Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Systematic Review on Inflammatory Bowel Disease Patients With Coronavirus Disease 2019: It Is Time to Take Stock

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BACKGROUND & AIMS: **Data on the clinical characteristics of patients with inflammatory bowel diseases (IBDs) with coronavirus disease 2019 (COVID-19) are scarce. The aim of our systematic review was to investigate symptoms and diagnostic–therapeutic management of IBD patients with COVID-19.**

METHODS: **We searched PubMed, Embase, Web of Science, and MedRxiv up to July 29, 2020, to identify all studies reporting clinical information on adult and pediatric IBD patients with confirmed COVID-19.**

RESULTS: **Twenty-three studies met our inclusion criteria, including 243,760 IBD patients. COVID-19 was diagnosed in 1028 patients (509 with Crohn's disease [49.5%], 428 with ulcerative colitis [41.6%], 49 with indeterminate colitis [4.8%], and 42 with missing data [4.1%]), accounting for a cumulative prevalence of 0.4%. Viral infection occurred more frequently in males than in females (56.5% vs 39.7%), and the mean age ranged from 14 to 85 years. The most common symptoms were fever (48.3%), cough (46.5%), and diarrhea (20.5%), and a COVID-19 diagnosis was achieved mainly through polymerase chain reaction analysis of nasopharyngeal swabs (94.4%) and chest computed tomography scans (38.9%). Hydroxychloroquine (23.9%), lopinavir/ritonavir (8.2%), steroids (3.2%), and antibiotics (3.1%) were the most used drugs. Overall, approximately a third of patients were hospitalized (30.6%), and 11.4% of them required admission to the intensive care unit. In total, 29 COVID-19–related deaths were reported (3.8%), and increasing age and the presence of comorbidities were recognized as risk factors for COVID-19 and negative outcomes.**

CONCLUSIONS: **Diarrhea occurs more frequently in IBD patients with COVID-19 than in the non-IBD population. Further studies are needed to define the optimal diagnostic–therapeutic approach in IBD patients with COVID-19.**

Keywords: COVID-19; SARS-CoV-2; Crohn's Disease; Ulcerative Colitis; Inflammatory Bowel Disease.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new β-coronavirus that was identified in China after the onset, in December 2019, of some pneumonia cases of unknown etiology.[1] Viral infection can be asymptomatic or cause the coronavirus disease 2019 (COVID-19), which is characterized by a wide range of clinical manifestations including respiratory and gastrointestinal symptoms up to severe events such as pneumonia, acute respiratory distress syndrome, and death.[2] The high transmission capacity and the rapid virus spread worldwide have led the World Health Organization to declare a pandemic state and national and international authorities to impose several precautions and prohibitions to limit the contagion up to the total lockdown.[3,4] As of June 12, 2020, there were 7,410,510 cases of COVID-19 that have been ascertained globally, with a total of 418,294 deaths.[5] Since the beginning of the health emergency, particular attention has been paid to the management of patients with chronic inflammatory bowel diseases (IBDs) because they frequently are treated with immunosuppressive drugs and therefore potentially are exposed to a greater infectious risk than the general population.[6] In addition,

Abbreviations used in this paper: aOR, adjusted odds ratio; COVID-19, coronavirus disease 2019; CD, Crohn's disease; IBD, inflammatory bowel disease; ICU, intensive care unit; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UC, ulcerative colitis.

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hospitals also profoundly have been reorganized to address the growing number of infected patients, to adapt to social distancing measures, and to prevent the infection risk, postponing or canceling nonessential activities and replacing outpatient visits with virtual clinics.[7,8] The British Society of Gastroenterology, the European Crohn's and Colitis Organization, and the International Organization for the Study of Inflammatory Bowel Disease promptly provided empiric recommendations for the management of patients with Crohn's disease (CD) and ulcerative colitis (UC).[9–11] However, knowledge of SARS-CoV-2 evolves daily and some doubts persist on the optimal approach in subjects treated with immunosuppressants, biologics, or small molecules. The aim of our study was to provide a systematic overview of the literature data on IBD patients with COVID-19 to report the clinical characteristics of disease, to identify any risk factors for severe/complicated disease, and to investigate the diagnostic–therapeutic management of IBD patients in this emergency setting.

What You Need to Know

Background

Little data are available on the clinical characteristics of inflammatory bowel disease (IBD) patients with COVID-19 and their diagnostic-therapeutic management is not well established.

Findings

IBD patients with COVID-19 have symptoms similar to IBD patients except for a higher percentage of diarrhea. The diagnostic-therapeutic approach does not differ between IBD and non-IBD patients with COVID-19.

Implications for patient care

Fecal test for new coronavirus detection could allow to differentiate infected patients from those with IBD re-exacerbation. In addition, IBD medications could play a role in the treatment of COVID-19.

Methods

We conducted a systematic review in accordance with the Cochrane Handbook[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of systematic reviews incorporating network meta-analysis.[13]

Data Sources and Search Strategy

We searched PubMed, Embase, Web of Science, and MedRxiv up to July 29, 2020, to identify all studies reporting information on IBD patients with COVID-19. The following medical subject heading terms were combined with the Boolean operators "AND" or "OR": "COVID-19," "coronavirus disease 2019," "SARS-CoV-2," "severe acute respiratory syndrome coronavirus 2," "new coronavirus," "Crohn's disease," "CD," "ulcerative colitis," "UC," "inflammatory bowel disease," "IBD." The search was restricted to human studies, although no language or time restrictions were applied. Titles and abstracts were scrutinized independently by all 3 authors (F.D., S.D., and L.P.B.) to identify eligible studies. Subsequently, full-text articles were examined for inclusion, and any disagreements were resolved through collegial discussion. Finally, the reference lists of the selected manuscripts were hand-searched to identify studies missed by the electronic search.

Selection Criteria

All studies meeting the following criteria were included: (1) adult and/or pediatric patients with a confirmed diagnosis of IBD; (2) studies reporting at least 1 confirmed case of COVID-19; and (3) studies addressing clinical management of IBD patients with COVID-19. Reviews, systematic reviews, meta-analyzes, guidelines, letters, and editorials that did not show original data were excluded from our work. Furthermore, all studies involving non-IBD patients were excluded if the IBD population data could not be distinguished. If some results were reported at multiple time points, the study with the most comprehensive data was included.

Data Extraction and Analysis

Each article was assessed qualitatively. All 3 authors extracted the following data from the selected studies: first author, journal and year of publication, study design, number of participants, patient characteristics (age, sex, concomitant treatments, IBD type), number of IBD patients with confirmed COVID-19, symptoms of COVID-19, diagnostic approach, COVID-19 therapy, hospitalizations, admission to the intensive care unit (ICU), number of deaths, and risk factors associated with COVID-19.

Quality of Studies

The Newcastle–Ottawa Scale (NOS) score was used to measure the quality of nonrandomized clinical trials, and the Jadad score was adopted for randomized clinical trials.[14,15] The NOS score ranges from 0 to 9. The NOS score is based on 8 items: representativeness of the exposed cohorts, selection of the nonexposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, comparability of cohorts on the basis of the design or analysis, assessment of the outcome, follow-up period is long enough for outcomes to occur, and adequacy of the follow-up evaluation. One point can be assigned to each item, except for cohort comparability (which can be

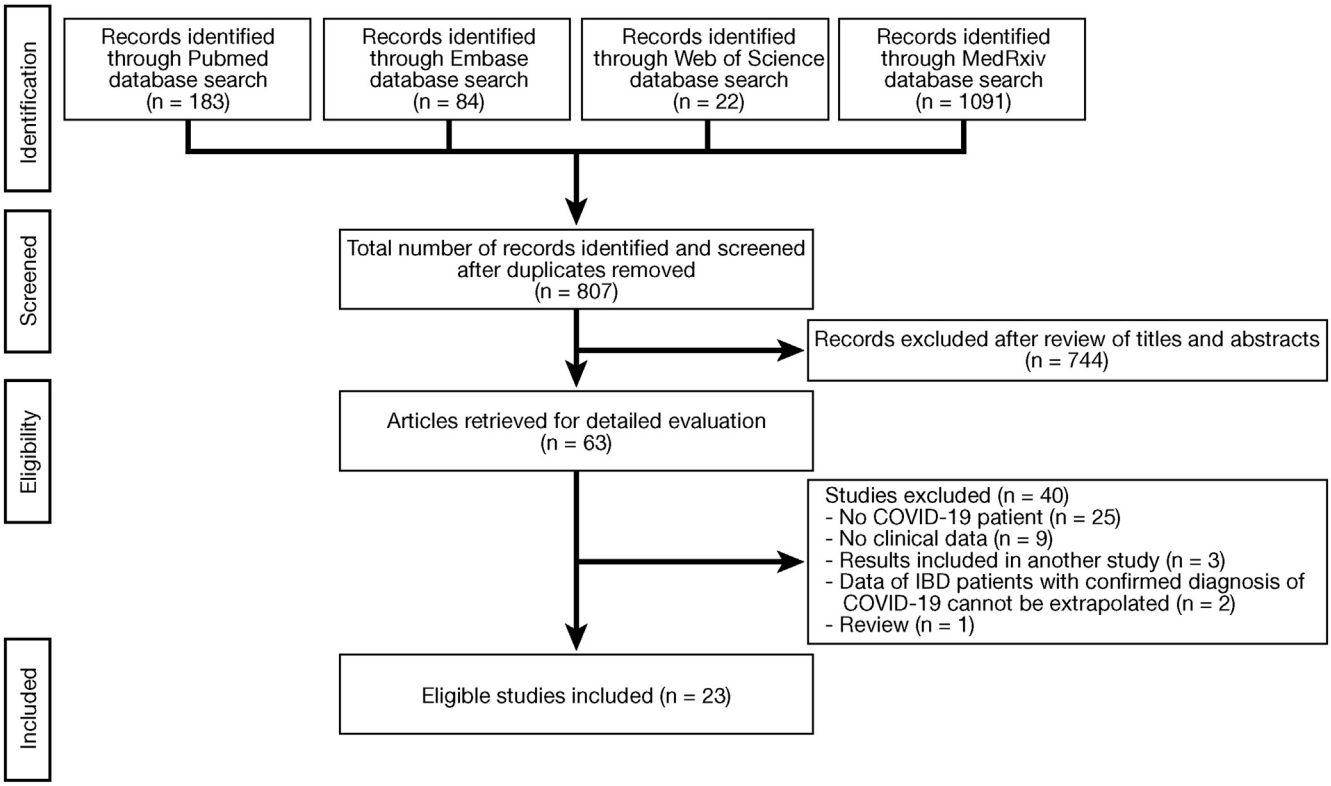

Figure 1. Flow chart of the search process. COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease.

assigned 2 points). A NOS score of 6 or higher was associated with high-quality studies, while scores of 3 or lower or between 4 and 5 indicated low- and moderate-quality studies, respectively. On the other hand, the Jadad score ranges from 0 to 5 and it assesses the following parameters: randomized study, appropriate randomization, double-blind study, appropriate double-blind study, and a description of withdrawals/dropouts. Each parameter is assigned 1 point and a study is defined as a high-quality study if the Jadad score is 3 or higher. All 3 authors graded the studies independently and any disagreements were discussed until their resolution.

Results

Study Characteristics

The flow chart of the search process is detailed in Figure 1. A total of 1380 articles were identified through our search (PubMed, 183; Embase, 84; Web of Science, 22, and MedRxiv, 1091). After removing duplicates and reviewing titles and abstracts, 63 studies were evaluated for full-text analysis. An additional 40 studies were excluded because they did not include COVID-19 patients (n = 25), did not evaluate clinical data (n = 9), results were included in another study (n = 3), data of IBD patients with a confirmed diagnosis of COVID-19 could not be extrapolated (n = 2), or data were not original (n = 1). Finally, 23 studies[16–38] were included in our systematic review. Most studies were case reports (12 [52.2%]),[16,18,19,22,27,29,32–36,38] followed by observational cohort studies (3 prospective [13.0%][17,21,25] and 6 retrospective studies [26.1%][20,24,26,28,31,37]) and case series (2 [8.7%])[23,30] (Tables 1 and 2). Most studies were of moderate quality according to the NOS score (15 [65.2%]),[16,19,20,22,26–28,30,31,38] while the remaining studies were classified as high-quality studies (8 [34.8%])[17,18,21,23–25,29] (Table 3).

Patient Characteristics

The overall study population consisted of 243,760 IBD patients. COVID-19 was diagnosed in 1028 patients (509 CD patients [49.5%], 428 UC patients [41.6%], 49 with indeterminate colitis [4.8%], and 42 with missing data [4.1%]), accounting for a cumulative prevalence of 0.4%. More than half of infected patients were male (581 [56.5%]), 408 were female (39.7%), and in 39 cases sex was not specified (3.8%). The mean age ranged from 14 to 85 years. Elderly patients (>65 y) with COVID-19 were found in 10 studies (43.5%),[16,17,20,23–26,31,37,38] pediatric cases (<18 y) were reported in 4 studies (17.4%),[21,29,30,36] and an infected pregnant patient was described in 1 case report (4.3%).[27] The ongoing drugs at the time of COVID-19 diagnosis were reported in almost all studies (20 [87.0%])[16–28,30,32–36,38] and were as follows: anti–tumor necrosis factor (243 of 790 [30.8%]), mesalamine (203 [25.7%]), thiopurine (83 [10.5%]), vedolizumab (79 [10.0%]), ustekinumab (77 [9.7%]), steroids (68 [8.6%]), combination therapy

Table 1. Patient Demographics and Main Characteristics of Case Series and Observational Cohort Studies

Study	Study design	Study population	COVID-19	Sex	Mean age, *y*	Ongoing therapy	Symptoms	Diagnosis	Treatment	Hospitalization	ICU	Mechanical ventilation	Death	Risk factors
Lukin et al[17]	Prospective cohort study	80 IBD, 160 controls	26 CD, 38 UC	135 males (56.3%)	48.7	Mesalamine, 20 (25%); anti-TNF, 16 (20%); steroids, 13 (16.2%); UST, 12 (15%); VDZ, 10 (8.0%); combination therapy, 4 (5.0%); thiopurines, 4 (5.0%); methotrexate, 3 (3.7%); TOFA, 1 (1.2%)	Cough, 54 (67.5%); fever, 53 (66.6%); diarrhea, 36 (45.0%); shortness of breath, 23 (28.8%); abdominal pain, 16 (20.0%); nausea, 12 (15%); vomiting, 10 (12.5%); myalgia/fatigue, 7 (8.8%); anorexia, 7 (8.8%); anosmia, 7 (8.8%); dysgeusia, 4 (5.0%)	NPS	/	17 (21.3%)	3 (17.6%)	2 (11.8%)	0	Diagnosis of UC was associated with emergency visit or admission
Rodríguez-Lago et al[20]	Retrospective cohort study	13 CD, 23 UC, 4 IC	13 CD, 23 UC, 4 IC	24 males (60%)	59	Mesalamine, 26 (65%); thiopurines, 8 (20%); steroids, 4 (10%); methotrexate, 3 (8%); UST, 3 (8%); combination therapy, 2 (5.0%); anti-TNF, 3 (8%); VDZ, 1 (3%)	Fever, 31 (77%); cough, 27 (67%); diarrhea, 8 (20%)	NPS	Hydroxychloroquine, 25 (63%); lopinavir/ritonavir, 15 (38%); antibiotic, 9 (23%); steroid, 5 (13%); oseltamivir, 1 (3%); tocilizumab, 1 (3%); anakinra, 1 (3%)	21 (52.5%)	0	/	2 (5%)	/
Brenner et al[21]	Prospective cohort study	312 CD (59.4%), 203 UC (38.7%), 7 IC (1.3%), 3 missing (0.6%)	312 CD (59.4%), 203 UC (38.7%), 7 IC (1.3%), 3 missing (0.6%)	276 males (52.6%)	42.9	Anti-TNF, 176 (33.5%); mesalamine, 117 (22.3%); UST, 55 (10.5%); thiopurines, 53 (10.1%); combination therapy, 52 (9.9%); VDZ, 50 (9.5%); systemic steroids, 37 (7.0%); other, 22 (4.2%); budesonide, 18 (3.4%); TOFA, 8 (1.5); methotrexate, 5 (1.0%)	/	/	Hydroxychloroquine, 98 (18.7%); other, 67 (12.8%); lopinavir/ritonavir, 28 (5.3%); chloroquine, 14 (2.7%); steroid, 12 (2.3%); oseltamivir, 6 (1.1%); tocilizumab, 5 (1.0%); remdesivir, 2 (0.4%)	161 (30.7%)	24 (4.6%)	21 (4.0%)	16 (3%)	Increasing age, ≥2 comorbidities, systemic corticosteroids, and mesalamine/sulfasalazine use were risk factors for ICU admission/ventilation/death

Taxonera et al[23]	Case series	920 CD (48.0%), 997 UC (52.0%)	7 CD, 5 UC	3 males (25.0%)	47.9	Mesalamine, 4 (33.3%); thiopurines, 3 (25.0%); anti-TNF, 3 (25.0%); methotrexate, 3 (25.0%); UST, 1 (8.3%); VDZ, 1 (8.3%)	Fever, 9 (75%); diarrhea, 9 (75%); cough, 6 (50%); myalgia, 6 (50%); dyspnea, 5 (41.7%); sore throat, 4 (33.3%); ageusia, 4 (33.3%); fatigue, 4 (33.3%); anosmia, 3 (25.0%); headache, 3 (25.0%); nausea/vomiting, 2 (16.7%)	NPS	Hydroxychloroquine, 8 (66.7%); antibiotic, 6 (5.0%); lopinavir/ritonavir, 4 (33.3%)	8 (66.7%)	1 (8.3%)	1 (8.3%)	2 (0.1%)	/	
Gubatan et al[24]	Retrospective cohort study	86 UC (51.2%), 66 CD (39.3%), 16 IC (9.5%)	3 UC, 2 CD	2 males (40.0%)	/	Mesalamine, 4 (80.0%); steroids, 1 (20.0%); thiopurines, 1 (20.0%); anti-TNF, 1 (20.0%)	Cough, 4 (80.0%); fever, 3 (60.0%); fatigue, 3 (60.0%); rhinopharyngitis, 3 (60.0%); myalgia, 3 (60.0%); sore throat, 2 (40.0%); dyspnea, 2 (40.0%); pneumonia, 2 (40.0%); diarrhea, 1 (20.0%); abdominal pain, 1 (20.0%); nausea/vomiting, 1 (20.0%)	/	/	/	/	/	1	Age >66 y was associated independently with increased risk of COVID-19
Bezzio et al[25]	Prospective cohort study	32 CD, 47 UC	32 CD, 47 UC	44 males (55.7%)	45	Anti-TNF, 29 (36.7%); mesalamine, 24 (30.4%); VDZ, 15 (18.9%); steroids, 9 (11.4%); thiopurines, 6 (7.6%); UST, 3 (3.8%); investigational drugs, 2 (2.5%); calcineurin inhibitors, 1 (1.3%)	Fever, 71 (89.9%); cough, 52 (65.8%); dysosmia or dysgeusia, 19 (24.0%); arthralgia or myalgia, 18 (22.8); dyspnea, 15 (19.0%); diarrhea, 12 (15.2%); rhinopharyngitis, 13 (16.4%); dysphonia 1 (1.2%); conjunctivitis, 1 (1.2%)	NPS, CT scan	/	22 (27.8%)	2 (2.5%)	2 (2.5%)	6 (7.6%)	Age >65 y, active IBD, and CCI score >1 were associated significantly with COVID-19–related death
Khan et al[26]	Retrospective cohort study	37,857 IBD	36 IBD (0.1%)	/	63	Anti-TNF, 2 (5.5%); thiopurines, 3 (8.3%)	/	Laboratory test	/	/	/	/	/	CCI score was associated significantly with the risk of COVID-19

Table 1. Continued

Study	Study design	Study population	COVID-19	Sex	Mean age, *y*	Ongoing therapy	Symptoms	Diagnosis	Treatment	Hospitalization	ICU	Mechanical ventilation	Death	Risk factors
Allocca et al[28]	Retrospective cohort study	6000 IBD	9 CD, 6 UC	4 males (26.7%)	39.1	Anti-TNF, 8 (53.3%); UST, 3 (20.0%); steroids, 2 (13.3%); thiopurines, 2 (13.3%); mesalamine, 1 (6.7%); VDZ, 1 (6.7%); investigational drugs, 1 (6.7%); calcineurin inhibitors, 1 (6.7%)	/	NPS	/	5 (33.3%)	0	/	0	/
Turner et al[30]	Case series	4 pediatric CD,[a] 2 pediatric UC, 1 pediatric IC	3 CD, 2 UC	2 males (40.0%)	16.4	Mesalamine, 3 (60.0%); thiopurines, 3 (60.0%); anti-TNF, 2 (40.0%); steroids, 1 (20.0%); VDZ, 1 (20.0%)	Cough, 3 (60.0%); fever, 2 (40.0%); fatigue, 1 (20.0%); rhinitis, 1 (20.0%); chest pain, 1 (20.0%); anosmia, 1 (20.0%); ageusia, 1 (20.0%)	/	/	0	0	0	0	/
Marafini et al[31]	Retrospective cohort study	397 CD, 269 UC, 6 IC	3 IBD	/	/	/	/	NPS	/	2 (66.6%)	/	/	1	/
Singh et al[37]	Retrospective cohort study	196,403 IBD, 19,776 non-IBD	101 CD, 93 UC, 38 IC	85 males (36.7%)	51.2	/	Cough, 56 (24.1%); fever, 38 (16.4%); dyspnea, 30 (12.9%); nausea, 25 (10.8%); vomiting, 25 (10.8%); fatigue, 20 (8.6%); diarrhea, 19 (8.2%); abdominal pain, 18 (7.7%); sore throat, 14 (6.0%); hypoxemia, 12 (5.2%)	/	/	56 (24.1%)	/	/	/	The risk of severe COVID-19 was higher in IBD patients who received corticosteroids up to 3 mo before the diagnosis of COVID-19

CD, Crohn's disease; CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IC, indeterminate colitis; ICU, intensive care unit; NPS, nasopharyngeal swab; TNF, tumor necrosis factor; TOFA, tofacitinib; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab; -, not applicable; /, not reported.

[a]One CD patient was excluded from the analysis because he was included in the Surveillance Epidemiology of Coronavirus Under Research Exclusion- Inflammatory Bowel Disease trial.

Table 2. Patient Demographics and Main Characteristics of Case Reports

Study	Study design	Study population	COVID-19	Sex	Mean age, *y*	Ongoing therapy	Symptoms	Diagnosis	Treatment	Hospitalization	ICU	Mechanical ventilation	Death	Risk factors
Mazza et al[16]	Case report	1 severe UC	1	F	80	Mesalamine	Fever, diarrhea, anemia, dry cough, pneumonia	NPS, CT scan	Noninvasive ventilation Lopinavir/ritonavir Hydroxychloroquine Steroid	1	0	0	1	/
Jacobs et al[18]	Case report	1 UC	1	F	33	TOFA	Fever, chills, cough, myalgias, sore throat, fatigue, night sweats	NPS	TOFA	0	0	0	0	/
Kunisaki et al[19]	Case report	1 UC	1	M	60	IFX + azathioprine Mesalamine	Cough and fever	NPS, CT scan	-	1	0	0	0	/
Tursi et al[22]	Case report	1 CD	1	M	30	Mesalamine Adalimumab	Fever Chest pain	NPS, CT scan	Noninvasive ventilation	1	0	0	0	/
Rosen et al[27]	Case report	1 severe UC during pregnancy	1	F	26	None	Abdominal pain, diarrhea, hematochezia, urgency	NPS	Steroid Antibiotic Hydroxychloroquine Cyclosporine	1	0	0	0	/
Dolinger et al[29]	Case report	1 pediatric CD	1	M	14	/	Fever, abdominal pain, erythematous maculopapular facial rash	/	Hydroxychloroquine Antibiotic Infliximab	1	0	0	0	/
Wolf et al[38]	Case report	1 CD	CD	M	85	None	Diarrhea, anorexia, fatigue, cough, weight loss	NPS	Bismuth subsalicylate	0	0	0	0	/
Di Ruscio et al[32]	Case report	1 severe UC	UC	F	60	Infliximab	Fever, cough, dyspnea, diarrhea, abdominal pain, fatigue	NPS, chest radiography, CT scan	Hydroxychloroquine, darunavir/cobicistat, supplemental oxygen	1	0	0	0	/
Bezzio and Saibeni[34]	Case report	1 severe UC	UC	M	40	Oral steroid	Diarrhea, abdominal pain, fever, cough	NPS, chest radiography	Azithromycin, hydroxychloroquine	1	0	0	0	/
Bezzio et al[33]	Case report	1 severe UC	UC	M	36	Mesalamine	Diarrhea, fever, dyspnea, cough	NPS, CT scan	Infliximab	1	0	0	0	/
Calabrese et al[35]	Case report	1 UC	UC	F	19	None	Fever, nausea, vomiting, diarrhea, anosmia, ageusia	NPS, CT scan	Hydroxychloroquine	1	0	0	0	/
Giulia and Patrizia[36]	Case report	1 severe pediatric CD	CD	F	17	Adalimumab	Fever, fatigue, dyspnea	NPS	None	1	0	0	0	/

CD, Crohn's disease; COVID-19, coronavirus disease 2019; F, female; IBD, inflammatory bowel disease; ICU, intensive care unit; IFX, infliximab; M, male; NPS, nasopharyngeal swab; TOFA, tofacitinib; UC, ulcerative colitis; -, not applicable; /, not reported.

Table 3. Quality of the Studies Included in the Systematic Review According to the Newcastle–Ottawa Scale

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Score
Mazza et al[16]	★		★	★	★				4
Lukin et al[17]	★	★	★	★	★	★	★	★★	9
Jacobs et al[18]	★		★	★	★	★	★		6
Kunisaki et al[19]	★		★	★	★				4
Rodríguez-Lago et al[20]	★		★	★	★	★			5
Brenner et al[21]	★		★	★	★	★	★		6
Tursi et al[22]	★		★	★	★				4
Taxonera et al[23]	★		★	★	★	★	★		6
Gubatan et al[24]	★		★	★	★	★	★		6
Bezzio et al[25]	★		★	★	★	★	★		6
Khan et al[26]	★		★	★	★				4
Rosen et al[27]	★		★	★	★				4
Allocca et al[28]	★		★	★	★				4
Dolinger et al[29]	★		★	★	★	★	★		6
Turner et al[30]	★		★	★	★				4
Marafini et al[31]	★		★	★	★				4
Wolf et al[38]	★		★	★	★				4
Di Ruscio et al[32]	★		★	★	★				4
Bezzio and Saibeni[34]	★		★	★	★				4
Bezzio et al[33]	★		★	★	★				4
Calabrese et al[35]	★		★	★	★				4
Giulia and Patrizia[36]	★		★	★	★				4
Singh et al[37]	★	★	★	★	★			★	6

NOTE. Items were as follows: 1, representativeness of the exposed cohort; 2, selection of the nonexposed cohort; 3, ascertainment of exposure; 4, demonstration that the outcome of interest was not present at the start of the study; 5, assessment of the outcome; 6, follow-up period was long enough for outcomes to occur; 7, adequacy of follow-up evaluation (>75% follow-up evaluation, or description for those lost); 8, comparability of cohorts on the basis of the design or analysis. Single stars, 1 point; double stars, 2 points.

(biological drug + thiopurine) (59 [7.5%]), other (27 [3.4%]), methotrexate (14 [1.8%]), and tofacitinib (10 [1.3%]). As for COVID-19 symptoms, they were reported in 19 studies (82.6%).[16–20,22–25,27,29,30,32–38] The most frequent symptoms were fever (217 of 449 [48.3%]), cough (209 [46.5%]), and diarrhea (92 [20.5%]), followed by dyspnea (55 [12.2%]), nausea (40 [8.9%]), and abdominal pain (39 [8.7%]) (Table 4).

Diagnosis and Treatment

Eighteen studies (78.3%)[16–20,22,23,25–28,31–36,38] evaluated the diagnostic approach in IBD patients with COVID-19. The polymerase chain reaction (PCR) analysis of the nasopharyngeal swabs was the most commonly adopted method (17 of 18 [94.4%]).[16–20,22,23,25,27,28,31–36,38] A chest computed tomography was performed in 7 studies (38.9%).[16,19,22,25,32–35] In 1 study (5.6%),[26] the diagnosis was achieved by laboratory test. The treatment of infected subjects was described in 14 articles (60.1%).[16,18,20–23,27,29,32–36,38] The most used drugs were hydroxychloroquine (140 of 586 [23.9%]), lopinavir/ritonavir (48 [8.2%]), steroids (19 [3.2%]), antibiotics (18 [3.1%]), and chloroquine (14 [2.4%]) (Table 5). Importantly, in 3 case reports the patients were treated with infliximab[29,33] or tofacitinib.[18]

Prognosis and Risk Factors

The percentage of severe COVID-19 (need for hospitalization, admission to the ICU, or mechanical ventilation) was reported in 21 articles (91.3%).[16–23,25,27–38] Overall, 302 of 987 patients (30.6%) were hospitalized and only a small part of them stayed in the ICU (28 of 246 [11.4%]). In 17 studies[16–19,21–23,25,27,29,30,32–36,38] the need for mechanical ventilation was described, with an average value of 3.7% patients (26 of 697). Moreover, the percentage of IBD patients who died from COVID-19 was investigated in all studies except 2,[26,37] with a total of 29 deaths in 760 cases (3.8%). It is noteworthy that in only 2 studies[17,37] was there a control group consisting of non-IBD patients with COVID-19. Interestingly, death and ICU admission were numerically lower in the IBD group than in the control group (24% vs 35%, respectively; $P = .352$).[17] Finally, 6 studies (26.1%)[17,21,24–26,37] explored the risk factors in infected IBD patients. The Charlson Comorbidity Index[26] (odds ratio [OR], 1.240; 95% CI, 1.106–1.3912; $P = .0002$) and age older than 66 years[24] (OR, 21.30; $P = .022$) were associated with an increased risk of COVID-19, while patients with a UC diagnosis[17] had higher rates of emergency visits or admissions (adjusted OR [aOR], 12.7; $P = .009$). Age older than 65 years (OR, 19.6; 95% CI, 2.95–130.6; $P = .002$), active IBD (OR, 8.45; 95% CI, 1.26–56.56; $P = .02$), and Charlson Comorbidity Index greater than 1 (OR, 16.66;

Table 4. Symptoms of IBD Patients With a Confirmed Diagnosis of COVID-19 in the Overall Population

Symptoms	N (%)
Fever	217/449 (48.3)
Cough	209/449 (46.5)
Diarrhea	92/449 (20.5)
Dyspnea	55/449 (10.5)
Nausea	40/449 (8.9)
Abdominal pain	39/449 (8.7)
Vomiting	39/449 (8.7)
Fatigue	39/449 (8.7)
Myalgia	35/449 (7.8)
Dysgeusia	23/449 (5.1)
Sore throat	21/449 (4.7)
Rhinopharyngitis	17/449 (3.8)
Anosmia	12/449 (2.7)
Hypoxemia	12/449 (2.7)
Anorexia	8/449 (1.8)
Ageusia	6/449 (1.3)
Headache	3/449 (0.7)
Chest pain	2/449 (0.4)
Night sweats	1/449 (0.2)
Dysphonia	1/449 (0.2)
Conjunctivitis	1/449 (0.2)
Hematochezia	1/449 (0.2)
Urgency	1/449 (0.2)
Skin rash	1/449 (0.2)
Weight loss	1/449 (0.2)

COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease.

95% CI, 1.80–153.9; $P = .01$) were associated with COVID-19–related deaths.[25] Similarly, increasing age (aOR, 1.04; 95% CI, 1.01–1.02), 2 or more comorbidities (aOR, 2.9; 95% CI, 1.1–7.8), systemic corticosteroids (aOR, 6.9; 95% CI, 2.3–20.5), and mesalamine/sulfasalazine use (aOR, 3.1; 95% CI, 1.3–7.7) were risk factors for severe COVID-19.[21] Interestingly, Singh et al[37] confirmed that IBD patients treated with steroids in the previous 3 months had a higher risk of severe COVID-19 than untreated (30.98% vs 19.25%; relative risk, 1.60; 95% CI, 1.01–2.57; $P = .04$), while no difference was found with the use of other immune-mediated therapies (relative risk, 1.01; 95% CI, 0.62–1.65; $P = .97$).

Table 5. Treatment of IBD Patients With a Confirmed Diagnosis of COVID-19 in the Overall Population

Treatment	N (%)
Hydroxychloroquine	140/586 (23.9)
Lopinavir/ritonavir	48/586 (8.2)
Steroid	19/586 (3.2)
Antibiotic	18/586 (3.1)
Chloroquine	14/586 (2.4)
Oseltamivir	7/586 (1.2)
Tocilizumab	6/586 (1.0)
Remdesivir	2/586 (0.3)
Noninvasive ventilation	2/586 (0.3)
Infliximab	2/586 (0.3)
Tofacitinib	1/586 (0.2)
Anakinra	1/586 (0.2)
Cyclosporine	1/586 (0.2)
Other	70/586 (11.9)

COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease.

Discussion

This was a systematic review reporting the prevalence, clinical characteristics, diagnostic/therapeutic management, and risk factors of IBD patients with a confirmed diagnosis of COVID-19. Twenty-three studies were included showing a COVID-19 prevalence of 0.4% in our IBD cohort. COVID-19 was found in more men than women (56.5% vs 39.7%), and patients of all ages, from children to the elderly, were involved also, as highlighted in the first reports from China on non-IBD individuals.[2,39] In line with general population data,[2] fever (48.3%) and cough (46.5%) were the most frequent symptoms in infected patients with IBD. Interestingly, approximately a fifth of the patients experienced diarrhea. Our previous pooled analysis[40] and 2 recent systematic reviews and meta-analyses[41,42] showed a cumulative prevalence of diarrhea of approximately 7% to 10% in patients with COVID-19. This high disparity could be related to the influence of the underlying disease on the number of evacuations, justifying the greater percentage of diarrhea in CD and UC patients than in the general population. On the other hand, SARS-CoV-2 has been isolated in the duodenum and rectum,[43] and a higher concentration of fecal calprotectin, a known inflammatory marker, has been found in infected patients with diarrhea compared with those without diarrhea (123.2 vs 17.3 μg/g; $P < .001$),[44] suggesting that viral gut tropism could worsen inflammatory status and symptoms of IBD patients. Unfortunately, it is extremely challenging to assign the symptom to the underlying disease or to the concomitant infection, making it difficult to interpret data. A COVID-19 diagnosis was achieved mainly through nasopharyngeal swabs (94.4%) and chest computed tomography scans (38.9%).

Surprisingly, although approximately 40% of stool samples have been reported as positive for fecal SARS-CoV-2,[42] no test for the presence of viral RNA shedding in the stool was performed in the included studies. To date, no clear evidence is available on the sensitivity of fecal PCR for the diagnosis of COVID-19. However, we hypothesize that fecal PCR may be useful in IBD patients to distinguish disease re-exacerbation from viral superinfection, allowing better patient management and targeted therapy. Hydroxychloroquine (23.9%) and lopinavir/ritonavir (8.2%) were the most frequently administered drugs in our cohort. Hydroxychloroquine is an antimalarial drug that proved to be effective in inhibiting in vitro replication of the new coronavirus.[45] However, data supporting its use in infected patients are still limited. A prospective observational study[46] conducted on 1376 patients with COVID-19 showed no

significant difference in the risk of intubation and death between hydroxychloroquine users and nonusers (hazard ratio, 1.04; 95% CI, 0.82–1.32), raising several doubts on its efficacy.

Similarly, inconclusive data have been reported regarding lopinavir/ritonavir. A randomized controlled trial[47] compared lopinavir/ritonavir with standard care (supplemental oxygen, noninvasive and invasive ventilation, antibiotics, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation) for the treatment of hospitalized COVID-19 patients. Lower 28-day mortality (19.2% vs 25.0%; 95% CI, −17.3 to 5.7) and shorter hospital stay (median, 12 vs 14 d; 95% CI, 0–3) and ICU stay (median, 6 vs 11 d; 95% CI, −9 to 0) were found in patients treated with the antiviral compared with the control group, but no significant difference between the 2 groups was detected regarding the primary end point of time to clinical improvement (median, 16 vs 16 d; hazard ratio, 1.31; 95% CI, 0.95–1.80; $P = .09$). Moreover, it is important to emphasize that in 3 case reports,[18,29,33] clinical remission of IBD patients with COVID-19 was achieved after treatment with infliximab or tofacitinib. These findings certainly are not sufficient to support the use of these drugs, but they provide numerous insights. Accumulating evidence has shown that COVID-19 severity is associated with a cytokine storm syndrome, characterized by an increase in interleukin 2, interleukin 7, granulocyte-colony stimulating factor, interferon-γ–inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α.[48] Based on these findings, it is legitimate to hypothesize that the use of biological drugs that selectively inhibit specific cytokines or small molecules that simultaneously block multiple cellular pathways may play a role in the treatment of these patients. In addition, the mortality rate that we found in IBD patients with COVID-19 (3.8%) was lower compared with the general population ($\sim$10%).[49,50] This could be explained by a lower rate of COVID-19 risk factors (increasing age and comorbidities) in IBD subjects. Importantly, more than half of the patients included in our study were treated with biologics or small molecules at the time of COVID-19 diagnosis, but it is not known if these drugs influenced the prognosis of infected IBD patients. Several ongoing studies are recruiting patients to assess the efficacy and safety of biologics (NCT04344249 and NCT04425538) and small molecules (NCT04373044, NCT04346147, and NCT04362943) for COVID-19 treatment and will allow us to understand if these drugs can be used in this setting.

Our systematic review addressed several practical aspects of managing IBD patients with COVID-19, including moderate- to high-quality studies and reporting data from a relevant number of patients. However, some limitations must be mentioned. First, no randomized clinical trial has been conducted to date in patients with IBD. Second, we excluded all studies reporting data collected in the Surveillance Epidemiology of Coronavirus Under Research Exclusion- Inflammatory Bowel Disease registry, but any overlaps resulting from non-explicit inclusion in the registry cannot be excluded. Nonetheless, the description of clinical symptoms was missing in the Surveillance Epidemiology of Coronavirus Under Research Exclusion- Inflammatory Bowel Disease database, although most of the evaluated articles provided this important information.

In conclusion, symptoms experienced by IBD patients with COVID-19 are similar to those occurring in the general population, except for a higher percentage of diarrhea. Currently, the diagnostic–therapeutic approach does not differ between IBD and non-IBD patients, but further studies are needed to evaluate whether fecal research of viral RNA and treatment with IBD drugs may play a role in the management of COVID-19 patients.

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Conflicts of interest
These authors disclose the following: Silvio Danese has served as a speaker, consultant and advisory board member for Schering-Plough, AbbVie, MSD, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, Johnson & Johnson, Nikkiso Europe GmbH, and Theravance; and Laurent Peyrin-Biroulet has served as a speaker, consultant, and advisory board member for Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, and Theravance. The remaining author discloses no conflicts.