGH: Advisory Board for BMS. The rest of the authors have no conflicts of interest to declare.

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of its potential effect on the gastrointestinal tract, including possible associations with IBD, irritable bowel syndrome (IBS), and various gastrointestinal malignancies [6,8]. However, the relationship between CCY and the risk of IBD development remains understudied. This study aimed to assess the association between prior CCY and the risk of developing *de novo* IBD using a large, real-world population database.

Patients and methods

We used the TriNetX Analytics platform to access de-identified electronic health records from 72 healthcare organizations in the United States, representing approximately 120 million individuals. The database includes patients from diverse sociodemographic backgrounds, geographic regions, and insurance types. Data are de-identified at the network level by a qualified expert, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. TriNetX has been widely used previously to assess disease risk following different exposures [9,10]. This retrospective cohort study evaluated the risk of developing IBD in patients with a history of CCY. Institutional Review Board (IRB) approval was not needed, as the data were de-identified.

Cohort definition

First, we identified patients above the age of 18 who underwent a CCY between January 1, 2010, and December 31, 2024. The control group consisted of adult patients who never underwent a CCY before or during the study period. We excluded patients with a prior history of IBD from both groups. Diagnoses and procedures were identified using their International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Current Procedural Terminology (CPT), and ICD-10 Procedure Coding System (PCS) codes (Supplementary file).

Propensity score matching

To reduce confounding bias as much as possible, we performed 1:1 propensity score matching (PSM) between the 2 groups. The matching variables used included demographics (age, sex, race/ethnicity), comorbidities, and medications used (Table 1).

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Outcome and statistical analysis

The primary outcome was the risk of developing IBD. We excluded patients who developed the outcome within only 3 months of the CCY procedure. Baseline characteristics of the 2 groups were presented as mean ± standard deviation (SD) or as frequency and percentage. We conducted time-to-event analyses using Kaplan-Meier analysis and calculated hazard ratios (HRs) with 95% confidence intervals (CIs), using Cox proportional hazards models. Statistical significance was defined as 2-sided P<0.05. Further subgroup analyses were carried out by stratifying cohorts based on age, sex and comorbidities. All statistical analyses were conducted using the TriNetX software with the browser-based real-time analytics feature, TriNetX Live (TriNetX LLC, Cambridge, MA).

Results

Baseline characteristic

We initially identified 631,239 adult patients who underwent CCY and 1,524,879 control patients with no history of CCY. After PSM, 570,317 were included in each group (Table 1).

Before PSM, patients in the CCY group were younger (mean age 48.5±18.1 vs. 53.4±18.7 years, P<0.001) and more likely to be female (68.2% vs. 54.2%, P<0.001) or Hispanic/Latino (17.8% vs. 5.7%, P<0.001) compared to the control cohort. They also had higher rates of being overweight/obese (26.6% vs. 21.8%, P=0.013), and had higher rates of using nonsteroidal anti-inflammatory drugs (NSAID) (45.1% vs. 36.7%, P<0.001) or proton pump inhibitors (35.4% vs. 21.3%, P<0.001). After PSM, the 2 groups were well balanced (Table 1). Mean follow up was 10.2 years post-CCY.

Clinical outcomes

In the propensity-matched cohort, CCY was associated with a significantly higher risk of developing IBD (adjusted HR [aHR] 1.29, 95%CI 1.22-1.35; P<0.001). Absolute incidence was 0.8% for the CCY group and 0.55% for the comparison group. The strongest association was observed in CD (aHR 1.83, 95%CI 1.69-1.99; P<0.001). The association with UC was not statistically significant (aHR 1.06, 95%CI 0.996-1.13; P=0.07) (Table 2).

Subgroup analyses showed that the greater risk of IBD was consistent across both sexes (male: aHR 1.26, 95%CI 1.15-1.37; female: aHR 1.21, 95%CI 1.14-1.30; both P<0.001). This higher risk was also seen for CD in both sexes. However, no significant association was found between CCY and UC in either males or females.

When stratified by age, patients younger than 60 years (aHR 1.33, 95%CI 1.24-1.42) and those aged ≥60 years (aHR 1.23, 95%CI 1.15-1.31) had an elevated risk of IBD (both P<0.001), with a consistently greater risk for CD across both age groups

Table 1 Baseline characteristics before and after propensity score matching between patients with and without history of cholecystectomy

Characteristics	Before propensity score matching			After propensity score matching		
	CCY (n=631,239)	Control (n=1,524,879)	SD	CCY (n=570,317)	Control (n=570,317)	SD
Age (mean±SD)	48.5±18.1	53.4±18.7	0.270	49.3±18.1	50.0±17.8	0.037
White	430,352 (71.1%)	1,043,506 (68.4%)	0.058	404,876 (71.0%)	400,130 (70.2%)	0.018
Female sex	412,777 (68.2%)	826,528 (54.2%)	0.290	379,360 (66.5%)	374,804 (65.7%)	0.017
Hispanic or Latino	107,759 (17.8%)	86,339 (5.7%)	0.384	75,434 (13.2%)	81,368 (14.3%)	0.030
Comorbidities & exposures						
Socioeconomic hazards	16,017 (2.6%)	46,348 (3.0%)	0.024	15,289 (2.7%)	15,917 (2.8%)	0.007
Overweight/obesity	161,232 (26.6%)	331,676 (21.8%)	0.114	148,734 (26.1%)	149,900 (26.3%)	0.005
Tobacco use	16,744 (2.8%)	69,681 (4.6%)	0.096	16,580 (2.9%)	17,287 (3.0%)	0.007
Alcohol disorders	16,919 (2.8%)	40,200 (2.6%)	0.010	16,154 (2.8%)	17,224 (3.0%)	0.011
Hypertension	207,617 (34.3%)	619,437 (40.6%)	0.131	201,462 (35.3%)	205,972 (36.1%)	0.017
Diabetes mellitus	89,378 (14.8%)	232,681 (15.3%)	0.014	84,989 (14.9%)	88,120 (15.5%)	0.015
Hyperlipidemia	132,418 (21.9%)	466,944 (30.6%)	0.200	130,255 (22.8%)	134,645 (23.6%)	0.018
Depression	40,277 (6.7%)	99,397 (6.5%)	0.005	38,466 (6.7%)	40,760 (7.1%)	0.016
Anxiety	89,418 (14.8%)	268,480 (17.6%)	0.077	85,246 (14.9%)	109,483 (19.2%)	0.113
Medications						
NSAIDs	272,761 (45.1%)	559,372 (36.7%)	0.171	254,353 (44.6%)	233,487 (40.9%)	0.074
PPIs	214,449 (35.4%)	324,988 (21.3%)	0.317	204,713 (35.9%)	119,724 (21.0%)	0.335
Sertraline	33,585 (5.5%)	93,909 (6.2%)	0.026	31,936 (5.6%)	39,355 (6.9%)	0.054
Ursodeoxycholate	7,171 (1.2%)	3,866 (0.3%)	0.110	3,963 (0.7%)	3,787 (0.7%)	0.004
Ibuprofen	135,079 (22.3%)	236,497 (15.5%)	0.174	120,936 (21.2%)	122,907 (21.6%)	0.008

CCY, cholecystectomy; SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

(18-60 years: aHR 1.74, 95%CI 1.57-1.94); ≥60 years: aHR 1.83, 95%CI 1.61-2.07). The risk for UC remained nonsignificant in both age groups, <60 and ≥60 years.

Among comorbidities and exposures, the risk of IBD in patients who had a CCY was elevated in patients with diabetes mellitus (aHR 1.22, 95%CI 1.12-1.33), tobacco use (aHR 1.43, 95%CI 1.19-1.72), obesity (aHR 1.15, 95%CI 1.07-1.23), aspirin use (aHR 1.16, 95%CI 1.07-1.25), and NSAID use (aHR 1.14, 95%CI 1.06-1.22), all with P≤0.001. Tobacco use was the only factor significantly associated with an elevated risk of UC (aHR 1.29, 95%CI 1.03-1.62; P=0.03). While diabetes mellitus, obesity, aspirin and NSAID use were significantly associated with a higher risk of IBD and CD, they showed no significant association with UC. A sensitivity analysis was also conducted by excluding cases of IBD that developed within 12 months post-CCY (aHR 1.13, 95%CI 1.07-1.19; P<0.001).

Discussion

CCY is one of the most commonly performed surgical procedures worldwide and is associated with positive outcomes [11]. In this large, propensity score-matched cohort study, we found that CCY was associated with a greater risk of developing CD, but had no significant association with the risk of UC. The higher risk of IBD was consistent across sex and age subgroups. Previous studies suggest a potential link between CCY and gastrointestinal disorders, but no randomized clinical trials have been conducted to establish causality. As a result, this relationship remains a gap in the literature.

CCY has been associated with a range of gastrointestinal complications. It has been reported that 2.1-57.2% of patients develop post-CCY diarrhea, and this is a part of post-CCY syndrome [12]. CCY has also been associated with a higher risk of gastrointestinal malignancies, including cancers of the stomach, colon, liver, pancreas and biliary tract [13,14]. This association may be driven by bile acid-mediated tumorigenesis, potentially through mechanisms involving oxidative stress, disruption of gut microbial balance, and activation of proinflammatory signaling pathways [15]. In addition, prior studies have reported associations between CCY and higher risks of IBS and microscopic colitis [6,16,17]. To date, however, no studies have reported a greater risk of IBD following CCY. While causality cannot be established, biologically plausible mechanisms may underlie this association, especially the

Table 2 Adjusted hazard ratios for inflammatory bowel disease, Crohn's disease, and ulcerative colitis following cholecystectomy: subgroup analysis by demographics and clinical factors

Subgroup	Inflammatory bowel disease		Crohn's disease		Ulcerative colitis	
	aHR (95% CI)	P-value	aHR (95% CI)	P-value	aHR (95% CI)	P-value
General	1.29 (1.22-1.35)	<0.001	1.83 (1.69-1.99)	<0.001	1.06 (0.996-1.13)	0.07
Sex						
Male	1.26 (1.15-1.37)	<0.001	1.99 (1.71-2.31)	<0.001	1.03 (0.93-1.14)	0.58
Female	1.21 (1.14-1.30)	<0.001	1.73 (1.56-1.92)	<0.001	0.99 (0.91-1.07)	0.76
Age						
18-60	1.33 (1.24-1.42)	<0.001	1.74 (1.57-1.94)	<0.001	1.07 (0.98-1.17)	0.17
>60	1.23 (1.15-1.31)	<0.001	1.83 (1.61-2.07)	<0.001	1.05 (0.97-1.13)	0.26
Comorbidities & exposures						
Diabetes mellitus	1.22 (1.12-1.33)	<0.001	1.92 (1.64-2.25)	<0.001	1.01 (0.91-1.12)	0.88
Tobacco use	1.43 (1.19-1.72)	<0.001	1.76 (1.32-2.33)	<0.001	1.29 (1.03-1.62)	0.03
Obesity	1.15 (1.07-1.23)	<0.001	1.69 (1.50-1.92)	<0.001	0.94 (0.86-1.03)	0.20
Aspirin	1.16 (1.07-1.25)	<0.001	1.75 (1.53-2.01)	<0.001	0.97 (0.88-1.06)	0.47
NSAIDs	1.14 (1.06-1.22)	0.001	1.57 (1.39-1.78)	<0.001	0.95 (0.86-1.04)	0.24

aHR, adjusted hazard ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs

potential effects of increased concentrations or the composition of bile acids in the colon, and changes in the microbiome.

In addition to their crucial role in fat digestion, bile acids serve as potent signaling molecules that regulate gut barrier integrity, immune responses and microbiota composition [18]. Primary bile acids are synthesized from cholesterol in hepatocytes, and are then modified by the gut microbiota into secondary bile acids upon entering the gastrointestinal tract [19]. Bile acid is stored in the gallbladder; thus, CCY alters the enterohepatic circulation of bile acids, resulting in continuous delivery of primary bile acids to the small intestine [20]. Studies show that increased levels of primary bile acids, along with decreased levels of secondary bile acids, are a hallmark in patients with IBD, and might also contribute to the development of colorectal cancers in this patient population [21-24]. Bile acids act as detergent molecules; in particular, the primary bile acid chenodeoxycholic acid and the secondary bile acid deoxycholic acid have been shown to trigger specific signaling pathways that disrupt intestinal epithelial barrier function and increase gut permeability [25]. This promotes microbial translocation and immune activation, contributing to the inflammation seen in IBD [15,26,27], and may potentially aggravate the potential to develop pouchitis in patients with IBD who have undergone colectomy [28]. Gut inflammation and dysbiosis further disturb the bile acid pool, creating a vicious cycle [20]. Giving further support to this model, a clinical improvement of diarrhea and other symptoms in IBD has been observed with the use of bile acid sequestrants, which mitigate the detrimental effects of excess primary bile acids on the intestinal mucosa [29-31].

The reason why in our study the association between CCY and IBD was specific to CD and not UC is not fully understood. Below, a few potential explanations will be discussed. CCY is known to alter the gut microbiota [32], which has been associated with Th1/Th17-dominant immune responses [33], seen in CD and not UC [34]. In addition, the increased levels of secondary bile acids in the colon after CCY were reported to have a protective or attenuating effect on UC activity [6,35]. CD more commonly involves the ileum and ileo-colonic region; thus, changes in bile acid delivery may have a larger impact on the sites that are typically involved in CD, rather than UC, which is limited to the colon [36]. Lastly, it is possible that the observed association could partly reflect early undiagnosed CD, rather than the true risk of CD caused by CCY, as patients with CD were reported to be more likely to develop gallstones, which might imply a greater risk of CCY than in patients with UC [37].

In our study, the possibility of diagnostic bias must be considered. Previous studies reported that patients with IBS were more likely to undergo CCY, probably having IBS symptoms mistaken for biliary disease [38]. A similar phenomenon may occur in patients with undiagnosed IBD who present with biliary-like symptoms. Furthermore, patients with IBD who had a CCY were reported to have worse diarrhea and a poorer quality of life [39,40], which could mean that patients with undiagnosed IBD may have exacerbation of symptoms after CCY, leading to further workup and unmasking undiagnosed IBD. However, to decrease the risk of diagnostic bias in our study, we excluded patients who were diagnosed with IBD within 3 months following CCY. These factors reveal the need for further research to clarify the temporal sequence and potential causal relationship between CCY and incident IBD.

This study carries some limitations that need to be discussed. First, although PSM improved balance across some confounders, it cannot account for unmeasured or unknown factors. Some examples include genetics, socioeconomic status and follow-up duration. This might influence both the likelihood of undergoing CCY and the subsequent risk of developing IBD. In addition, given the high prevalence of post-CCY diarrhea, it is possible that some patients were mistakenly diagnosed with that, rather than IBD. This might further decrease the true incidence of IBD detected. Finally, differences in coding, diagnostics and follow-ups across health systems might have introduced detection bias.

In conclusion, our study showed an elevated risk of CD after CCY. Even after adjustment for common confounders, the risk remained across demographic groups and clinical subgroups. This highlights the need for high clinical awareness regarding gastrointestinal symptoms following CCY. Further research is needed to study the underlying mechanisms linking CCY to alterations in the gastrointestinal barrier and the pathogenesis of CD.

Summary Box

What is already known:

- Cholecystectomy (CCY) alters bile acid metabolism and gut microbiota, potentially impacting gastrointestinal health
- CCY has been associated with several gastrointestinal conditions, including bile acid diarrhea and microscopic colitis
- The relationship between CCY and the risk of developing inflammatory bowel disease (IBD) remains unclear

What the new findings are:

- In our study, CCY was associated with a higher risk of *de novo* IBD (adjusted hazard ratio [aHR] 1.29, 95% confidence interval [CI] 1.22-1.35) in a large propensity-matched cohort
- The association was driven by Crohn's disease (aHR 1.83, 95%CI 1.69-1.99), with no significant difference in patients with ulcerative colitis
- The greater risk was consistent across age and sex groups

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