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Brief Report - Clinical

New Gastrointestinal Symptoms Are Common in Inflammatory Bowel Disease Patients With COVID-19: Data From an International Registry

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Introduction

Coronavirus disease 2019 (COVID-19) can cause gastrointestinal (GI) symptoms. A prior meta-analysis suggested that up to 17.6% of COVID-19 patients have GI symptoms.[1] Data are conflicting on the association of GI symptoms with COVID-19 outcomes, with some reports suggesting worse prognosis among those with GI symptoms while others finding improved outcomes.[2–4] There are limited data on COVID-19 and GI symptoms among inflammatory bowel disease (IBD) patients. A single-center study of 80 IBD patients with COVID-19 observed that they were more likely to present with abdominal pain and diarrhea than non-IBD controls.[5] In addition, a prior systematic review on just over 400 patients found nearly one-quarter of IBD patients with COVID-19 had diarrhea.[6] Using a large, international database, we aimed to describe new onset GI symptoms and their association with clinical outcomes in patients with IBD who develop COVID-19.

Methods

We used the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) database, a global registry to understand COVID-19 outcomes in IBD patients previously described.[7] We recorded all new GI symptoms during the time of COVID-19 infection. We performed descriptive statistics using χ^2 or Fisher exact test for categorical variables and Wilcoxon rank-sum or *t* test for continuous variables. We also performed sensitivity analyses of new GI symptoms, comparing patients in remission vs active disease by physician global assessment (PGA) at time of COVID-19 diagnosis. Physician global assessment was reported as remission, mild, moderate, or severe. Multivariable logistic regression assessed the independent association of new GI symptoms with the odds of death due to COVID-19 adjusting for age, sex, race, number of comorbidities, baseline corticosteroid use, and tumor necrosis factor (TNF) antagonist use.

Results

Of 2 917 IBD patients with COVID-19, 764 (26.2%) experienced new GI symptoms. The most commonly reported new GI symptom was diarrhea, and the second most common symptom was abdominal pain (Table 1). New GI symptoms were more common among IBD patients with active disease but were also frequently seen among IBD patients in remission (29.4% vs 23.3%, $P < .01$). The specific new GI symptoms reported were similar between patients in and not in remission with the exception of abdominal pain, which was more frequent with active disease. In addition, patients with new GI symptoms were more likely to be older, female, have active disease, be of Asian race, and have at least 1 comorbidity (Table 2). There was no difference in new GI symptoms comparing Crohn's disease and ulcerative colitis. Patients on any medication—but in particular TNF antagonist monotherapy—were less likely to report new GI symptoms. On bivariate analyses, IBD patients with new GI symptoms were more likely to be hospitalized (31.4% vs 19.2%, $P < .001$) but were not more likely to require intensive care/ventilator (5.8% vs 4.6%, $P = .18$) or die due to COVID-19 (2.0% vs 2.5%, $P = .39$). On multivariable analysis, new GI symptoms were not significantly associated with risk of death due to COVID-19 (adjusted odds ratio, 0.72; 95% confidence interval, 0.38–1.36).

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Table 1. Description of gastrointestinal symptoms among inflammatory bowel disease patients with COVID-19.

GI symptoms	All Patients		Active IBD		IBD in Remission		*P*[a]
	N	(%)	N	(%)	N	(%)	
Any	764		340		382		
Abdominal pain	259	34%	149	44%	101	26%	<.001
Diarrhea	609	80%	283	83%	290	76%	.02
Nausea	180	24%	82	24%	94	25%	.88
Vomiting	95	12%	41	12%	47	12%	.92
Other	79	10%	35	10%	36	9%	.70

[a]*P* values comparing GI symptoms in active IBD compared with IBD in remission

Discussion

New GI symptoms are common among IBD patients with COVID-19. Diarrhea was the most predominant symptom. New GI symptoms are likely not explained by underlying IBD disease activity, as a substantial number of patients in remission reported new GI symptoms. Although IBD patients with new GI symptoms were more likely to be hospitalized, they were not more likely to die due to COVID-19. To our knowledge, this is the largest report of GI symptoms in IBD patients with COVID-19 to date.

Prior studies on GI symptoms often included anorexia, which may not be specific to the GI tract. Reported rates of diarrhea, abdominal pain, and nausea vomiting in COVID-19 patients have been around 10%.[1,8] Compared with these prior findings, our results suggest that IBD patients may be more likely to have new GI symptoms in the setting of COVID-19 than the

Table 2. Demographics and clinical characteristics of inflammatory bowel disease patients with and without new gastrointestinal symptoms during COVID-19.

Characteristic	New GI Symptoms (*n* = 764)	No New GI Symptoms (*n* = 2,153)	*P*
Age in years, mean (SD)	43 (17)	40 (18)	.002
Female, n (%)	424 (55.5)	1,019 (47.3)	.001
Race, n (%)			
White	589 (77.1)	1,732 (80.4)	.05
Black	60 (7.9)	124 (5.8)	.04
Asian	55 (7.2)	99 (4.6)	.006
Any comorbidity, n (%)	280 (36.6)	670 (31.1)	.005
Disease type, n (%)			
Crohn's disease	431 (56.4)	1,204 (55.9)	.93
Ulcerative colitis	319 (41.8)	898 (41.7)	
IBD disease activity, n (%)			
Remission	382 (50)	1,257 (58.4)	<.001
Mild	158 (20.7)	409 (19)	
Moderate	138 (18.1)	303 (14.1)	
Severe	44 (5.8)	106 (4.9)	
Medication, n (%)			
Any medication	696 (91.1)	2,026 (94.1)	.004
TNF antagonist monotherapy	176 (23)	758 (35.2)	<.001
Thiopurine monotherapy	75 (9.8)	193 (9.0)	.48
Integrin antagonist monotherapy	82 (10.7)	227 (10.5)	.88
IL-12/23 antagonist monotherapy	81 (10.6)	167 (7.8)	.02
Oral corticosteroid	53 (6.9)	159 (7.4)	.68
Mesalamine/sulfasalazine	251 (32.9)	641 (29.8)	.11
Therapies used to treat COVID-19			
Any medication	433 (20.1)	261 (34.2)	<.001
Remdesivir	26 (1.2)	3 (0.4)	.05
Chloroquine	39 (1.8)	9 (1.2)	.24
Hydroxychloroquine	197 (9.2)	133 (17.4)	<.001
Oseltamivir	19 (0.9)	10 (1.3)	.31
Lopinavir/ritonavir	52 (2.4)	27 (3.5)	.10
Tocilizumab	15 (0.7)	7 (0.9)	.55
Corticosteroids	75 (3.5)	40 (5.2)	.03
Other	242 (11.2)	169 (22.1)	<.001

Abbreviations: IBD, inflammatory bowel disease; GI, gastrointestinal; COVID-19, Coronavirus disease 2019; SD, standard deviation; TNF, tumor necrosis factor; IL, interleukin

general population. An electronic-records database with 232 IBD patients also found that IBD patients were more likely to have a code for GI symptoms than non-IBD COVID-19 patients.[8] Our results are also consistent with a previous systematic review that included 449 IBD patients with COVID-19; 20.5% of patients reported diarrhea, 8.9% nausea, and 8.7% abdominal pain.[6] Last, we observed no association between presence of GI symptoms and risk of needing intensive care/ventilator or dying from COVID-19 in IBD patients.

Strengths of this study include the large sample size, assessment of GI symptoms relative to pre-COVID-19 IBD symptoms, stratification by disease activity, and evaluating association with COVID-19 outcomes. Limitations include retrospective study design, the risk of reporting bias, and reliance on PGA for disease activity assessment.

In summary, new GI symptoms are common in IBD patients with COVID-19 and are not associated with an increased risk of death due to COVID-19. Our findings suggest that an increase in GI symptoms in IBD patients should prompt consideration of a COVID-19 diagnosis. Further studies are needed to understand if GI symptoms impact COVID-19 prognosis and if COVID-19 can trigger IBD flares or alter subsequent disease course.

Author Contribution

R.C.U. and W.R. contributed to study conception, study design, data analysis and interpretation, manuscript preparation, and manuscript editing. X.Z. contributed to data analysis and interpretation and manuscript editing. M.A., E.J.B., J.F.C., and M.D.K. contributed to study design, data interpretation, and manuscript editing. All authors have reviewed and approved the final draft of the manuscript.

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Conflicts of Interest

R.C.U. has served as an advisory board member or consultant for AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, and Takeda; research support from AbbVie, Boehringer Ingelheim, and Pfizer. J.F.C. has received research grants from AbbVie, Janssen Pharmaceuticals and Takeda; received payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals, Shire, and Takeda; received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Landos, Ipsen, Medimmune, Merck, Novartis, Pfizer, Shire, Takeda, Tigenix, Viela Bio; and holds stock options in Intestinal Biotech Development and Genfit. M.D.K. has consulted for AbbVie, Janssen, and Takeda; is a shareholder in Johnson & Johnson; and has received research support from AbbVie and Janssen. W.R. has served as a speaker for Abbott Laboratories, Abbvie, Aesca, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult. He has been a consultant for Abbott Laboratories, Abbvie, Aesca, Algernon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, Astra Zeneca, Avaxia, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernest & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestle, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, Parexel, PDL, Periconsulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, Tigenix, UCB, Vifor, Zealand, Zyngenia, and 4SC. He has been an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zealand, Zyngenia, and 4SC. He has received research funding from Abbott Laboratories, Abbvie, Aesca, Centocor, Falk Pharma GmbH, Immundiagnsotik, and MSD.

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