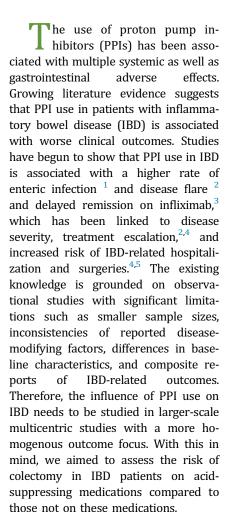
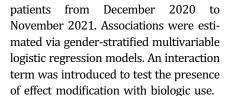
# **RESEARCH LETTER**

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



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



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<sup>1</sup> and alter cell and mucosal immunity.6 The use of PPIs has been shown to increase the risk of gastroenteritis<sup>7,8</sup> 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 (	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 Male	148,380 101,600	59.4 40.6	121,040 86,885	58.2 41.8	
Race White Non-White	184,840 65,140	73.9 26.1	157,660 50,265	75.8 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 CD	3.12 (2.92–3.32) 2.09 (1.88–2.32)	<.001 <.001	1.71 (1.59–1.83) 1.43 (1.27–1.60)	<.001 <.001			
PPI UC CD	7.11 (6.53–7.74) 2.48 (2.23–2.76)	<.001 <.001	6.32 (5.74–6.96) 1.87 (1.66–2.11)	<.001 <.001			
Biologic use UC CD	2.28 (2.09–2.51) 2.65 (2.27–3.10)	<.001 <.001	0.74 (0.67–0.82) 1.74 (1.46–2.06)	<.001 <.001			
Female gender UC CD	0.79 (0.74–0.84) 0.79 (0.71–0.88)	<.001 <.001	0.71 (0.66–0.76) 0.71 (0.64–0.79)	.001 .001			
Caucasian race UC CD	1.02 (0.95–1.11) 0.92 (0.82–1.03)	.5143 .1864	0.76 (0.70–0.82) 0.74 (0.66–0.84)	<.001 <.001			
Smoking UC CD	1.68 (1.56–1.81) 1.14 (1.01–1.28)	<.001 .0325	1.08 (1.00–1.17) 0.83 (0.74–0.94)	.027 .005			
Obesity UC CD	1.96 (1.83–2.10) 1.83 (1.63–2.04)	<.001 <.001	1.61 (1.50–1.73) 1.58 (1.41–1.77)	<.001 <.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

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## Conflict of Interest:

The authors disclose no conflicts.

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## **Ethical Statement:**

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.