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Research Article

The Risk of Hospitalization due to COVID-19 in Patients with Inflammatory Bowel Disease

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Abstract

Objectives: The novel coronavirus SARS-CoV2 became a worldwide pandemic in 2020. It is known that patients with inflammatory bowel disease (IBD) are at an increased risk of infection, particularly when on immunosuppressive therapy. The outcomes of COVID-19 in IBD patients remain somewhat unclear.

Methods: This Finnish retrospective observational cohort study enrolled 74 patients with an established IBD diagnosis and a confirmed COVID-19 infection. Patient data (age, sex, body mass index, IBD type, biochemical and clinical activity, comorbidities [Charlson comorbidity index [CCI]) and symptoms of COVID-19 were compared with hospitalization due to the COVID-19 infection.

Results: We found that older age ($p < 0.01$) and comorbidities (CCI score higher than one [$p < 0.01$]) were associated with hospitalization due to COVID-19 infection. In contrast, none of the studied pharmacological treatments for IBD, IBD type or disease activity were associated with a higher risk of hospitalization.

Conclusion: Our study shows that comorbidities and older age are associated with hospitalization due to COVID-19. On the other hand, different pharmacological treatments for IBD were not linked to a higher risk of hospitalization.

Keywords: Inflammatory bowel diseases; Crohn's disease; Ulcerative Colitis; COVID-19; Immunosuppressive Treatment

Introduction

The coronavirus pandemic is a worldwide health crisis brought on by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2), which causes a COVID-19 (coronavirus disease 2019) infection [1]. The disease has continued to spread globally and was classified as a pandemic on 11 March 2020, by the World Health Organization [2]. Clinical symptoms in COVID-19 vary between patients, but most individuals have a mild form of the disease with no or flu-like symptoms, including a dry cough, fever, runny nose and fatigue. Additional symptoms may comprise shivering, throat pain, anosmia, headache, joint pain, nausea and diarrhoea [3,4]. In more severe forms of the disease, marked inflammation and progressive pneumonia occur, leading to difficulties in breathing. A COVID-19 infection has often proved to be more severe in patients over 60 years of age. Furthermore, most patients with COVID-19 requiring hospitalization or intensive care unit (ICU) admission have been shown to have at least one comorbidity, such as chronic lung or heart disease, diabetes or conditions that affect their immune system [5]. In addition, smokers have been suggested to develop more severe symptoms of COVID-19 and are more likely to be admitted to intensive care, to need mechanical ventilation or to die than to non-smokers [6].

The treatment of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), frequently includes immunosuppressant medications [7-10]. The immunomodulators commonly used in IBD are corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-tumour necrosis factor agents or other

biologicals. Their modes of action differ from each other, but they all compromise, to some extent, the patient's immune response [11]. This may increase the patient's risk of viral and bacterial infections and adverse outcomes of COVID-19 [12,13]. However, published data on possible associations of immunosuppressive therapy with severe COVID-19 remain inconsistent. Data extracted from the international registry Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD; 1,439 cases, 112 with severe COVID-19) suggest an increased risk with thiopurines either combined with biologicals or as a monotherapy [14], whereas data from the French national health system (268,185 IBD patients, 600 hospitalizations) indicate no such association [15]. So far, there is no clear evidence for an increased risk of more severe outcomes in patients with IBD in the context of COVID-19. This study aimed to describe how COVID-19 presents and evolves in patients with IBD and to identify potential risk factors that may predict the severity and outcomes of a COVID-19 infection in IBD patients.

Methods

This was a retrospective, observational cohort study. All eligible patients were adults (18 years and older) with an established diagnosis of CD or UC and a confirmed diagnosis of COVID-19, which was defined as the PCR-confirmed presence of the SARS-CoV-2 genome in a nasopharyngeal swab. The Hospital District of Helsinki and Uusimaa is the largest hospital district in Finland, covering a population of more than 1.7 million. The IBD registry is an integrated platform of the hospital patient data system and comprises 5,194 secondary or tertiary care patients with an IBD diagnosis, treated mostly with immunosuppressants and biologicals. We identified IBD patients with a COVID-19 diagnosis by performing a search combining the hospital district's COVID-19 registry and the IBD registry. The more detailed patient and disease data were collected retrospectively from the patient electronic charts in April 2021. For all eligible patients, we collected the following data: age, sex, ethnicity, pregnancy, body mass index, IBD type, IBD duration, surgical IBD treatment, pharmacological IBD treatment, other comorbidities (expressed with the Charlson Comorbidity Index [CCI] [16] signs and symptoms of COVID-19 (fever, cough, dyspnoea, dysosmia/dysgeusia, pharyngitis, diarrhoea, arthralgia-myalgia/asthenia, rhinitis, dysphonia, headache, abdominal pain, nausea/vomiting, thrombosis), antibiotic and anticoagulant therapies for COVID-19, COVID-19 outcomes (hospitalization on a regular ward and in an ICU as well as death), and smoking status.

Data on faecal calprotectin (FC) as a surrogate marker of inflammation were recorded 0–6 months before the COVID-19 infection, during the COVID-19 infection and after the COVID-19 infection. Values considered to be normal for FC were < 200 µg/g [17,18]. The last registration on clinical activity of IBD was assessed based on patient charts. Clinical disease activity was determined according to the presence or absence of symptoms due to IBD (number of bowel movements, presence or absence of abdominal pain and presence of blood on defecation). The Charlson Comorbidity Index (CCI) is a validated and easily applicable method of estimating the disease severity and the risk of death from a comorbid disease. It has also been shown that a higher mean CCI score is significantly associated with mortality and disease severity in COVID-19 patients [19].

Statistical analysis

Statistical analysis was performed using the R software environment (version R-3.6.2). Differences in the hospitalization status and the studied variables were tested for significance using logistic regression, where the age and BMI of the patients served as confounding factors. Statistical significance was set at $p < 0.05$. The values are presented as numeric with percentage or as mean with SD.

Ethical considerations

Permission to conduct the study was received from the institutional review board of Helsinki University Hospital. As this was a retrospective, non-interventional patient records review study, no ethics committee approval was required.

Results

Study population

Between 29 January 2020 and 15 April 2021, 74 patients with IBD (CD n = 32 [43%], UC n = 42 [57%]) had been diagnosed with a COVID-19 infection. The patients' baseline characteristics are shown in (Table 1). Within the six months prior to the COVID-19 infection, 18% (n = 13) of the CD patients and 18% (n = 13) of UC patients had an active IBD. Based on the available data, 22% (n = 7) of the CD and 24% (n = 10) of the UC patients had a biochemically active disease, whereas 28% (n = 9) of the CD and 19% (n = 8) of the UC patients had a clinically active disease. Six percent (n = 2) of the CD patients and 19% (n = 8) of the UC patients were not on any pharmacological treatment for IBD at the time of COVID-19 diagnosis. At the time of COVID-19 diagnosis, three patients (4%) were on systemic corticosteroid and thiopurine combination therapy; of these, only one UC patient was hospitalized on a regular ward and did not require ICU admission. We identified only one patient who was on concomitant medication with systemic corticosteroids, thiopurine and biologicals, and this patient was not hospitalized. Seven CD patients (22%) and eight UC patients (19%) were treated with thiopurine and biologicals, of these, one patient with CD and one with UC were hospitalized on a regular ward. Overall, two patients were pregnant, and neither of them was hospitalized. Nearly three-quarters (72%, n = 23) of the CD patients and two-thirds (60%, n = 25) of the UC patients had no significant comorbidities (CCI 0). One comorbidity was present in 22% (n = 7) of the CD patients and in 19% (n = 8) of the UC patients. Hence, only 15% of all patients had two or more comorbidities. Seven patients (9%) had asthma, while none had been diagnosed with chronic obstructive pulmonary disease. For 36 patients, an FC value determined 0–6 months prior

to the COVID-19 infection was available: the average value for CD patients was 279 μg/g and for UC patients 421 μg/g (FC range in all patients 5–1,600 μg/g, SD 482 μg/g). During the study period, 13 (18%) patients were hospitalized, four (5%) were admitted to an intensive care unit, and one patient died (Table 2). Except for the patient who eventually died, no-one needed mechanical ventilation. Among all hospitalized patients, the average number of days spent on a regular ward due to COVID-19 was 3.7 for CD, 6.3 for UC and 5.7 for all patients. Most patients (n = 62, 84%) were not on antibiotic therapy at the time of the COVID-19 infection. After the COVID-19 diagnosis had been established, 43% (n = 32) of all patients and 100% of those hospitalized received thrombosis prophylaxis.

Table 1: Characteristics of the IBD patients.

	Crohn's disease	Ulcerative colitis	Overall
Age at the time of COVID-19, years, average (range)	38.2 (19–70)	40.2 (19–71)	39.4 (19–71)
Female, n (%)	17 (53%)	21 (50%)	38 (51%)
Male, n (%)	15 (47%)	21 (50%)	36 (49%)
Scandinavian, n (%)	25 (78%)	39 (93%)	64 (86%)
Patients, n (%)	32 (43%)	42 (57%)	74 (100%)
Montreal classification for CD, n (%)			
Inflammatory B1	6 (19%)		
Stricturing B2	10 (31%)		
Penetrating B3	1 (3%)		
Ileum L1 (or + L4), Upper GI L4	8 (25%)		
Colon L2 (or + L4)	9 (28%)		
Ileocolon L3 (or + L4)	15 (47%)		
Montreal classification for UC, n (%)			
Proctitis E1		0 (0%)	
Left Colon E2		12 (29%)	
Extensive colitis E3		30 (71%)	
Duration (years from diagnosis), average (SD)	13.8 (12.3)	11.7 (9.7)	12.6 (10.9)
Surgical treatment, n (%)	13 (41%)	10 (24%)	23 (31%)
Pharmacological treatment, n (%)			
None	2 (6%)	8 (19%)	10 (14%)
Any pharmacological IBD treatment	30 (94%)	34 (81%)	64 (86%)
Aminosalicylates	4 (13%)	23 (55%)	27 (36%)
Thiopurines	18 (56%)	19 (45%)	37 (50%)
Systemic corticosteroids	2 (6%)	6 (14%)	8 (11%)
Methotrexate	0 (0%)	1 (2%)	1 (1%)
Biologicals	15 (47%)	13 (31%)	28 (38%)
Anti-TNF	11 (34%)	11 (26%)	22 (30%)
Vedolizumab	2 (6%)	2 (5%)	4 (5%)
Ustekinumab	2 (6%)	0 (0%)	2 (3%)
Tofacitinib	0 (0%)	0 (0%)	0 (0%)
Corticosteroids and thiopurines combination	1 (3%)	2 (2%)	3 (4%)
Systemic corticosteroid, thiopurines and biologicals combination	0 (0%)	1 (2%)	1 (1%)
Biologicals and thiopurines combination	7 (22%)	8 (19%)	15 (20%)
Body Mass Index (in the past 0–24 months), average (SD)	26.4 (4.6)	28.4 (7.2)	27.6 (6.3)
Charlson Comorbidity Index, n (%)			
0	23 (72%)	25 (60%)	48 (65%)
1	7 (22%)	8 (19%)	15 (20%)
2	0 (0%)	5 (12%)	5 (7%)

3	1 (3%)	1 (2%)	2 (3%)
4	1 (3%)	1 (2%)	2 (3%)
5	0 (0%)	1 (2%)	1 (1%)
6	0 (0%)	1 (2%)	1 (1%)
Charlson Comorbidity Index, average (SD)	0.4 (0.9)	0.9 (1.4)	0.7 (1.2)
Smoking (now or previously), n (%)	16 (50%)	10 (24%)	26 (35%)

Table 2: COVID-19-related symptoms, IBD activity and duration of hospitalization.

COVID-19 related symptoms, n (%)	Crohn's disease	Ulcerative colitis	Overall
None	2 (7%)	2 (5%)	4 (6%)
Flu-like symptoms	6 (21%)	3 (8%)	9 (13%)
Fever	11 (38%)	20 (51%)	31 (46%)
Cough	15 (52%)	23 (59%)	38 (56%)
Dysosmia or dysgeusia	5 (17%)	5 (13%)	10 (15%)
Arthralgia or myalgia	7 (24%)	4 (10%)	11 (16%)
Dyspnoea	6 (21%)	12 (31%)	18 (26%)
Diarrhoea	5 (17%)	11 (28%)	16 (24%)
Rhino-pharyngitis	16 (55%)	19 (49%)	35 (51%)
Headache	13 (45%)	11 (28%)	23 (34%)
Abdominal pain	3 (10%)	5 (13%)	8 (12%)
Vomiting/nausea	3 (10%)	3 (8%)	6 (9%)
Death	1 (3%)	0 (0%)	1 (1%)
Thrombosis	0 (0%)	0 (0%)	0 (0%)
Active disease biochemically (0–6 months prior to COVID-19), faecal calprotectin > 200 µg/g, n (%)	7 (22%)	10 (24%)	17 (23%)
Active disease clinically (0–6 months prior to COVID-19), n (%)	9 (28%)	8 (19%)	17 (23%)
Active disease endoscopically (0–6 months prior to COVID-19), n (%)	5 (16%)	4 (10%)	9 (12%)
Any activity (clinical, biochemical, endoscopic; 0–6 months prior to COVID-19)	13 (18%)	13 (18%)	26 (35%)
Faecal calprotectin 0–6 months prior to COVID-19, average (SD)	279.4 (422.7)	420.6 (537.9)	350.0 (482.1)
Faecal calprotectin 3 months after COVID-19, average (SD)	283.3 (421.2)	313.7 (303.6)	(346.8)
No antibiotics during COVID-19 infection, n (%)	29 (91%)	33 (79%)	62 (84%)
Hospitalized patients, n (%)	3 (9%)	10 (24%)	13 (18%)
Hospitalization days (regular ward), average	3.7	6.3	5.7
Intensive care days, average	22.0	2.7	7.5
Total no of hospitalization days, average (SD)	11.0 (11.3)	7.1 (3.7)	8.0 (5.8)

SD: standard deviation.

COVID-19 symptoms

The most common COVID-19 symptoms, presented in Table 2, were cough (56%), rhino-pharyngitis (51%), fever (46%), headache (34%), dyspnoea (26%), diarrhoea (24%), arthralgia/myalgia (16%), dysosmia/dysgeusia (15%), flu-like symptoms (13%), abdominal pain (12%) and nausea/vomiting (9%). Five percent did not develop any symptoms due to the COVID-19 infection. No thromboembolic complications were diagnosed.

Factors predicting hospitalization

In all statistical analyses age, body mass index (BMI) and sex were examined simultaneously with the variable, and each variable was also examined alone. Increasing age was associated with a higher risk of hospitalization ($p < 0.01$), presented in (Figure 1A). With a CCI of two or more, the risk of hospitalization was significantly increased ($p < 0.01$ vs CCI 0–1), as seen in (Figure 1B). When the points for age were omitted from the CCI score, patients

who had points due to an underlying medical condition were still more likely to be hospitalized ($p < 0.01$ vs no underlying medical condition).

Factors not predicting hospitalization

We could not demonstrate any significant association between BMI and risk of hospitalization, although there was a trend towards such a risk ($p = 0.09$). Interestingly, there was a significant association between BMI and hospitalization when one patient with a BMI of 54 was removed as an outlier ($p = 0.02$) (Figure 1C). Neither sex nor IBD type (UC or CD) had a significant impact on COVID-19 outcomes. There was no significant difference in hospitalizations among patients on biological medication, thiopurines or systemic corticosteroids, nor among patients who were taking any of the said medications as a combined therapy.

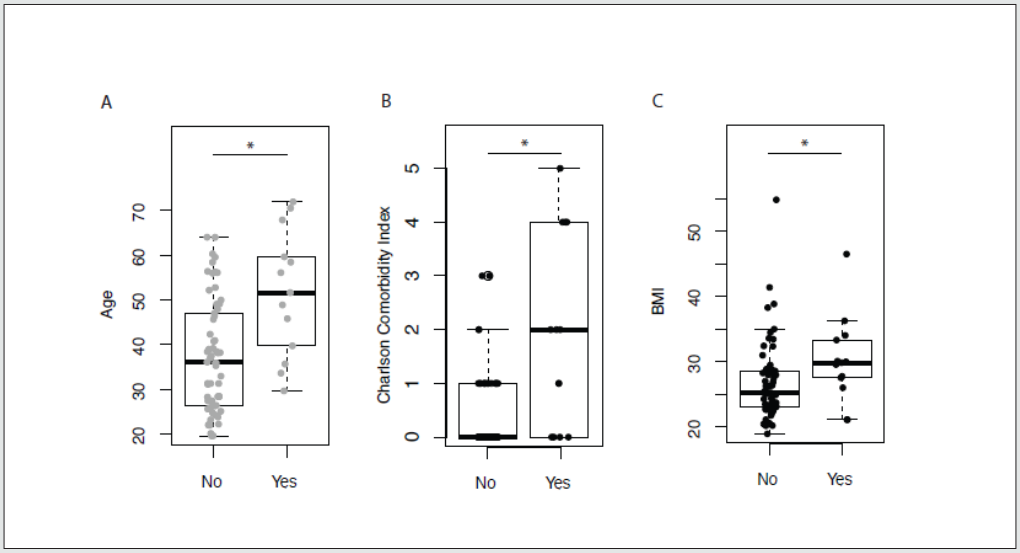

Figure 1: Factors predicting hospitalization. 1A) Age and risk of hospitalization. 1B) The Charlson Comorbidity Index (CCI) and risk of hospitalization. 1C) BMI and risk of hospitalization.

Patients (n = 17, 23% of all patients) who had biochemically active IBD (FC more than 200 µg/g during the past 6 months prior to COVID-19) were not hospitalized significantly more often than those with no preceding biochemical activity (n = 26, 35%); there was a non-significant tendency towards more frequent hospitalizations, but significance was not achieved due to the small number of patients. Neither previous clinical nor endoscopically active disease could be associated with hospitalization. Clinical, biochemical and endoscopic activity, as well as the results of patient records, were all examined at the same time for any indication of active disease prior to COVID-19, but there was still no significant change in hospitalization rates.

Discussion

Our study, which aimed at identifying risk factors for COVID-19 in IBD patients confirms previous findings indicating an association between hospitalization and both comorbidities and older age. Importantly, the use of any medication as maintenance therapy for IBD was not associated with an increased risk of a more severe COVID-19 infection or an undesirable outcome. The data of SECURE-IBD are likely to drive treatment recommendations for IBD during the COVID-19 pandemic. Immunosuppressive medications, especially thiopurines, used to treat IBD may result in a degree of immunosuppression, which has been hypothesized to lead to a more severe COVID-19 infection. Most of the patients in the IBD registry were on immunosuppressive treatment and were therefore thought to be at a higher risk of a severe COVID-19 infection. A recently published review article by Al-Ani and colleagues encourages the continuing of usual maintenance medications and highlights the importance of avoiding corticosteroids [20]. The finding of our study are in line with previous studies. In the case of an IBD flare-up, the risks and benefits of the treatments should be carefully discussed with the patient. More severe COVID-19 has been associated with older age and obesity [21-24]. Moreover, earlier studies have shown male sex to be a risk factor for more severe COVID-19 [25,26]. In the present study no significant association between sex and a higher risk of hospitalization was found. In the context of obesity, it is believed that the excess amount of adipose tissue causes inflammation and an impairment in the immune response. However, no significant correlation between BMI and the risk of hospitalization was found in our study. On the other hand, we found a significant association between age and hospitalization. It has been previously reported in studies of the general population that patients with comorbidities have a higher risk of more severe COVID-19 symptoms [27,28]. This was also seen in our population of IBD patients. Brenner and colleagues have

found that increased age, comorbidities and, contrary to our study, also systemic corticosteroids are associated with severe COVID-19 in IBD patients [29].

Between 29 January 2020, when the first COVID-19 case in Finland was confirmed, and 15 April 2021, a total of 48,438 cases had been reported in the Hospital District of Helsinki and Uusimaa, which constitutes 2.8% of the population of 1.7 million [30]. In the present study, we identified 74 (1.4%) out of 5,194 patients in the IBD registry with a confirmed COVID-19 diagnosis since the beginning of the pandemic. The proportion of IBD patients with confirmed COVID-19 is less than half of the corresponding proportion of the general population of the same geographical area. Earlier studies have indicated that patients with IBD are at risk of serious opportunistic infections, particularly when they are treated with immunosuppressive medication. However, the findings of our study suggest that patients with IBD are not at a higher risk of contracting the SARS-COV-2 than the general population. This could be partly explained by a more rigorous hygiene routine. The patients in the Uusimaa Region have received detailed hygiene and health instructions from the specialized IBD nurses since the beginning of the pandemic. In the future, more data are needed on the social impact that the pandemic may have had on these immunocompromised patients. This study has some limitations. Firstly, the number of patients was limited as the incidence of COVID-19 in Finland has remained relatively low. Secondly, the lack of data in the patient records made it challenging to find variables associated with an unfavorable outcome and a higher risk of hospitalization. Additionally, during the pandemic, patients have tended not to attend scheduled laboratory follow-up tests, resulting in missing data. Despite these limitations, we believe that this study reflects well the real-life situation in clinical practice and provides important data on the COVID-19 infection in the IBD population.

The present study also has several strengths. Firstly, as the COVID-19 registry of the hospital district covers all reported cases in the region, it is extremely unlikely that a COVID-19-positive patient included in the IBD registry would have been missed in our search. Secondly, this study was performed in a country with a high IBD prevalence of one percent of the population [31] and with, consistent IBD treatment patterns and active patient organization counselling in place. All patients have equal access to treatment, and most hospital districts have specialized nurses who are trained to treat patients with IBD and advise them on travelling, vaccinations and hygiene. The observation period of this study mainly took place before the national vaccinations against COVID-19 started. Although no vaccine data is available for this study population, the number of COVID-19-vaccinated patients can be neglected, as IBD patients on immunosuppressive therapy were among the groups to receive the vaccine, starting from mid-April 2021. Some of the newest COVID-19 strains that have emerged after the data collection for this study have been found to be more infectious and linked to a higher mortality rate. Future studies will show whether the outcome of COVID-19 will differ from today's studies.

Conclusion

This is the first report on the characteristics and outcomes of COVID-19 in patients with IBD in Finland, a country with a high prevalence of IBD and low prevalence of COVID-19. We found that comorbidities and older age were associated with a negative COVID-19 outcome such as hospitalization. On the other hand, immunosuppressive treatment for IBD was not associated with the risk of hospitalization or death. The lower incidence of COVID-19 infections among IBD patients in comparison to the general population may be explained by the rigorous hygiene measures undertaken particularly by patients on immunosuppressive therapy.

Author Contributions

Statement of authorship: study design (MK, PM, Ca B, PA), statistical analysis (JJ, JA), initial manuscript drafting (MK), critical revision and final approval (all authors).

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