



Original Article

Inflammatory Bowel Disease Clinical Activity is Associated with COVID-19 Severity Especially in Younger Patients

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Abstract

Background and Aims: Age is a major prognostic factor for COVID-19 outcomes. The effect of inflammatory bowel disease [IBD] activity on COVID-19 is unclear. We examined the relationship between IBD activity and COVID-19 severity according to age.

Methods: We included IBD patients diagnosed with COVID-19, reported to SECURE-IBD between March 13, 2020 and August 3, 2021. Clinical IBD activity was measured by physician global assessment [PGA]. COVID-19-related outcomes were [1] intensive care unit [ICU] admission, ventilation or death, and [2] hospitalization. Using generalized estimating equations, we determined adjusted odds ratios [aOR, 95% confidence interval] for moderate and severe PGA vs clinical remission/mild PGA, controlling for demographics, medications and COVID-19 diagnosis period. We performed stratified analyses by age [≤ 50 vs > 50 years].

Results: Among 6078 patients, adverse COVID-19 outcomes were more common with active IBD: ICU/ventilation/death in 3.6% [175/4898] of remission/mild, 4.9% [45/920] of moderate and 8.8% [23/260] of severe [$p < 0.001$]; and hospitalization in 13% [649/4898] of remission/mild, 19% [178/920] of moderate and 38% [100/260] of severe [$p < 0.001$]. Stratified by decade, effect sizes were larger for younger patients. In patients ≤ 50 years, severe PGA was independently associated with ICU/ventilation/death (aOR 3.27 [1.15–9.30]) and hospitalization (aOR 4.62 [2.83–7.55]). In

contrast, severe PGA was not independently associated with COVID-19 outcomes in those older than 50 years.

Conclusions: Clinically active IBD may be a risk factor for severe COVID-19, particularly in younger patients. IBD disease control, including through medication compliance, and strategies to mitigate the risk of COVID-19 infection amongst patients with active IBD [e.g. distancing, immunization] are key to limit adverse COVID-19 outcomes.

Key Words: COVID-19; disease activity; inflammatory bowel disease

1. Introduction

The coronavirus disease of 2019 [COVID-19] pandemic, caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], represents a global health crisis. Increasing age¹ and comorbid disease² are well-recognized risk factors for severe infection and poor outcomes. Inflammatory bowel disease [IBD], including Crohn's disease [CD] and ulcerative colitis [UC], is a chronic inflammatory disorder of the gastrointestinal [GI] tract that affects millions of individuals worldwide.³⁻⁵ IBD often requires treatment with immune-modifying medications, such as corticosteroids, thiopurines and biologics.

Outcomes for COVID-19 are worse for the elderly in both the general population and those with IBD. However, IBD patients infected with SARS-CoV-2, particularly those on corticosteroids, may have worse outcomes regardless of their age. Risk factors for poor outcomes may also vary across the age spectrum. The Surveillance Epidemiology Under Research Exclusion for IBD [SECURE-IBD] registry is a large, international registry of IBD patients with COVID-19 derived from active surveillance and reporting by treating physicians. In previous analyses of SECURE-IBD, corticosteroids were associated with an increased risk of severe COVID-19, defined as intensive care unit [ICU] admission, invasive ventilation or death.^{6,7} In addition, compared to anti-tumour necrosis factor- α [anti-TNF] monotherapy, thiopurine monotherapy, thiopurine plus anti-TNF, and 5-aminosalicylates [5ASA]/sulfasalazine were independently associated with worse outcomes.⁶

In addition to medication-related effects, IBD patients may have worse COVID-19 outcomes as a result of gastrointestinal inflammation, potentially related to the mucosal expression of angiotensin-converting enzyme 2 [ACE2] in the gastrointestinal tract.⁸ This hypothesis invokes the potential role of gut inflammation and IBD activity as a mediator of COVID-19 severity. In an earlier SECURE-IBD analysis including 525 patients, clinically active disease was significantly associated with an increased risk of the composite outcome of hospitalization or death, and there was a trend toward an increased risk of ICU admission, ventilation or death.⁷ A more recent study from the UK, however, found no increased risk of poor COVID-19 outcomes in patients with acute severe UC.⁹

As the relationship between IBD activity and COVID-19 severity remains unclear, we evaluated the impact of IBD clinical disease activity on COVID-19 outcomes, while accounting for the confounding effects of medications and other factors. We specifically explored the modifying effect of age on the association between IBD activity and COVID-19 severity.

2. Materials and Methods

2.1. Study design, setting and participants

This is a retrospective cohort study utilizing data from an active surveillance registry [SECURE-IBD]. Individuals of any age with any

type of IBD who developed COVID-19 and were reported to the SECURE-IBD registry between March 13, 2020 and August 3, 2021 were eligible for inclusion. Patients missing IBD activity (Physician Global Assessment [PGA]) or age were excluded.

2.2. Data source

The SECURE-IBD database [www.covidibd.org] was developed to monitor COVID-19 outcomes in paediatric and adult IBD patients. SECURE-IBD is an international collaboration supported by several regional and national organizations, as previously described.⁷ Healthcare providers voluntarily reported polymerase chain reaction [PCR]- or antibody-confirmed COVID-19 cases in IBD patients. Healthcare providers were instructed to report cases regardless of severity, after a minimum disease duration of 7 days and after sufficient time had elapsed to determine the final illness outcome [resolution or death]. Research Electronic Data Capture [REDCap],¹⁰ a secure, web-based electronic data capture tool hosted at the University of North Carolina at Chapel Hill, was used for data collection and management. Quality control measures were performed as previously described.⁶

2.2.1. Variables

The list of variables included in SECURE-IBD has been outlined elsewhere.⁶ We examined two adverse COVID-19 outcomes: 'severe' COVID-19 [primary outcome], a composite of ICU admission, mechanical ventilation or death, as previously defined,⁶ and COVID-19-related hospitalization. The exposure of interest was clinical IBD activity, measured by PGA. PGA was analysed as a three-level variable, combining clinical remission and mild PGA into a single reference category, against which moderate PGA and severe PGA were compared. We examined the following covariates: age, sex, comorbidities [defined as none, one or two or more], IBD type [defined as UC/IBD-unclassified or CD], systemic corticosteroids [defined as intravenous or oral corticosteroids, excluding local release formulations such as ileal-release budesonide], anti-TNF monotherapy [defined as anti-TNF without a thiopurine or methotrexate], anti-TNF combination therapy (defined as anti-TNF plus an immunomodulator [thiopurine or methotrexate]), immunomodulator monotherapy [defined as a thiopurine or methotrexate without anti-TNF], 5ASA/mesalamine, race/ethnicity [defined as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian and other/mixed], body mass index [BMI], country gross domestic product [GDP] and other medications [anti-integrins, ustekinumab]. Recognizing that, over time, changes have occurred in COVID-19 management and variants [both with implications on outcomes], we also adjusted for period of COVID-19 diagnosis. For analyses, we dichotomized COVID-19 diagnosis period, using Joinpoint regression [<https://surveillance.cancer.gov/joinpoint/>, v.4.8.0.1] to identify the inflection month at which outcome rates changed significantly. This month was found to

be November 2020 [Supplementary Figure 1]. We therefore defined two COVID-19 diagnosis periods, March 2020 to October 2020, and November 2020 to July 2021 [including those diagnosed August 1–3, 2021]. Variables with >10% missing data were excluded from primary analyses, but we explored their effects in sensitivity analyses.

2.3. Statistical analysis

Continuous variables were summarized using medians (interquartile range [IQR]) and categorical variables using frequencies [%]. We compared patient and disease characteristics across PGA categories using the Kruskal–Wallis and Chi-squared tests for continuous and categorical variables, respectively.

Given the clustering of participants by country, we used generalized estimating equations [GEEs] to examine the association between PGA and outcomes, in univariate and multivariable fashion. For multivariable models, we included the following covariates a priori based on clinical relevance and demonstration of significance in previous studies: age, sex, comorbidities, IBD type, corticosteroids, anti-TNF monotherapy, anti-TNF combination therapy, immunomodulator monotherapy, 5ASA/sulfasalazine and period of COVID-19 diagnosis. We included additional confounders in multivariable GEE models only if they changed the univariate estimate for PGA by $\geq 10\%$ [‘change in estimate approach’].¹¹ This change in estimation approach was repeated for each model; as a result, not all of the adjusted models presented in the results include the same combinations of covariates.

To explore for potential effect modification by age, we determined [using GEEs] the unadjusted odds ratios [ORs] of ICU admission/ventilation/death and hospitalization for severe PGA [vs remission/mild PGA] by decade and plotted them using forest plots. We also repeated the above GEE analyses stratified by age. As for COVID-19 diagnosis period, we used Joinpoint regression to guide the choice of age cut-off [found to be 50 years].

Results are reported as unadjusted ORs and adjusted ORs [aOR] with 95% confidence intervals [95% CI]. Two-sided p -values < 0.05 were considered statistically significant. We performed all analyses using SAS University Edition v.3.8 [SAS Institute].

2.4. Ethical considerations

Each SECURE-IBD survey item met criteria for deidentified data, in accordance with the Health Insurance Portability and Accountability Act [HIPAA] Safe Harbor De-Identification standards. The UNC-Chapel Hill Office for Human Research Ethics has determined that the storage and analysis of de-identified data for this project does not constitute human subjects research as defined under US federal regulations [45 CFR 46.102 and 21 CFR 56.102] and does not require institutional review board approval.

2.5. Role of the funding source

The funding source had no role in the study design, collection, analysis or interpretation of the data, writing of the report, or the decision to submit the paper for publication.

3. Results

3.1. Patient characteristics

A total of 6078 cases from over 60 countries were included after excluding 342 [5.3%] cases with missing PGA and/or age data. Thirty-four per cent of included cases were from the USA, 8.1% Russia, 7.8% Spain, 5.5% Netherlands, 3.6% Germany, 3.6% UK, 3.0% Italy, 2.9% Belgium, 2.4% Canada, 2.2% Brazil, 2.1% Austria

and 2.1% France, with the remainder of countries each accounting for <2% of the cohort. Patient and disease characteristics are summarized in Table 1 for the overall cohort, and by PGA category. Comorbidity details are provided in Supplementary Table 1. Forty-nine per cent of patients were male and the median age at diagnosis of SARS-CoV-2 was 38 [IQR 26–52] years. The distribution of IBD activity by PGA was as follows: 80.6% clinical remission or mild activity, 15.1% moderate and 4.3% severe. BMI was the only variable with >10% missing data and was therefore excluded from primary analyses [examined in sensitivity analyses].

3.2. Outcomes

Fifteen per cent of patients [$N = 927$] required hospitalization and 4.0% [$N = 243$] experienced the composite outcome of ICU, ventilation or death. Supplementary Figure 1 depicts the results of Joinpoint regression applied to the proportion of patients experiencing adverse outcomes by month of COVID-19 diagnosis. An initial downward trend is appreciable for both outcomes, with a change in slope from November 2020 onwards. There was no interaction between COVID-19 diagnosis period and PGA for either outcome.

Figure 1 contrasts outcomes by IBD activity category. ICU/ventilation/death was significantly more frequent in patients with more active IBD [4.9% of moderate PGA and 8.8% of severe PGA, compared to 3.6% of remission/mild PGA, $p < 0.001$]. The same was true for hospitalization [19% of moderate PGA and 38% of severe PGA, compared to 13% of remission/mild PGA, $p < 0.001$].

3.3. Association between disease activity and outcomes

Table 2 summarizes the unadjusted associations between PGA and COVID-19 outcomes and unadjusted associations for covariates. Compared to remission/mild activity, patients with moderate PGA [OR 1.46, 95% CI 1.17–1.84] and severe PGA [OR 2.56, 95% CI 1.76–3.70] were significantly more likely to experience the composite outcome of ICU/ventilation/death. Similarly, patients with moderate PGA [OR 1.59, 95% CI 1.37–1.84] and severe PGA [OR 3.74, 95% CI 2.86–4.90] were significantly more likely to be hospitalized for COVID-19. In stratified analyses by IBD type, the effect sizes for moderate and severe PGA were larger for both outcomes in CD compared to UC/IBD-U [Supplementary Table 2]. Age over 50 years was an important risk factor for both ICU/ventilation/death [OR 8.72, 95% CI 5.96–12.77] and hospitalization [OR 3.23, 95% CI 2.82–3.70].

Table 3 summarizes the results of multivariable GEE analyses. IBD activity remained independently associated with hospitalization [moderate PGA: aOR 1.48, 95% CI 1.23–1.79; severe PGA: aOR 3.24, 95% CI 2.34–4.50]. However, the association between IBD activity and ICU/ventilation/death was lost after adjusting for the covariates shown. Covariates associated with increased risk of both adverse outcomes included diagnosis earlier in the pandemic [March to October 2020], older age, comorbidities and systemic corticosteroids, while anti-TNF monotherapy was protective. Male sex was associated with an increased risk of hospitalization.

A sensitivity analysis including BMI for the outcome of ICU/ventilation/death yielded almost identical PGA effect estimates [moderate PGA: aOR 1.20, 95% CI 0.84–1.73; severe PGA: aOR 1.46, 95% CI 0.73–2.92].

3.4. Effect modification by age

Supplementary Figure 2 plots unadjusted ORs for severe PGA [vs remission/mild activity] according to age by decade for ICU/

Table 1. Demographic and disease characteristics, overall and by clinical IBD activity [PGA] category

Variable	Overall [N = 6078]	PGA remission/ mild [N = 4898]	PGA moderate [N = 920]	PGA severe [N = 260]	p-value
N [%] or median [IQR]					
COVID-19 period					
Mar 20 to Oct 20	2729 [45%]	2150 [44%]	431 [47%]	148 [57%]	<0.001
Nov 21 to Jul 21	3349 [55%]	2748 [56%]	489 [53%]	112 [43%]	
Country GDP [trillion USD]	1.84 [0.91–21.4]	1.84 [0.91–21.4]	1.74 [0.91–21.4]	1.70 [0.76–21.4]	0.25
Male	2916/5990 [49%]	2334/4830 [48%]	445/908 [49%]	137/252 [54%]	0.17
Age [years]	38 [26–52]	38 [26–52]	38 [27–52]	37 [26–48]	
≤50 years	4419 [73%]	3552 [73%]	664 [72%]	203 [78%]	0.68
>50 years	1659 [27%]	1346 [27%]	256 [28%]	57 [22%]	0.14
Ethnicity					
Hispanic	772/5733 [13%]	612/4629 [13%]	129/866 [15%]	21/238 [13%]	0.19
White	4315/5733 [75%]	3495/4629 [76%]	648/866 [75%]	172/238 [72%]	
Black	260/5733 [5%]	205/4629 [4%]	38/866 [4%]	17/238 [7%]	
Asian	216/5563 [4%]	180/4629 [4%]	23/866 [3%]	13/238 [5%]	
Other/mixed	170/5733 [3%]	137/4629 [3%]	28/866 [3%]	5/238 [2%]	
IBD type					
CD	3472/6052 [57%]	2854/4876 [59%]	499/916 [54%]	119 [45%]	<0.001
UC/IBD-U	2580/6052 [43%]	2022/4876 [41%]	417/916 [46%]	141 [54%]	
BMI ≥30 ¹	896/5175 [17%]	732/4148 [18%]	134/800 [17%]	30/227 [13%]	0.21
BMI ¹	24.3 [21.6–28.0]	24.5 [21.8–28.0]	24.1 [21.2–27.8]	22.5 [19.6–26.1]	<0.001
Comorbidities					
None	4178 [69%]	3384 [69%]	613 [67%]	181 [70%]	0.29
1	1314 [22%]	1051 [21%]	215 [23%]	48 [18%]	
≥2	586 [10%]	463 [9%]	92 [10%]	31 [12%]	
Systemic corticosteroids	400 [7%]	118 [2%]	169 [18%]	113 [43%]	<0.001
Anti-TNF mono [no IMM]	1954 [32%]	1666 [34%]	236 [26%]	52 [20%]	<0.001
Anti-TNF combo [with IMM]	602 [10%]	488 [10%]	88 [10%]	26 [10%]	0.93
With thiopurine	468 [8%]	372 [8%]	73 [8%]	23 [9%]	0.73
With MTX	135 [2%]	117 [2%]	15 [2%]	3 [1%]	0.18
IMM mono [no anti-TNF]	702 [12%]	571 [12%]	104 [11%]	27 [10%]	0.80
Thiopurine [without TNF]	611 [10%]	499 [10%]	89 [10%]	23 [9%]	0.72
MTX [without TNF]	92 [2%]	73 [1%]	15 [2%]	4 [2%]	0.95
Anti-integrin	665 [11%]	516 [11%]	118 [13%]	31 [12%]	0.11
Ustekinumab	556 [9%]	405 [8%]	122 [13%]	29 [11%]	<0.001
Tofacitinib	101 [2%]	69 [1%]	27 [3%]	5 [2%]	0.004
Mesalamine/sulfasalazine	1847 [30%]	1431 [29%]	320 [35%]	96 [37%]	<0.001

BMI, body mass index; CD, Crohn's disease; GDP, gross domestic product; IBD-U, IBD-unclassified; IMM, immunomodulator; MTX, methotrexate; OR, odds ratio; PGA, physician global assessment; TNF, tumour necrosis factor; UC, ulcerative colitis; USD, US dollars.

¹If denominator not shown, no missing data.

¹15% missing data.

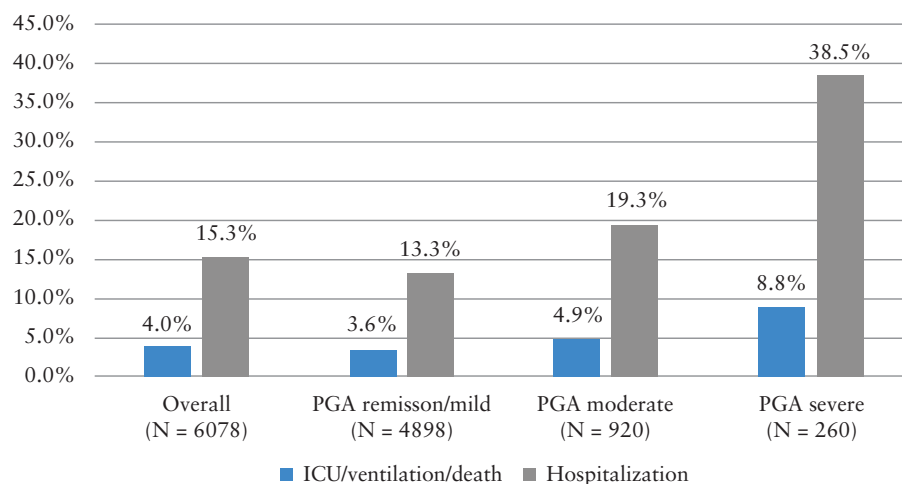


Figure 1. Proportion of patients experiencing adverse COVID-19 outcomes by PGA category [$p < 0.001$ for both outcomes].

Table 2. Unadjusted associations of demographic and disease characteristics with COVID-19 outcomes [using univariate GEE models]

Variable	ICU/ventilation/death	<i>p</i> -value	Hospitalization	<i>p</i> -value
	OR [95% CI]		OR [95% CI]	
PGA				
Remission/mild	Reference		Reference	
Moderate	1.46 [1.17–1.84]	0.0011	1.59 [1.37–1.84]	<0.001
Severe	2.56 [1.76–3.70]	<0.001	3.74 [2.86–4.90]	<0.001
COVID-19 period				
Nov 21 to Jul 21	Reference		Reference	
Mar 20 to Oct 20	2.35 [1.67–3.30]	<0.001	2.44 [1.76–3.39]	<0.001
Country GDP [trillions USD]	0.97 [0.95–0.997]	0.029	1.01 [0.93–1.09]	0.87
Age [years]				
≤50 years	Reference		Reference	
>50 years	8.72 [5.96–12.77]	<0.001	3.23 [2.82–3.70]	<0.001
Age [years]	1.06 [1.06–1.07]	<0.001	1.04 [1.03–1.05]	<0.001
Sex				
Female	Reference		Reference	
Male	1.31 [0.94–1.82]	0.12	1.33 [1.12–1.59]	0.012
Comorbidities				
None	Reference		Reference	
1	3.07 [2.30–4.11]	<0.001	2.14 [1.83–2.51]	<0.001
≥2	14.39 [10.73–19.31]	<0.001	5.98 [4.56–7.85]	<0.001
Ethnicity				
White	Reference		Reference	
Hispanic	1.25 [0.77–2.02]	0.37	1.36 [1.06–1.73]	0.014
Asian	1.52 [0.84–2.76]	0.17	1.82 [1.24–2.67]	0.0021
Black	2.74 [1.96–3.84]	<0.001	2.29 [1.96–2.67]	<0.001
Other/mixed	1.03 [0.53–2.01]	0.93	1.56 [0.98–2.47]	0.061
BMI	1.01 [1.01–1.02]	<0.001	1.01 [1.004–1.02]	0.0038
IBD type				
CD	Reference		Reference	
UC/IBD-U	1.67 [1.37–2.05]	<0.001	1.38 [1.21–1.58]	<0.001
Systemic corticosteroids	3.92 [2.92–5.27]	<0.001	3.00 [2.31–3.90]	<0.001
Anti-TNF mono [no IMM]	0.34 [0.24–0.49]	<0.001	0.55 [0.48–0.62]	<0.001
Anti-TNF combo [with IMM]	0.82 [0.51–1.32]	0.41	0.85 [0.66–1.10]	0.22
IMM mono [without anti-TNF]	1.16 [0.80–1.69]	0.44	1.13 [0.95–1.34]	0.18
Mesalamine/sulfasalazine	1.96 [1.48–2.60]	<0.001	1.55 [1.30–1.83]	<0.001
Anti-integrin mono [no IMM]	1.21 [0.68–2.17]	0.51	1.03 [0.88–1.21]	0.67
Ustekinumab mono [no IMM]	0.50 [0.31–0.84]	0.0079	0.67 [0.53–0.85]	0.0010

BMI, body mass index; CD, Crohn's disease; GDP, gross domestic product; GEE, generalized estimating equation; IBD-U, IBD-unclassified; ICU, intensive care unit; IMM, immunomodulator; OR, odds ratio; PGA, physician global assessment; TNF, tumour necrosis factor; UC, ulcerative colitis; USD, US dollars.

ventilation/death and hospitalization. These plots illustrate that the magnitude of effect varies with age; the strength of the association between IBD activity and adverse outcomes is greatest in younger patients, especially those <50 years.

3.5. Analyses stratified by age

Figure 2 depicts the results of Joinpoint regression applied to the proportion of patients experiencing adverse COVID-19 outcomes by decade. A statistically significant change in slope is observed at 50 years for both ICU/ventilation/death and hospitalization. We therefore used a cut-off of 50 years [≤50 vs >50 years] for age-stratified analyses. In total, 9.6% [423/4419] and 1.2% [54/4419] of patients ≤50 years experienced hospitalization and ICU/ventilation/death, respectively, compared to 30% [504/1659] and 11% [189/1659], respectively, of patients >50 years, highlighting the major influence of older age on COVID-19 severity.

Supplementary Tables 3 and 4 summarize age-stratified unadjusted and adjusted analyses, respectively. In adjusted analyses, with the exception of the association between moderate PGA and

hospitalization [which had a similar effect estimate for both age groups], younger patients displayed a stronger association between IBD activity and adverse outcomes. Specifically, in the ≤50 group, severe PGA was associated with an increased risk of ICU/ventilation/death [aOR 3.27, 95% CI 1.15–9.30, compared to aOR 0.89, 95% CI 0.37–2.15, in the >50 group] and hospitalization [aOR 4.62, 95% CI 2.83–7.55, compared to aOR 0.90, 95% CI 0.39–2.09, in the >50 group]. Sensitivity analyses including BMI were associated with similar results [Table 4 footnote]. In adjusted analyses, the negative effect of comorbidities, corticosteroids and earlier COVID-19 diagnosis period, and the protective effect of anti-TNF monotherapy on the outcome of ICU/ventilation death were greater in patients ≤50 years.

Recognizing that a small number of patients >50 years had severe PGA [as shown in Table 1], we repeated the above age-stratified analyses combining moderate and severe PGA [i.e. remission/mild PGA vs moderate/severe PGA]. In this analysis, there were 313 patients >50 years with moderate/severe PGA. Results are shown in Supplementary Table 4, again illustrating the greater magnitude of effect for active IBD in younger vs older patients.

Table 3. Adjusted associations of demographic and disease characteristics with COVID-19 outcomes [using multivariable GEE models]

Variable ¹	ICU/ventilation/death ^{2,3}	<i>p</i> -value	Hospitalization ⁴	<i>p</i> -value
	aOR [95% CI]		aOR [95% CI]	
PGA				
Remission/mild	Reference		Reference	
Moderate	1.18 [0.89–1.57]	0.26	1.48 [1.23–1.79]	<0.001
Severe	1.56 [0.85–2.85]	0.15	3.24 [2.34–4.50]	<0.001
COVID-19 period				
Nov 21 to Jul 21	Reference		Reference	
Mar 20 to Oct 20	1.86 [1.42–2.44]	<0.001	2.28 [1.71–3.03]	<0.001
Age [years]	1.05 [1.04–1.06]	<0.001	1.03 [1.02–1.04]	<0.001
Sex				
Female	Reference		Reference	
Male	1.15 [0.81–1.62]	0.43	1.30 [1.09–1.55]	0.0030
Comorbidities				
None	Reference		Reference	
1	2.05 [1.59–2.65]	<0.001	1.72 [1.49–1.99]	<0.001
≥2	5.57 [4.40–7.04]	<0.001	3.42 [2.69–4.35]	<0.001
IBD type				
CD	Reference		Reference	
UC/IBD-U	1.23 [0.93–1.64]	0.15	1.10 [0.91–1.32]	0.32
Systemic corticosteroids	2.99 [2.09–4.28]	<0.001	1.87 [1.37–2.53]	<0.001
Anti-TNF mono [no IMM]	0.54 [0.34–0.86]	0.0098	0.71 [0.60–0.83]	<0.001
Anti-TNF combo [with IMM]	1.14 [0.59–2.21]	0.69	0.97 [0.76–1.25]	0.84
IMM mono [without anti-TNF]	1.16 [0.72–1.88]	0.54	1.06 [0.84–1.34]	0.62
Mesalamine/sulfasalazine	1.18 [0.84–1.65]	0.33	1.12 [0.86–1.45]	0.42

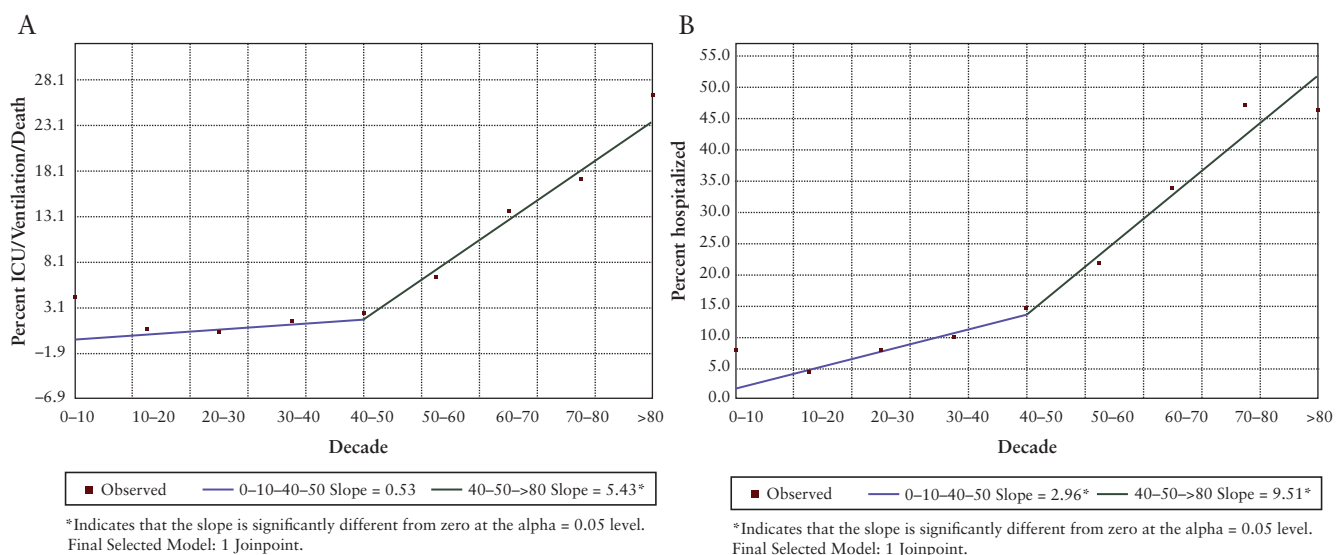
aOR, adjusted odds ratio; CD, Crohn's disease; GEE, generalized estimating equation; IBD-U, IBD-unclassified; IMM, immunomodulator; PGA, physician global assessment; TNF, tumor necrosis factor; UC, ulcerative colitis

¹Age, sex, comorbidities, IBD type, corticosteroids, anti-TNF monotherapy, anti-TNF combination therapy, immunomodulator monotherapy and SASA included a priori based on clinical relevance; only body mass index [BMI] changed estimate for PGA by ≥10% [for outcome of ICU/ventilation/death only] – included in sensitivity analysis only due to large percentage of missing data.

²In total, 114 observations missing, 240 events.

³Sensitivity analysis including BMI: 998 observations missing, 175 events, aOR for moderate PGA – 1.20 [95% CI 0.84–1.73], aOR for severe PGA – 1.46 [95% CI 0.73–2.92].

⁴In total, 114 observations missing, 912 events.

**Figure 2.** Joinpoint regression. Proportion of patients experiencing ICU/ventilation/death [A] and hospitalization [B] by decade.

4. Discussion

In this analysis of 6078 patients reported to the SECURE-IBD registry, we found that active IBD, reflected by moderate or severe

PGA vs clinical remission or mild PGA, was associated with a significantly increased risk of severe COVID-19, defined as ICU admission, ventilation or death, and COVID-19-related hospitalization. The

Table 4. Adjusted associations of demographic and disease characteristics with COVID-19 outcomes stratified by age [using multivariable GEE models]

Variable ¹	≤50 years			>50 years		
	ICU/vent/death ^{2,3}	p-value	Hospitalization ^{4,5}	ICU/vent/death ^{6,7}	p-value	Hospitalization ^{8,9}
	aOR [95% CI]		aOR [95% CI]	aOR [95% CI]		aOR [95% CI]
PGA						
Remission/mild	Reference		Reference	Reference		Reference
Moderate	1.62 [0.74–3.59]	0.23	1.44 [1.02–2.03]	1.10 [0.94–1.29]	0.22	1.53 [1.14–2.06]
Severe	3.27 [1.15–9.30]	0.026	4.62 [2.83–7.55]	0.89 [0.37–2.15]	0.80	0.90 [0.39–2.09]
COVID-19 period						
Nov 21 to Jul 21	Reference		Reference	Reference		Reference
Mar 20 to Oct 20	2.46 [1.49–4.09]	<0.001	2.24 [1.69–2.97]	1.65 [1.14–2.37]	0.0073	2.23 [1.53–3.24]
Country GDP [trillions USD]	—		0.99 [0.97–1.02]	—		—
Age [years]	1.04 [1.003–1.09]	0.034	1.03 [1.01–1.04]	1.04 [1.02–1.05]	<0.001	1.03 [1.02–1.05]
Sex						
Female	Reference		Reference	Reference		Reference
Male	1.18 [0.98–1.42]	0.076	1.18 [0.98–1.42]	1.25 [0.81–1.93]	0.31	1.45 [1.07–1.95]
Comorbidities						
None	Reference		Reference	Reference		Reference
1	2.44 [1.77–3.36]	<0.001	1.74 [1.49–2.04]	1.65 [1.04–2.60]	0.032	1.73 [1.31–2.29]
≥2	5.64 [2.17–14.64]	<0.001	2.81 [1.83–4.31]	4.53 [3.58–5.73]	<0.001	3.54 [2.70–4.65]
Ethnicity						
White	Reference		Reference	Reference		Reference
Hispanic	3.68 [1.63–8.31]	0.0018	1.83 [1.25–2.67]	1.22 [0.81–1.84]	0.34	1.20 [0.91–1.57]
Asian	0.21 [0.08–0.56]	0.0018	0.70 [0.56–0.88]	1.48 [0.81–2.68]	0.20	1.93 [0.82–4.58]
Black	—		1.16 [0.87–1.55]	2.22 [1.33–3.68]	0.0022	2.74 [1.99–3.76]
Other/mixed	—		1.06 [0.82–1.38]	1.64 [0.76–3.50]	0.20	1.79 [0.73–4.39]
IBD type						
UC/IBD-U	—		Reference	Reference		Reference
Systemic corticosteroids	3.68 [1.63–8.31]	0.0018	1.83 [1.25–2.67]	1.14 [0.80–1.63]	0.48	1.21 [0.93–1.58]
Anti-TNF mono [no IMM]	0.21 [0.08–0.56]	0.0018	0.70 [0.56–0.88]	2.89 [1.77–4.72]	<0.001	2.20 [1.39–3.49]
Anti-TNF combo [with IMM]	—		1.16 [0.87–1.55]	0.66 [0.37–1.16]	0.15	0.68 [0.51–0.90]
IMM mono [without anti-TNF]	—		1.06 [0.82–1.38]	1.04 [0.42–2.59]	0.93	0.73 [0.44–1.22]
Mesalamine/sulfasalazine	—		0.98 [0.81–1.19]	1.20 [0.66–2.21]	0.55	1.17 [0.86–1.58]
CD	—		0.98 [0.81–1.19]	1.16 [0.85–1.58]	0.36	1.18 [0.76–1.84]

¹OR, adjusted odds ratio; CD, Crohn's disease; GEE, generalized estimating equation; IBD-U, IBD-unclassified; IMM, immunomodulator; PGA, physician global assessment; TNF, tumour necrosis factor; UC, ulcerative colitis.
²Age, sex, comorbidities, IBD type, corticosteroids, anti-TNF monotherapy, anti-TNF combination therapy, immunomodulator monotherapy and SASA included in all models a priori based on clinical relevance [except for ICU/ventilation/death in ≤50 year group due to small number of events – see below]; other variables included if they changed estimate for PGA by ≥10% (body mass index [BMI] included in sensitivity analysis only due to large percentage of missing data).
³In total, 54 events only so covariates restricted to COVID-19 diagnosis period, age, comorbidities, corticosteroids and anti-TNF monotherapy based on clinical/statistical significance.
⁴Sensitivity analysis including BMI: 590 observations missing, 45 events, aOR for moderate PGA – 2.09 [95% CI 0.82–5.03], aOR for severe PGA – 3.46 [95% CI 1.04–11.52].
⁵In total, 149 observations missing, 411 events.
⁶Sensitivity analysis including BMI: 716 observations missing, 326 events, aOR for moderate PGA – 1.52 [95% CI 1.05–2.20], aOR for severe PGA – 4.56 [95% CI 2.64–7.90].
⁷In total, 128 observations missing, 174 events.
⁸Sensitivity analysis including BMI: 414 observations missing, 121 events, aOR for moderate PGA 0.97 [95% CI 0.71–1.32], aOR for severe PGA – 0.75 [95% CI 0.23–2.49].
⁹In total, 128 observations missing, 468 events.
¹⁰Sensitivity analysis including BMI: 414 observations missing, 360 events, aOR for moderate PGA – 1.42 [95% CI 1.02–1.98], aOR for severe PGA – 0.98 [95% CI 0.38–2.53].

strength of the association between active IBD and adverse outcomes varied with age and was greatest in younger patients. In multivariable analyses adjusting for confounding factors, such as medication exposure, the association between severe clinical disease activity and COVID-19 outcomes was seen only in patients ≤ 50 years.

A few studies have previously explored the effect of IBD activity on COVID-19 outcomes. In an analysis of 209 paediatric IBD patients from the SECURE-IBD registry, moderate/severe clinical activity was associated with an increased risk of hospitalization,¹² but the small sample size precluded adjustment for confounding variables, and outcomes such as ICU admission and death were too few to examine. In a prospective Italian study of 79 IBD patients with SARS-CoV-2, clinical IBD activity was identified as a risk factor for COVID-19 pneumonia and death.¹³ Again, multivariable analyses could not be performed due to small sample size. In a Danish nationwide IBD cohort study, amongst 76 patients with COVID-19, no independent association was observed between clinical or biochemical IBD activity and the outcomes of hospitalization, ICU admission, ventilation or death.¹⁴ Important differences with our study include the much smaller sample size and definition of active IBD as any degree of activity [including mild]. A longitudinal cohort study of 119 IBD patients from New York found that those with active IBD [clinically, endoscopically or biochemically] and those receiving corticosteroids were more likely to be infected with SARS-CoV-2, though without explicit comment on the link between IBD activity and severity of the infection.¹⁵ Beyond IBD, there is a robust body of literature supporting that poor control of other chronic diseases, such as diabetes mellitus, confers an increased risk of severe COVID-19.¹⁶

Our findings suggest that active IBD may be a particularly important modifiable risk factor for severe COVID-19 in younger patients. This may be because, in older patients, factors such as age, comorbidities and medications are primary drivers of risk, whereas in younger patients, disease activity plays a more prominent role. Differential practices by age for COVID-19 testing [possibly less testing of younger patients with mild disease] and shielding practices [possibly greater protective practices in older individuals] may also be relevant.

Several mechanisms may explain the independent association between IBD activity and COVID-19 severity. First, ACE2, the primary SARS-CoV-2 receptor, is widely expressed at the luminal surface of the GI tract.^{8,17} Transcriptomic analyses of intestinal biopsies demonstrate that inflammation influences ACE2 gene expression in a location-specific manner.^{18–20} The role of ACE2 in modulating COVID-19 progression is not entirely clear; although higher expression increases viral uptake by the host, ACE2 has important anti-inflammatory properties, which may help prevent the secondary ‘cytokine storm’ in severe COVID-19.²⁰ The effect of gut inflammation on ACE2 expression represents an important putative mechanism by which IBD activity may influence COVID-19 outcomes. Network analyses show that IBD and COVID-19 pathways intersect molecularly and share several ‘key driver genes’.¹⁸ In addition, in severe COVID-19, thromboembolic complications are a major driver of significant morbidity and mortality.^{21–24} Active IBD, especially moderate–severe exacerbations requiring hospitalization, is an established risk factor for venous thromboembolism,^{25,26} and could potentially confer an incremental risk of thromboembolic complications in the setting of COVID-19, although this has yet to be demonstrated. Lastly, active IBD may be associated with poorer general health, which may place individuals at an increased risk of adverse COVID-19 outcomes. Notably, the association between IBD activity and more severe viral infection is not unique to COVID-19;

IBD disease activity is an established risk factor for viral replication and worse outcomes with other viruses such as EBV and CMV,^{27,28} though it is difficult to disentangle the effects of chronic inflammation from immunosuppressive treatment.

Our finding of an association between active IBD and COVID-19 severity has several practical implications. First, it supports the position endorsed by North American and European societies that patients should continue their IBD therapies during the SARS-CoV-2 pandemic,^{29,30} to not precipitate a disease flare. Second, patients with moderately to severely active IBD should be counselled to adhere to practices that minimize their risk of contracting COVID-19 [such as staying home from school and/or work], given their risk of worse outcomes if they become infected. This is particularly applicable to younger patients, based on our findings. Our observations may also have implications for vaccine prioritization. Recent evidence suggests that IBD patients on anti-TNF have attenuated serological responses to SARS-CoV2 vaccines and that, accordingly, delayed second dosing should be avoided in such patients.³¹ Our results suggest that younger patients with severe IBD may warrant vaccine prioritization as well, including adherence to the recommended interval between vaccine doses. Along the same lines, our findings may also have implications for vaccine booster doses in the IBD population.

The strengths of our study include its very large size and international nature, the multivariable analyses controlling for multiple confounders, as well as our exploration of the effect of disease activity across the age spectrum.

We do, however, acknowledge several important limitations intrinsic to the study design and available data. First, reporting bias and selection bias are significant possible limitations given the use of a registry based on voluntary reporting. That said, the registry spans multiple countries, and the full spectrum of IBD activity and therapies [a surrogate for disease severity] was captured in our dataset. Nevertheless, our findings may not be generalizable to the broader IBD population. Given the observational nature of the data, our findings are associational, and causality cannot be inferred. An additional important limitation relates to the use of PGA, a subjective rating, as the indicator of disease activity, with no data available on biomarkers or endoscopic activity. In addition, the timing of PGA assessment may not have been precisely contemporaneous with COVID-19 diagnosis. Lastly, COVID-19-related GI symptoms may have influenced PGA assessment. While these are important limitations, there are several elements that appear to lend face validity to our findings. First, although there is probably variability in how PGA was applied, we explored the effect of using a different method to categorize PGA [remission or mild vs moderate or severe] and found similar results. Second, we generally observed a gradient effect, whereby severe PGA was associated with greater magnitudes of effect than moderate PGA. Although the PGA remains a subjective clinical assessment, it has been the reference standard in developing numerous indices,^{32,33} in both CD and UC, and its use is commonplace in clinical practice. Lastly, while physicians were instructed to report COVID-19-related complications, we cannot rule out the possibility that some outcomes [particularly hospitalization] were IBD-related.

In conclusion, we have demonstrated an association between clinically active IBD and adverse COVID-19 outcomes. Importantly, this association appears to vary with age, with a stronger relative effect in younger patients. These findings reinforce the importance of maintaining IBD disease control during the current pandemic and may support the implementation of strategies to mitigate the risk of SARS-CoV-2 infection [distancing, immunization] in IBD patients with severe disease to prevent poor COVID-19 outcomes.

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Conflict of Interest

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Author Contributions

A.R.: study concept and design; analysis and interpretation of data; drafting of the manuscript; statistical analysis; data verification. C.L.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. E.I.B.: study concept and design; critical revision of the manuscript for important intellectual content; study supervision. G.J.W.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. N.A.K.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. M.E.K.: analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. G.G.K.: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. M.D.K.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; data verification. R.C.U.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. J.F.C.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. E.J.B.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. M.A.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. W.R.: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. A.M.G.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision. S.S.: study concept and design; interpretation of data; critical revision of the manuscript for important intellectual content; study supervision. All authors had full access to all the data in the study and accept responsibility to submit for publication. Writing Assistance: None.

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Data Sharing

The data dictionary is available at <https://covidibd.org/>. Study data for SECURE-IBD are available upon request by contacting the Steering Committee

at COVID.IBD@unc.edu. Data will be shared after approval of a study proposal, with a signed data access agreement.

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Supplementary Data

Supplementary data are available at ECCO-JCC online.

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