RESEARCH LETTER

Gastric Acid Suppression Is Associated With Higher Rates of Colectomy in Patients With Inflammatory Bowel Disease

The use of proton pump inhibitors (PPIs) has been associated with multiple systemic as well as gastrointestinal adverse effects. Growing literature evidence suggests that PPI use in patients with inflammatory bowel disease (IBD) is associated with worse clinical outcomes. Studies have begun to show that PPI use in IBD is associated with a higher rate of enteric infection [1] and disease flare [2] and delayed remission on infliximab,[3] which has been linked to disease severity, treatment escalation,[2,4] and increased risk of IBD-related hospitalization and surgeries.[4,5] The existing knowledge is grounded on observational studies with significant limitations such as smaller sample sizes, inconsistencies of reported disease-modifying factors, differences in baseline characteristics, and composite reports of IBD-related outcomes. Therefore, the influence of PPI use on IBD needs to be studied in larger-scale multicentric studies with a more homogenous outcome focus. With this in mind, we aimed to assess the risk of colectomy in IBD patients on acid-suppressing medications compared to those not on these medications.

We queried a multicenter database (Explorys Inc, IBM) incorporating records from 26 major healthcare systems in the United States. Adult patients diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) from January 2010 to November 2021 were identified. Among this cohort, race, gender, obesity, biologic use, PPI or histamine 2 receptor blocker (H2RB) use, and tobacco use were examined. The primary outcome of interest was colectomy rates in IBD patients from December 2020 to November 2021. Associations were estimated via gender-stratified multivariable logistic regression models. An interaction term was introduced to test the presence of effect modification with biologic use.

From January 2010 to November 2021, a total of 249,980 patients were identified to have a diagnosis of Crohn's disease, and 207,925 had a diagnosis of UC. Forty-two-point-four percent of CD and 41.8% of UC patients had been prescribed PPI. H2RB use was also similar between UC (26.3%) and CD (27.2%), as shown in Table 1. Among the CD patients, 1450 underwent colectomy in 2020–2021, while 3835 patients with UC had a colectomy. PPI use was associated with significantly higher odds of colectomy in UC (adjusted odds ratio (aOR): 6.32 (5.74–6.96), $P < .001$), as well as CD (aOR: 1.87 (1.66–2.11), $P < .001$) (Table 2).

H2RB use and Obesity were similarly associated with higher rates of colectomy. On the other hand, female gender or Caucasian race was associated with lower rates of colectomy. Concurrent use of biologics with PPIs was shown to significantly mitigate the risk of colectomy in both UC (aOR: 0.78 (0.62–0.98), $P < .03$) and CD (aOR: 0.44 (0.31–0.63), $P < .00$). Similarly, biologics mitigated the risk of colectomy in UC (aOR: 0.11 (0.09–0.14), $P < .00$) and CD (aOR: 0.60 (0.38–0.95), $P < .03$) patients who were using H2RBs.

In this large population-based cohort study, PPI and H2RB use were associated with a significantly higher risk of colectomy in IBD patients. This risk was most pronounced in UC patients using PPI. Patients using biologics had a lower risk of colectomy, and biologic use also mitigated the increased risk in patients using H2RB and PPI. These findings persisted after multivariate adjustments for gender, race, smoking, obesity, and biologic use, which seemed to be caused by PPI and H2RB.

Although much more remains to be investigated, potential mechanisms have been linked to the reduction of gastric acid secretion and hypochlorhydria, which leads to the disruption of the antimicrobial acid barrier and promotes downstream dislocation of oral bacteria; gut dysbiosis, may increase the risk of enteric infections[1] and alter cell and mucosal immunity.[6] The use of PPIs has been shown to increase the risk of gastroenteritis[7,8] and C. difficile infection,[9] which can mimic or trigger IBD flares.[10] Our findings support the hypothesis by showing similar but less robust outcome trends in H2RB use in IBD patients. H2RBs are considered less potent acid suppressants than PPIs, which correlates with observed differences in the colectomy rates.

This is the first and largest multicenter US database study published to date showing that PPI and H2RB use is

Table 1. Baseline Characteristics

	CD (n = 249,980)		UC (n = 207,925)	
Variables	n	Prevalence (%)	n	Prevalence (%)
H2RB use	67,985	27.2	54,590	26.3
PPI use	105,870	42.4	86,900	41.8
Biologic use	180,245	72.1	150,400	72.3
Gender				
Female	148,380	59.4	121,040	58.2
Male	101,600	40.6	86,885	41.8
Race				
White	184,840	73.9	157,660	75.8
Non-White	65,140	26.1	50,265	24.2
Tobacco use	56,985	22.8	37,775	18.2
Obesity	50,770	20.3	45,715	22.0
Colectomy	1450	0.6	3835	1.8

Table 2. Odds of Colectomy in IBD

Variables	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
H2RB				
UC	3.12 (2.92–3.32)	<.001	1.71 (1.59–1.83)	<.001
CD	2.09 (1.88–2.32)	<.001	1.43 (1.27–1.60)	<.001
PPI				
UC	7.11 (6.53–7.74)	<.001	6.32 (5.74–6.96)	<.001
CD	2.48 (2.23–2.76)	<.001	1.87 (1.66–2.11)	<.001
Biologic use				
UC	2.28 (2.09–2.51)	<.001	0.74 (0.67–0.82)	<.001
CD	2.65 (2.27–3.10)	<.001	1.74 (1.46–2.06)	<.001
Female gender				
UC	0.79 (0.74–0.84)	<.001	0.71 (0.66–0.76)	.001
CD	0.79 (0.71–0.88)	<.001	0.71 (0.64–0.79)	.001
Caucasian race				
UC	1.02 (0.95–1.11)	.5143	0.76 (0.70–0.82)	<.001
CD	0.92 (0.82–1.03)	.1864	0.74 (0.66–0.84)	<.001
Smoking				
UC	1.68 (1.56–1.81)	<.001	1.08 (1.00–1.17)	.027
CD	1.14 (1.01–1.28)	.0325	0.83 (0.74–0.94)	.005
Obesity				
UC	1.96 (1.83–2.10)	<.001	1.61 (1.50–1.73)	<.001
CD	1.83 (1.63–2.04)	<.001	1.58 (1.41–1.77)	<.001

CI, confidence interval.

associated with increased colectomy rate in IBD patients. Our study has several limitations. First, although multivariate adjustments have been utilized for known disease-modifying factors, we cannot completely exclude residual confounds. Second, this is a large database observational study conducted on the platform with deidentified patient-related data, which limits individual chart review for data validation. For the same reason, important patient-related data such as the duration of PPI use or dosage and the number of years since the patient had other comorbid conditions were missed. Therefore, it is difficult to extrapolate causality and dose–response relationships by the nature of the study. Third, in using this database, we were unable to establish a temporal relationship between gastric acid suppression and colectomy. We addressed this limitation by including only patients who had a colectomy within the last year of the study. One further limitation is that claims-based administrative databases are vulnerable to missing or incorrectly entering codes.

Providers should be vigilant about PPI and H2RB use in IBD. Aggressive screening of IBD patients for PPI and H2RB use and verifying indication and treatment duration could eliminate unnecessary acid suppressants and decrease the need for colectomy. Further prospective studies are needed to validate the findings and explore the underlying mechanism.

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Abbreviations used in this paper: **aOR, adjusted odds ratio; CD, Crohn's disease; H2RB, histamine 2 receptor blocker; IBD, inflammatory bowel disease; PPI, proton pump inhibitor; UC, ulcerative colitis**

Most current article

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The data were accessed through the IBM Explorys Electronic Health Record Database following relevant licensure obtained; therefore, institutional review board approval was not needed to conduct this study. This study followed the IBM Explorys Research Data Use Agreement.

Data Transparency Statement:
This study utilized the IBM Explorys Electronic Health Record Database.

Reporting Guidelines:
STROBE.