



Presence of Comorbidities Associated with Severe Coronavirus Infection in Patients with Inflammatory Bowel Disease

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Abstract

Background Comorbidities increase the risk of coronavirus disease 2019 (COVID-19) hospitalization and mortality. As many comorbidities are common in patients with inflammatory bowel diseases (IBD), we sought to investigate the effects of comorbidities in these patients on infection severity.

Aim To evaluate association between individual comorbidities and COVID-19 infection severity among patients with IBD.

Methods Data were obtained from SECURE-IBD, an international registry created to evaluate COVID-19 outcomes in patients with IBD. We used multivariable regression to analyze associations between eleven non-IBD comorbidities and a composite primary outcome of COVID-19-related hospitalization or death. Comorbidities were first modeled individually, adjusting for potential confounders. Next, to determine the independent effect of comorbidities, we fit a model including all comorbidities as covariates.

Results We analyzed 2,035 patients from 58 countries (mean age 42.7 years, 50.6% male). A total of 538 patients (26.4%) experienced severe COVID-19. All comorbidities but a history of stroke and obesity were associated with severe infection in our initial analysis, with adjusted odds ratios ranging from 1.9 to 3.7. In a model including all comorbidities significantly associated with the composite outcome in the initial analysis, as well as other confounders, most comorbidities remained significant, with the highest risk in chronic kidney disease and chronic obstructive pulmonary disease.

Conclusion Many non-IBD comorbidities are associated with a two to threefold increased risk of COVID-19 hospitalization or death among patients with IBD. These data can be used to risk-stratify and guide treatment and lifestyle decisions during the ongoing pandemic.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Coronavirus disease · Chronic kidney disease · Chronic obstructive pulmonary disease

Abbreviations

5-ASA 5-Aminosalicylates
aOR Adjusted odds ratio

CD	Crohn's disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
IBD	Inflammatory bowel disease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SECURE-IBD	Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

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Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Although COVID-19 infection generally presents as a mild or moderate illness, the infection can cause hospitalization, need for respiratory support, and death [1, 2]. Since its emergence in December 2019, COVID-19 has spread to over 200 different countries, resulting in over 123 million infections and 2.7 million deaths as of mid-March 2021 [3]. Worldwide estimates for mortality due to COVID-19 are estimated to range from 0.01% to over 20%, depending on patient age [4, 5]. The severity of disease is also impacted by factors such as age, sex, and comorbidities [6]. In particular, the presence of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer are important predictors of severe COVID-19 infection [7].

The effect of inflammatory bowel disease (IBD) and its treatments on the severity of COVID-19 infections is less understood. Two previous multicenter studies evaluated the risk of COVID-19 infection in patients with IBD, both finding the disease may present more severely in these patients when compared to the general population. These studies separately found hospitalization rates of patients with IBD who contracted COVID-19 to be close to 30%, much greater than seen in the general population [8, 9]. Patients with IBD may be predisposed to these more severe clinical outcomes compared to the larger, unaffected population for a number of reasons. First, immune-mediated diseases such as IBD can be associated with ongoing systemic inflammation and may predispose to thrombosis [10, 11]. Both elevated C-reactive protein (CRP) and d-Dimer levels are predictors of the severity of COVID-19 infection, and as patients with IBD may start from an initial position of vulnerability, it is possible that COVID-19 outcomes are worse in these patients [12, 13]. Second, the frequent use of immunosuppressant medications may also affect the clinical course of COVID-19 infection. It has previously been demonstrated that patients with IBD on immunosuppressant medication are at greater risk for morbidity from certain infectious processes, and this may be the case for COVID-19 as well [14]. Conversely, corticosteroid treatment and possibly other immunosuppressant therapy may provide a mortality benefit in severe COVID-19 infection, likely by blunting the effects of the cytokine mediated surge [14–16]. Finally, patients with IBD have a significantly higher prevalence of comorbid medical conditions, including respiratory disease, cardiovascular disease, and cancer compared to patients without IBD [17]. The presence of these comorbidities may place patients with IBD at risk for more severe COVID-19 infection,

and indeed, existing multicenter research mentioned previously has demonstrated that a higher Charlson Comorbidity Index is associated with more severe COVID-19 outcomes [8].

Our group has previously published research utilizing an international database of patients with IBD who were infected with COVID. A key finding was that, in patients with IBD, increasing age and number of comorbidities were significantly associated with the severity of COVID-19 [18]. However, the relative effect of specific comorbidities in patients with IBD has not yet been established. We aimed to evaluate the impact of individual comorbidities on COVID-19 severity among patients with IBD. Based on prior research demonstrating associations between comorbidities and severe COVID-19 outcomes in the general population, as well as in patients with IBD, we hypothesized that most, if not all, comorbidities would be significantly associated with greater COVID-19 severity [6–8].

Methods

Data Source

This research utilized the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) database. The creation of this database has been previously described [18]. In brief, healthcare providers reported demographic information of patients with IBD with confirmed COVID-19, as well as IBD treatments and outcomes of COVID-19 infection. Furthermore, reporters provided information regarding eleven comorbidities: asthma, cancer, cardiovascular disease, chronic liver disease, CKD, diabetes, a history of stroke, hypertension, obesity, COPD, and other chronic lung disease. Reporters were asked “Does the patient have any of the following comorbidities (check all that apply)?” and provided with a list of comorbidities to select from, as well as the opportunity to enter any other comorbidities afflicting the patient. Reporters are requested to submit cases after one week of symptoms and sufficient time has passed to observe the clinical course of the illness through resolution or death [18].

Quality Control

We identified potential duplicate records with matching age, sex, IBD disease type, country, and state (United States only), and reviewed these manually. Reports from nonvalid email addresses were flagged as potential errors and we performed a Google search of reporters and practice locations to confirm legitimacy of reports.

Statistical Analyses

This analysis utilized all reports to SECURE-IBD through November 8, 2020. Patient and disease characteristics were summarized by means and standard deviations for the continuous variables and by count and percentages for the categorical variables (Table 1). Our primary outcome was COVID-19 related hospitalization or death. We first analyzed associations between each individual comorbidity and COVID-19 hospitalization or death using separate logistic regressions. Covariates included patient age and sex, as well as other variables that were significantly different between patients with and without the comorbidity in bivariate analysis.

We next examined the independent effect of each comorbidity, adjusting for other comorbidities as well as patient age, patient sex, and IBD medication use, including 5-aminosalicylates (ASA), biologic therapy (any tumor necrosis factor, IL-12/23, or integrin antagonist), and corticosteroids using logistic regression. Comorbidities found to not be statistically significant using separate logistic regression models were not incorporated into the final multivariable model.

All statistical analyses were carried out in R (R Core Team, 2019) and used the Tidyverse package [19, 20]. An alpha level < 0.05 was considered statistically significant for all comparisons.

Results

Data from 58 countries describing 2035 COVID-19 cases in patients with IBD were reported to the SECURE-IBD registry at the time of the study and included for analysis. The mean patient age was 42.7 years, 1030 (50.6%) patients were male, and 1139 (56.0%) had Crohn's disease (CD). Among the 2035 patients, 538 (26.4%) experienced COVID-19 hospitalization or death, and 64 (3.1%) died. The most common comorbidity was hypertension (12.6%), followed by cardiovascular disease (7.1%) and diabetes (5.8%). The study population is further summarized in Table 1.

In the first analysis, we performed separate logistic regressions for each comorbidity, adjusting for age, sex, and the other variables shown in Table 2. All examined comorbidities were statistically significant except for a history of stroke [adjusted odds ratio (aOR) 1.62, 95% confidence interval (CI) 0.71–3.70] and obesity (aOR 1.07, 95% CI 0.80–1.43). Most comorbidities were associated with a two to threefold odds of hospitalization or death (Table 2). The highest aORs were observed for CKD (aOR 3.73, 95% CI 1.84–7.56) and COPD (aOR 3.55, 95% CI 1.66–7.58).

Next, we evaluated the independent effects of each comorbidity in a single model, adjusting for all other comorbidities, as patients with one comorbidity could be more likely

Table 1 Baseline demographic and clinical characteristics of IBD patients with COVID-19 reported to the SECURE-IBD registry until August 2020

Characteristic ^a	All patients	
	N	%
Total number of patients	2035	
Age (mean, SD)	42.7	17.9
Male gender	1030	51%
Ethnicity		
White	1620	80%
Black	145	7%
Asian	112	6%
Other	156	7%
Hispanic/Latinx		
Yes	352	17%
No	1281	63%
Unknown	402	20%
Disease type		
Crohn's disease	1139	56%
Ulcerative colitis	854	42%
IBD unspecified	42	2%
Biologic therapy	1203	59%
5-ASA	630	31%
Immunomodulators	460	23%
Corticosteroids	206	10%
Janus kinase Inhibitors	25	1%
Other IBD treatment	67	3%
No IBD treatment	65	3%
Cardiovascular disease	144	7%
Diabetes	118	6%
Asthma	107	5%
COPD	43	2%
Other chronic lung disease	34	2%
Hypertension	256	13%
Cancer	43	2%
History of stroke	29	1%
Chronic kidney disease	48	2%
Chronic liver disease	69	3%
Obesity (BMI ≥ 30)	335	16%
Cigarette smoker	84	4%
Other tobacco user	16	1%

SECURE-IBD Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease, *COVID-19* coronavirus disease 2019, *SD* standard deviation, *5-ASA* 5-aminosalicylic acid, *IBD* inflammatory bowel disease, *COPD* chronic obstructive pulmonary disease, *BMI* body mass index

^aUnless otherwise specified, percentages do not include missing values or "unknown." For all characteristics, less than 4% of data was missing and unknown, respectively, for each category. Percentages and n from each subcategory may not add up to the exact number of total reported cases due to missing values and/or non-mutually exclusive variables

Table 2 Association of non-IBD comorbidities and adverse COVID-19 outcomes (hospitalization and death) in IBD patients with COVID-19 in the SECURE-IBD registry in separate models

Comorbidity	aOR (95% CI) ^a	P value
Asthma ^b	1.88 (1.21–2.92)	0.005
Cancer ^c	1.96 (1.01–3.81)	0.047
Cardiovascular disease ^d	1.86 (1.25–2.78)	0.002
Chronic liver disease ^e	2.33 (1.39–3.89)	0.001
Chronic kidney disease ^f	3.73 (1.84–7.56)	<0.001
COPD ^g	3.55 (1.66–7.58)	0.001
Diabetes ^h	2.73 (1.79–4.18)	<0.001
History of stroke ⁱ	1.62 (0.71–3.70)	0.249
Hypertension ^j	2.01 (1.48–2.73)	<0.001
Obesity ^k	1.07 (0.80–1.43)	0.635
Other chronic lung disease ^l	3.02 (1.39–6.55)	0.005

SECURE-IBD Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *aOR* adjusted odds ratio, *CI* confidence interval

^aEach comorbidity was tested in a separate model after adjusting for variables other than comorbidities that were significantly associated with the outcome on bivariate analyses

^bAdjusted for age, sex, race, and ethnicity

^cAdjusted for age, sex, race, biologic therapy, 5-ASA, immunomodulators, and cigarette use

^dAdjusted for age, sex, biologic therapy, 5-ASA, corticosteroids, and cigarette use

^eAdjusted for age and sex

^fAdjusted for age, sex, race, biologic therapy, and corticosteroids

^gAdjusted for age, sex, biologic therapy, 5-ASA, and corticosteroids

^hAdjusted for age, sex, race, ethnicity, biologic therapy, and 5-ASA

ⁱAdjusted for age, sex, race, biologic therapy, and cigarette use

^jAdjusted for age, sex, race, biologic therapy, 5-ASA, and cigarette use

^kAdjusted for age, sex, biologic therapy, 5-ASA, and corticosteroids

^lAdjusted for age, sex, race, biologic therapy, 5-ASA, corticosteroids, and cigarette use

to have others (Table 3). As previously observed, increased patient age (aOR 1.03, 95% CI 1.02–1.04) and use of corticosteroids (aOR 2.90, 95% CI 2.09–4.03) were associated with higher odds of hospitalization or death. Associations with male sex (aOR 1.22, 95% CI 0.97–1.53) and use of 5-ASA (aOR 1.13, 95% CI 0.88–1.45) were not statistically significant. The use of biologic therapy was observed to have a protective association (aOR 0.51, 95% CI 0.40–0.65). Overall, the effect size for most comorbidities was similar in this fully adjusted analysis compared to individual analysis of each comorbidity. CKD (aOR 3.02, 95% CI 1.45–6.31) and COPD (aOR 2.92, 95% CI 1.32–6.48) remained the most detrimental comorbidities. However, the odds of association of adverse COVID-19 outcomes with cancer (aOR 1.87, 95% CI 0.94–3.75) and cardiovascular disease (aOR 1.34, 95%

Table 3 Association of non-IBD comorbidities and adverse COVID-19 outcomes (hospitalization and death) in IBD patients with COVID-19 in the SECURE-IBD registry in a composite model

Variable ^a	aOR (95% CI)	P value
Asthma	1.96 (1.24–3.11)	0.004
Diabetes	1.95 (1.22–3.11)	0.005
Cancer	1.87 (0.94–3.75)	0.076
Cardiovascular disease	1.34 (0.87–2.06)	0.186
Chronic liver disease	1.97 (1.14–3.39)	0.015
Chronic kidney disease	3.02 (1.45–6.31)	0.003
COPD	2.92 (1.32–6.48)	0.008
Hypertension	1.50 (1.07–2.10)	0.018
Other chronic lung disease	2.38 (1.06–5.35)	0.035
Age	1.03 (1.02–1.04)	<0.001
Male sex	1.22 (0.97–1.53)	0.083
5-ASA	1.13 (0.88–1.45)	0.343
Corticosteroids	2.90 (2.09–4.03)	<0.001
Biologic therapy	0.51 (0.40–0.65)	<0.001

SECURE-IBD Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, 5-ASA 5-aminosalicylic acid, *aOR* adjusted odds ratio, *CI* confidence interval

^aThese variables were incorporated into a multivariable logistic regression, with hospitalization or death as the response variable

CI 0.87–2.06) were attenuated and no longer statistically significant in the fully adjusted model. Directions and magnitudes of all effects were similar when the outcome variable was a need for mechanical ventilation or patient death.

Discussion

We used an international dataset of over 2000 reports of COVID-19 infection in patients with IBD to understand the relative effects of comorbidities on the severity of COVID-19. Consistent with literature in the general population, we observed that most non-IBD comorbidities are associated with a two to threefold risk of hospitalization or death. Given the high comorbidity burden for patients with IBD, these findings represent an important factor in risk-stratifying patients during the course of this pandemic and may be used to inform clinical care discussions as well as lifestyle decisions regarding returning to work, school, and other normal activities.

This study builds upon prior work indicating that, among patients with IBD, the presence of comorbidities is a risk factor for more severe COVID-19. Bezzio et al. found a strong association between Charlson Comorbidity Index and death among patients with IBD affected by COVID-19 (OR 16.66, 95% CI 1.80–153.9), research by Singh et al.

indicated that patients with IBD that experienced severe COVID-19 had a greater presence of comorbidities ($P < 0.05$ for essential hypertension, diabetes mellitus, ischemic heart diseases, heart failure, cerebrovascular diseases, and chronic kidney disease), and prior work from our group indicated that the presence of at least two non-IBD comorbidities was positively associated with the risk of intensive care hospitalization and/or death (aOR 2.9, 95% CI 1.1–7.8) [8, 18, 21]. Our analyses similarly demonstrated that most comorbidities were associated with worse COVID-19 outcomes. Furthermore, each statistically significant comorbidity had an odds ratio greater than 1.8, indicating that the resulting increase in the odds of hospitalization or death is relatively high. CKD and COPD conferred the greatest risk, both with odds ratios greater than 3.5. After a second analysis adjusting for the independent effects of each comorbidity, CKD and COPD remained the most detrimental comorbidities. The associations of these two comorbidities with severity of COVID-19 infection are consistent with prior research. Studies conducted within the general population that examined the effects of both CKD and COPD showed both comorbidities to confer greatly increased risk of severe infection. Thus, our findings in the IBD population are consistent with this prior literature [22, 23]. A history of stroke was not statistically significant. This result is surprising, as prior research suggested that this comorbidity is a significant predictor of severe COVID-19 infection among the general population [24]. This may be attributable to the fact that stroke patients are often placed on oral anticoagulants, which may have a protective effect in the prothrombotic milieu of COVID-19 infection [25]. Furthermore, obesity was not statistically significant. This, too, is in contrast to other research suggesting that obesity is a strongly detrimental factor in COVID-19 infection in the general population [26]. However, this prior study did not account for the same comorbidities as did this research, and it is possible that the observed effect of obesity was mediated by other comorbid conditions.

As with prior analyses of data from SECURE-IBD, we found that steroid use was associated with adverse COVID-19 outcomes while biologic use was protective [18]. In contrast to prior work, associations between 5-ASA/mesalamine and COVID-19 hospitalization or death were not significant, perhaps owing to tighter control of confounding by non-IBD comorbidities in this larger analysis with more granular assessment of individual comorbidities.

This study's strength stems largely from the SECURE-IBD database, a large international registry created through the collaborative effort of healthcare providers across the world which allowed us to analyze over 2,000 COVID-19 infections in patients with IBD. Nevertheless, IBD providers may not have fully reported the presence of comorbidities, leading to misclassification of exposure that may have slightly attenuated observed associations. Another limitation

is the potential for reporting bias. Data came from a convenience sample, which seems to over-represent white patients from the United States. Furthermore, the dataset might also over-represent severe infection. It may be that a doctor is more likely to be aware of or report a COVID-19 infection that presents more severe symptoms than one that does not. Further, it was unexpected that cancer was not significantly linked with severe infection in the independent effects analysis, as it has previously shown association with severe infection in the general population [7]. Perhaps this discrepancy was due to the lack of granularity with regards to cancer type, stage, treatment, and other clinical details in the SECURE IBD database which may have diluted the effect of active cancer, including metastatic cancer or cancers currently treated with chemotherapy. Lastly, it is important to acknowledge that this analysis is observational, and the correlation described throughout this research does not necessarily imply causation due to the possibility of unmeasured confounding and/or pure chance.

As COVID-19 continues to sweep through our society as we approach a new normal, it is important for patients and doctors to be able to stratify and assess risk, especially for patients with IBD who may already be predisposed to worse clinical outcomes. As expected, we found patient age and corticosteroid use linked with more severe COVID-19, as were many of the comorbidities we analyzed. In particular, CKD and COPD greatly increased risk of severe infection. These findings can be used to help patients and their providers make informed decisions about returning to normal activities and the level of precautions that should be taken.

Conclusion

Many comorbidities are associated with severe COVID-19 infection among patients with IBD. CKD and COPD were the most detrimental of all comorbidities in the study, both conferring approximately a threefold-increased risk of severe infection.

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Declarations

Conflict of interest RP reports no conflict of interest. XZ reports no conflict of interest. RCU has served as a consultant and/or advisory board member for Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer and Takeda. He has received research support from AbbVie, Boehringer Ingelheim and Pfizer. He is supported by a Career Development

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Ethical statement Each SECURE-IBD survey item met criteria for de-identified data, in accordance with the 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 federal regulations [45 CFR 46.102 and 21 CFR 56.102] and does not require IRB approval.

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