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Severe Activity of Inflammatory Bowel Disease is a Risk Factor for Severe COVID-19

Fabio Salvatore Macaluso, MD,[*] Alessandra Giuliano, MD,[*] Walter Fries,[†] Anna Viola, MD,[†] Alfredo Abbruzzese, MD,[†] Maria Cappello, MD,[‡] Enrica Giuffrida MD,[‡] Lucio Carrozza, MD,[‡] Antonino Carlo Privitera, MD,[§] Antonio Magnano, MD,[¶] Concetta Ferracane, MD,[¶] Giuseppe Scalisi, MD,[‖] Maria Giovanna Minissale, MD,[**] Emiliano Giangreco, MD,[††] Serena Garufi, MD,[‡‡] Carmelo Bertolami, MD,[§§] Ugo Cucinotta, MD,[¶¶] Francesco Graziano, MD,[¶¶, ‖‖] Angelo Casà, MD,[*] Sara Renna, MD, PhD,[*] Giulia Teresi, MD,[*] Giulia Rizzuto, MD,[*] Mariella Mannino, MD,[*] Marcello Maida, MD,[§§] and Ambrogio Orlando, MD,[*] Sicilian Network for Inflammatory Bowel Disease (SN-IBD)

From the *Inflammatory Bowel Disease Unit, "Villa Sofia-Cervello" Hospital, Palermo, Italy
[†]Inflammatory Bowel Disease Unit, Policlinico "G. Martino," Messina, Italy
[‡]Gastroenterology and Hepatology Section, Promise, University of Palermo, Palermo, Italy
[§]Inflammatory Bowel Disease Unit, "Cannizzaro" Hospital, Catania, Italy
[¶]Gastroenterology Unit, Policlinico "Vittorio Emanuele," Catania, Italy
[‖]Gastroenterology Unit, A.R.N.A.S. "Garibaldi," Catania, Italy
**Gastroenterology and Endoscopy Unit, "Buccheri La Ferla Fatebenefratelli" Hospital, Palermo, Italy
[††]Gastroenterology Unit, "Guzzardi" Hospital, Vittoria, Italy
[‡‡]Gastroenterology Unit, "S. Elia- M. Raimondi" Hospital, Caltanissetta, Italy
[§§]Gastroenterology Unit, "Papardo Piemonte" Hospital, Messina, Italy
[¶¶]Pediatric Gastroenterology and Cystic Fibrosis Unit, University of Messina, Messina, Italy
[‖‖]Pediatric Unit, "Villa Sofia-Cervello" Hospital, Palermo, Italy

Address correspondence to: Fabio Salvatore Macaluso, MD, IBD Unit, "Villa Sofia-Cervello" Hospital, Viale Strasburgo 233, 90146 Palermo, Italy (fsmacaluso@gmail.com).

Background: Data from the first wave of the coronavirus disease 2019 (COVID-19) pandemic suggested that patients with inflammatory bowel disease (IBD) are not at higher risk of being infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than the general population and that a worse prognosis is not associated with immunomodulatory drugs, with the possible exception of systemic steroids.

Methods: This retrospective, observational study included consecutive IBD patients from the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) cohort who had a SARS-CoV-2 infection diagnosis (polymerase chain reaction–confirmed presence of the viral genome in a nasopharyngeal swab) during the second COVID-19 pandemic wave (September 2020 to December 2020). Data regarding demographics, IBD features and treatments, and comorbidities were analyzed in correlation with COVID-19 clinical outcomes.

Results: Data on 122 patients (mean age, 43.9 ± 16.7 years; males, 50.0%; Crohn's disease, 62.3%; ulcerative colitis, 37.7%) were reported. Twelve patients developed COVID-19-related pneumonia (9.8%), 4 (3.3%) required respiratory assistance (nonmechanical ventilation or orotracheal intubation), and 4 died (case fatality rate, 3.3%). In a multivariable analysis, age (odds ratio [OR], 1.034; 95% CI, 1.006–1.147; $P = .032$) and severe IBD activity (OR, 13.465; 95% CI, 1.104–164.182; $P = .042$) were independent predictors of COVID-19-related pneumonia, while severe IBD activity (OR, 15.359; 95% CI, 1.320–178.677; $P = .030$) was the only independent predictor of severe COVID-19, a composite endpoint defined as the need for respiratory assistance or death. A trend towards a protective role of tumor necrosis factor α inhibitors on pneumonia development was reported ($P = .076$).

Conclusions: In this cohort of patients with IBD and SARS-CoV-2 infection, severe IBD activity was the only independent risk factor for severe COVID-19.

Lay Summary

This retrospective, observational study on patients with inflammatory bowel disease and severe acute respiratory syndrome coronavirus 2 infection showed that severe inflammatory bowel disease activity was the only independent risk factor for severe coronavirus disease 2019.

Key Words: biologics, immunosuppression, SARS-CoV-2, SN-IBD

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic[1,2] and its related disease, coronavirus disease 2019 (COVID-19), represent the global health crisis of our time. The pathogenesis of COVID-19 is based on the subtle balance between positive and negative effects of the host's immune response against the virus. On the one hand, the immune system is fundamental to reducing viral replication; on the other hand, the overproduction of proinflammatory cytokines (the so-called "cytokine storm") can favor the development of the most severe forms of COVID-19.[3] This scenario is even more complex in patients with chronic immune-mediated diseases, including inflammatory bowel diseases (IBD), due to the interplay between chronic inflammation, the immune response against the virus, and the effects of immunomodulatory drugs used in these patients.[4] Even though evidence on the interaction between COVID-19 and IBD is rapidly expanding, there is still an unmet need to fully understand this topic. Most of the scientific literature refers to the first COVID-19 wave (February 2020 to June 2020), but data from the second wave (September 2020 to December 2020) are constantly emerging.[5–20] Current evidence indicates that there is no difference between IBD patients and the general population in the incidences and main clinical outcomes of COVID-19 (ie, rate of hospitalization, need for respiratory assistance, death). Risk factor analyses have repeatedly found significant associations of age and comorbidities with adverse COVID-19 outcomes, while data on other variables, including IBD activity and use of aminosalicylates, thiopurines, and corticosteroids, are partially conflicting. Data regarding patients with SARS-CoV-2 during 2020 are still a precious source of information to improve our understanding of this complex scenario.

The aim of our study was to assess clinical features of SARS-CoV-2 infection in patients with IBD, including COVID-19-related symptoms, interventions, and outcomes, and to investigate potential risk factors for adverse COVID-19 outcomes.

Methods

Patients and Outcomes

This is a retrospective, observational cohort study analyzing clinical data regarding the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD). The SN-IBD is composed of 16 centers licensed to prescribe biologics in Sicily (Italy), managing about 15,000 IBD patients treated with both conventional and advanced therapies. Physicians of the SN-IBD were invited to collect data on IBD patients who were diagnosed with SARS-CoV-2 infection between September 1, 2020, and December 31, 2020. Patients were included if they had an established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) for at least 6 months and had a positive polymerase chain reaction (PCR) test confirming the presence of the SARS-CoV-2 genome in a nasopharyngeal swab.

The following data were collected for each patient and inserted into a structured database: age, gender, type of disease (CD or UC), smoking habit, presence of comorbidities, Charlson comorbidity index score, pregnancy status, disease duration, disease location and behavior according to the Montreal classification, disease activity, and concomitant medications for IBD. Disease activity was evaluated clinically with the Harvey-Bradshaw Index for CD (remission,< 5; mild activity, 5–7; moderate activity, 8–16; severe activity > 16) and with the partial Mayo score for UC (remission, < 2; mild activity, 2–4; moderate activity, 5–7; severe activity, > 7). Signs and symptoms of SARS-CoV-2 infection, COVID-19 interventions (including the need for hospitalization, noninvasive ventilation, orotracheal intubation, and medical therapy), and outcomes were collected. Three COVID-19 outcomes were analyzed: (1) development of pneumonia as documented by computed tomography; (2) exitus; and (3) severe COVID-19, a composite endpoint consistent with the existing COVID-19 literature,[21] defined as the need for ventilatory assistance or death.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. As this is a retrospective, observational study, no ethical approval was needed, in agreement with local legislation.

Statistics

Continuous variables were reported as means ± SDs, whereas categorical variables were summarized as frequencies and percentages. Independent-samples *t*-tests and χ^2 tests were used for comparisons of continuous and categorical variables, respectively.

Logistic regression models were performed to assess the presence of variables independently associated with pneumonia and severe COVID-19. As candidate factors, we selected the following variables: age, gender, type of disease (CD or UC), smoking habit, presence of comorbidities, Charlson comorbidity index score, disease duration, disease location and behavior, disease activity, concomitant medications for IBD, and signs and symptoms of SARS-CoV-2 infection. A P value ≤ .05 was considered statistically significant.

All statistical analyses were performed using SPSS v. 25.0 for Macintosh (SPSS Inc., Chicago, IL).

Results

Patients

Baseline characteristics of patients are shown in Table 1. There were 122 patients included (CD, 62.3%; UC, 37.7%). The estimated cumulative frequency was 0.0081% (122 of 15,000 IBD patients). The mean age was 43.9 ± 16.7 years, with equal proportions of males and females. Four patients were diagnosed with SARS-CoV-2 infection during pregnancy. At least 1 comorbidity was reported in approximately 1 out of 3 patients (30.7%; mean Charlson comorbidity index score, 0.47). Notably, 7 patients had hypertension (5.7%), 4 had coronary artery disease (3.3%), 2 (1.6%) had chronic obstructive pulmonary disease, 3 (3.3%) had type 2 diabetes, and 2 (1.6%) had obesity. Inflammatory bowel disease activity at the time of SARS-CoV-2 infection diagnosis was as follows: 71 (58.2%) patients were in clinical remission, 25 (20.5%) had mild activity, 22 (18.0%) had moderate activity, and 4 (3.3%) had severe disease. Approximately half of patients (54.1%) were on treatment with 5-aminosalicilates, while systemic corticosteroids were used in 26 (21.7%) patients and 2 out of 3 patients were treated with biologics, including anti–tumor necrosis factors (anti-TNFs; 40.5%), vedolizumab (18.0%), and ustekinumab (8.2%).

Table 1. Baseline characteristics of patients.[a]

Variable	All patients (*n* = 122)	Crohn disease (*n* = 76)	Ulcerative colitis (*n* = 46)
Gender, *n* (%)			
Male	61 (50.0)	39 (51.3)	22 (47.8)
Female	61 (50.0)	37 (48.7)	24 (52.2)
Age, years, mean ± SD	43.9 ± 16.7	42.9 ± 16.6	45.5 ± 16.9
Active smokers, *n* (%)	19 (15.6)	16 (21.1)	3 (6.5)
Comorbidities, *n* (%)	37 (30.3)	24 (31.6)	13 (28.3)
Charlson comorbidity index	0.47 ± 1.1	0.49 ± 1.2	0.42 ± 1.1
Pregnancy, *n* (%)	4 (3.3)	3 (3.9)	1 (2.2)
Disease duration, years, mean ± SD	12.4 ± 9.4	11.8 ± 9.1	13.2 ± 9.8
Disease localization, *n* (%)			
L1 (ileal)		31 (40.8)	
L2 (colonic)		7 (9.2)	
L3 (ileocolonic)		38 (50.0)	
E1 (proctitis)			8 (17.4)
E2 (left-sided)			20 (43.5)
E3 (extensive)			18 (39.1)
Disease activity, *n* (%)			
Remission	71 (58.2)	48 (65.8)	23 (50.0)
Mild	25 (20.5)	14 (18.4)	11 (23.9)
Moderate	22 (18.0)	12 (15.8)	10 (21.7)
Severe	4 (3.3)	2 (2.6)	2 (4.3)
Concomitant medications for IBD, n (%)			
5-aminosalicilates	66 (54.1)	24 (31.6)	42 (91.3)
Corticosteroids	26 (21.7)	13 (17.3)	13 (28.9)
Thiopurines	8 (6.7)	5 (6.8)	3 (6.5)
Anti-TNFs	49 (40.5)	30 (40.0)	19 (41.3)
Vedolizumab	22 (18.0)	8 (10.5)	14 (30.4)
Ustekinumab	10 (8.2)	10 (13.2)	0 (0)

[a]Abbreviations: IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

COVID-19-Related Symptoms, Interventions, and Outcomes

The most frequently recorded symptoms were fever (58.2%), cough (41.0%), and anosmia/ageusia (40.2%). Diarrhea was reported by 18.0% of patients. The same proportion of patients (18.0%) were asymptomatic (Table 2). Twelve patients developed COVID-19-related pneumonia (9.8%), 4 (3.3%) required respiratory assistance (nonmechanical ventilation or orotracheal intubation), and 4 died (case fatality rate, 3.3%). None of the 4 pregnant patients had pneumonia. All patients who developed pneumonia were hospitalized. The majority of patients did not receive specific therapy for COVID-19 (except for symptomatic therapy): 23 (28.1%) received systemic steroids and antibiotics, 2 (2.5%) received steroids, 2 (2.5%) received antibiotics only, and 1 patient (1.2%) was treated with Remdesivir. Considering that 3 out of the 4 patients who required respiratory assistance died, and that 1 patient died due to a sudden cardiac death while being hospitalized for COVID-19-related pneumonia (no respiratory assistance was reported), 5 subjects fulfilled the criteria for severe COVID-19.

Table 2. COVID-19-related symptoms, interventions, and outcomes.[a]

	All patients (*n* = 122)	Crohn disease (*n* = 76)	Ulcerative colitis (*n* = 46)
COVID-19-related symptoms, *n* (%)			
Pharyngodynia	29 (23.8)	19 (25.0)	10 (21.7)
Cough	50 (41.0)	27 (35.5)	23 (50.0)
Fever	71 (58.2)	43 (56.6)	28 (60.9)
Dyspnea	17 (13.9)	12 (15.8)	5 (10.9)
Ageusia/anosmia	49 (40.2)	34 (44.7)	15 (32.6)
Rhinitis	19 (15.6)	9 (11.8)	10 (21.7)
Arthromyalgia	33 (27.0)	20 (26.3)	13 (28.3)
Diarrhea	22 (18.0)	12 (15.8)	10 (21.7)
Conjunctivitis	8 (6.6)	6 (7.9)	2 (4.3)
No symptoms	22 (18.0)	13 (17.1)	9 (19.6)
COVID-19-related interventions, *n* (%)			
Hospitalization	12 (9.8)	7 (9.2)	5 (10.9)
Noninvasive ventilation	1 (0.8)	1 (1.3)	0 (0)
Intubation	3 (2.5)	2 (2.6)	1 (2.2)
Medical therapy	1 (1.2)	1 (1.3)	0 (0)
Antivirals (Remdesivir)	2 (2.5)	2 (2.6)	0 (0)
Antibiotics only	2 (2.5)	2 (2.6)	0 (0)
Steroids	23 (28.1)	14 (18.4)	9 (100.0)
Steroids plus antibiotic			
COVID-19-related outcomes, *n* (%)			
Pneumonia	12 (9.8)	7 (9.2)	5 (10.9)
Severe COVID-19	5 (4.1)	3 (3.9)	2 (4.3)
Exitus	4 (3.3)	2 (2.6)	2 (4.3)

[a]Abbreviation: COVID-19, coronavirus disease 2019.

We analyzed the association between factors at baseline, COVID-19-related pneumonia, and severe COVID-19. As there was a marked overlap between patients who died and those with severe COVID-19, we did not analyze the outcome of exitus. In the univariable analysis, COVID-19-related pneumonia was associated with age ($P < .001$), the mean Charlson comorbidity index score ($P < .001$), and severe IBD activity ($P < .001$). A trend towards a protective role of anti-TNFs on pneumonia development was reported ($P = .076$). In the multivariable analysis, age (odds ratio [OR], 1.034 per unit increase; 95% CI, 1.006–1.147; $P = .032$) and severe IBD activity (OR, 13.465; 95% CI, 1.104–164.182; $P = .042$) were confirmed as independent predictors of COVID-19-related pneumonia (Table 3). In the univariable analysis, severe COVID-19 was associated with age ($P = .03$), the mean Charlson comorbidity index score ($P < .001$), and severe IBD activity ($P < .001$). In the multivariable analysis, only severe IBD activity (OR, 15.359; 95% CI, 1.320–178.677; $P = .03$) was confirmed as an independent predictor of severe COVID-19 (Table 4).

Discussion

The intense interest on the interplay between COVID-19 and chronic inflammatory diseases, including IBD, is generating a considerable amount of partially conflicting data. Further

Table 3. Univariable and multivariable analyses of variables associated with COVID-19-related pneumonia.[a]

Variable	Univariable analysis			Multivariable analysis	
	No pneumonia (n = 110)	Pneumonia (n = 12)	P value	Odds Ratios (95% CI)	P value
Age, years	41.6 ± 15.1	64.7 ± 16.9	.001	1.074 (1.006–1.147)	.032
Charlson comorbidity index	0.29 ± 0.8	2.1 ± 2.2	<.001	1.300 (0.781–2.163)	.313
Severe IBD activity	1 (0.9)	3 (25.0)	<.001	13.465 (1.104–164.1)	.042
Anti-TNFs	47 (43.1)	2 (16.7)	.076	0.663 (0.093–4.735)	.682

[a]Abbreviations: COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

Table 4. Univariable and multivariable analyses of variables associated with severe COVID-19.[a]

Variable	Univariate analysis			Multivariate analysis	
	No severe Covid (N = 117)	Severe Covid (N = 5)	P value	Odds Ratios (CI-95%)	P value
Age, years	42.9 ± 16.1	66.4 ± 16.3	.030	1.073 (0.969–1.188)	.176
Charlson comorbidity index	0.4 ± 1.0	2.4 ± 2.3	<.001	1.219 (0.592–2.507)	.591
Severe IBD activity	2 (1.7)	2 (40.0)	<.001	15.359 (1.320–178.7)	.029

[a]Abbreviations: COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease

evidence is needed. Our retrospective, multicenter cohort study generated 3 main findings: (1) age and severe IBD activity were independent predictors for COVID-19-related pneumonia; (2) severe IBD activity was the only risk factor for severe COVID-19; and (3) IBD treatments were not associated with adverse outcomes, while a trend towards a protective role of anti-TNFs on pneumonia development was reported.

In line with all other cohort studies, our findings confirm that the great majority of IBD patients have a mild course of SARS-CoV-2 infection, and about 20% are asymptomatic. The low number of adverse outcomes is probably influenced by the young age (mean age, 43.9 years) and overall healthy status of the cohort (1 out of 3 patients with comorbidities). The outcome of SARS-CoV-2 infection in IBD patients is likely to be even more favorable than reported herein, as it is likely that there was a certain proportion of asymptomatic or paucisymptomatic infected patients who were undiagnosed, with an underestimation of the calculated cumulative frequency and an overestimation of the case-fatality rate (3.3%). One must keep in mind that this issue is present in all cohort studies, including those unrelated to IBD.

Another interesting finding emerging from our analysis is the relatively low frequency of diarrhea (22%) during COVID-19. Diarrhea is a frequent complaint of patients with COVID-19,[22] and this has been attributed to the ability of SARS-CoV-2 to enter gastrointestinal epithelial cells.[23] One would expect a higher frequency of diarrhea in IBD patients, especially as some patients might have complained of gastrointestinal symptoms due to the activity of the underlying IBD, and not due to the viral infection. These findings, in our opinion, support the notion that the gut is not a relevant target organ in the pathogenesis and severity of SARS-CoV-2 infection.

The identification of risk factors associated with adverse outcomes related to COVID-19 is crucial for promptly recognizing those high-risk patients with IBD who could benefit from preventive measures to reduce this risk—that is, therapy with monoclonal antibodies—in case of a SARS-CoV-2 infection. Severe IBD activity emerged as the most prominent risk factor, corresponding with findings obtained in other cohorts.[8,19] Severe disease activity should be considered in IBD patients as an adjunctive and relevant comorbidity able to adversely affect the course of COVID-19. This issue emphasizes the importance of achieving good control of IBD with the currently available medical options, particularly during the peaks of pandemic waves. Regarding the interaction between immunomodulatory treatments for IBD and severity of COVID-19, some series observed an association between systemic corticosteroid use and adverse COVID-19 outcomes,[7,9,13] while other cohorts found a correlation between negative outcomes and the use of aminosalicylates[9,20] or thiopurines, alone or in combination with anti-TNFs.[20] Treatment with anti-TNFs was not associated with an adverse course of COVID-19, and a protective effect was even hypothesized.[9] A similar protective effect could be deduced from our cohort: although we did not possess the statistical power to clearly demonstrate this point, the trend towards a protective role of anti-TNFs on pneumonia development is of great interest. Given that TNF-α is involved in the "cytokine storm" syndrome of COVID-19 across key points of the cytokine cascade,[24] anti-TNFs could be beneficial in this context, at least on a speculative level.[25]

This study has strengths and limitations. The main strengths lie in a clear diagnosis of SARS-CoV-2 infection, confirmed by PCR in all patients, and in the definition of COVID-19-related pneumonia, demonstrated with computed tomography. Limitations are related to the retrospective design of the study, small sample size, and low number of observed adverse COVID-19 outcomes, as also expressed by the wide CIs found for the independent predictors. This last point, in particular, does not make it easy to draw firm conclusions.

Conclusions

While considering the above limitations, our real-world, multicenter study showed that severe IBD activity was an independent predictor for COVID-19-related pneumonia and severe COVID-19, while IBD treatments were not associated with adverse outcomes. These findings should be kept in mind for risk stratification of IBD patients with COVID-19 and management of IBD patients with SARS-CoV-2 infection. Available data suggest that physicians should feel confident in continuing immunomodulatory treatments that maintain IBD remission during the COVID-19 pandemic.

Funding

None declared.

Conflicts of Interest

F.S.M. served as an advisory board member and/or received lecture grants from AbbVie, Biogen, Galapagos, Janssen, MSD, Pfizer, Samsung Bioepis, and Takeda Pharmaceuticals. W.F. served as an advisory board member and/or received lecture grants from AbbVie, Biogen, MSD, Pfizer, Mundipharma, Zambon, Janssen, Sandoz, and Takeda Pharmaceuticals. M.C. served as an advisory board member for AbbVie, MSD, and Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Chiesi, and Takeda Pharmaceuticals. S.R. served as an advisory board member for AbbVie and MSD Pharmaceuticals, and received lecture grants from AbbVie, Janssen, MSD, and Takeda Pharmaceuticals. A.O. served as an advisory board member for AbbVie, Galapagos, MSD, Janssen, Pfizer, Samsung Bioepis, and Takeda Pharmaceuticals, and received lecture grants from AbbVie, Galapagos, MSD, Sofar, Chiesi, Janssen, Pfizer, and Takeda Pharmaceuticals.

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