



Analysis of COVID-19 and Inflammatory Bowel Disease: An in-depth literature review

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Abstract

Introduction: The world is experiencing some of the most complex consequences of the pandemic, with an accelerated growth of cases and deaths and a huge burden for the health systems, especially in immunocompromised individuals. In the healthcare system, the extent of impact of COVID-19 in patients with chronic diseases like inflammatory bowel disease (IBD) need its scientific attention.

Methods: An extensive literature search was done using 'COVID – 19', 'SARS-CoV-2', 'IBD' using google scholar, clinical trials.gov, and PubMed indexed journals.

Results: SARS-CoV-2 has been isolated in the duodenum and rectum, and a higher concentration of fecal calprotectin, a known inflammatory marker, has been found in infected patients with diarrhea compared with those without diarrhea (123.2 vs 17.3 $\mu\text{g/g}$; $P < .001$), suggesting that viral gut tropism could worsen inflammatory status and symptoms of IBD patient. In gist, symptoms experienced by IBD patients with COVID-19 are similar to those occurring in the general population, except for a higher percentage of diarrhea.

Conclusions: The aim of our study is to compare the incidence and clinical outcomes of COVID-19 in patients with IBD to the general population by using literature review. With increased risk of acquisition of COVID-19 in IBD patients, these patients can be asymptomatic or can present with typical symptoms of sore throat, fever, cough, dyspnea, sputum production, myalgia, fatigue, and headache.

Background

Understanding COVID-19 and its real time burden

COVID-19 is an infectious syndrome predominantly involving the respiratory system with a diverse spectrum of presentations and outcomes [1,2]. It is caused by a novel strain of a known virus called SARS-CoV-2 that was first reported in Wuhan, China and went on to become a worldwide disease. On 30 January 2020, the WHO declared COVID-19 to be a Public Health Emergency of International Concern. The risk of disease and

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How to Cite:

Vijayan *et al.*, "Analysis of COVID-19 and Inflammatory Bowel Disease: An in-depth literature review". *AIJR Preprints*, 351, Version 1, 2021.

death is of global concern but the severity is higher in the older age cohort and those with comorbidities or immunocompromised [3,4].

COVID-19 and IBD

Overall, both doctors and patients are predominantly focused on two main issues, one being the risk of COVID-19 in IBD patients and second being the risk of consuming biological treatment or immunomodulators and its impact on incidence of COVID-19 in IBD patients. Patients with IBD are usually a high risk group, more so when being managed with steroids, immunomodulators [5] Immunosuppressant treatment enhances probability of opportunistic viral infections [6]. Data collected from China [7] and Italy [8] suggests patients with IBD are at lower risk of acquiring severe form of COVID 19.[9]

Gastrointestinal symptoms

According to several papers published in the journal Gastroenterology, COVID-19 positive patients with IBD present with gastrointestinal symptoms, like diarrhea, vomiting and abdominal pain before breathing difficulty and other respiratory symptoms[10,11] RNA of virus is present in stool sample or rectal swabs of COVID-19 suspected patients showing viral stool shedding though symptoms aren't proportional to stool positivity. Viral gastrointestinal infection and transmission can persist in feco-oral route even after clearance of sputum in respiratory tract.

Rationalizing the need: Understanding the Goals and Objectives

Currently, the relationship between IBD and COVID-19 is poorly known. To be able to provide the present evidence on the clinical correlation between COVID-19 and IBD, a systematic review of the literature was performed on COVID-19 cases with IBD presenting concurrently.

Aims and Objectives

The primary objective was to assess the risk of hospitalization, Intensive Care Unit (ICU) admission, and mortality of IBD patients with COVID-19. The secondary objective was to correlate the variations in Management modalities to the outcome of COVID-19 in the population and to deduce if they are susceptible to certain treatment modality. The third objective was to evaluate the typical clinical presentation of COVID-19 in IBD patients.

Understanding the treatment modalities

Immunosuppressive drugs have been used as a choice of treatment for patient diagnosed with IBD. As the name suggests immunosuppressive drugs put the patient at risk for infection with COVID. The patients on these drugs have weak immune system ascribed to their medications. The risk of infection also depends on the type and dosage of the drug. Patients with COVID infection were found to have low WBC counts which is known as leucopenia. A few immunosuppressive drugs like azathioprine have side effects of leucopenia. Consequently both the infection and the drug's side effects exaggerate the risk of being prone to severe illness and complications.

Understanding the varied presentations

While most of them present with flu like illness and respiratory difficulty; nausea, diarrhea, anosmia, joint pains, loss of taste have also been other presentations of the COVID spectrum. There has been an evidence that ACE 2 receptors present on the gastric, duodenal and rectal epithelium are the target to the virus. The patients with IBD have mucosal inflammation in the terminal ileum and the colon. Coincidentally, the ACE2 receptors which are the target for the SARS Cov virus are in higher proportion in the above mentioned regions of the intestine making IBD patients more susceptible to the infection.

Impact of COVID-19 on IBD

Consequently, there is a concern that IBD patients are at greater risk of developing COVID-19 and at increased risk of progressing to a more severe clinical course or even death compared to the general population. Viral infection can be asymptomatic or cause the coronavirus disease 2019 (COVID-19), which is characterized by a wide range of clinical manifestations including respiratory and gastrointestinal symptoms up to severe events such as pneumonia, acute respiratory distress syndrome, and death. Since the beginning of the health emergency, particular attention has been paid to the management of patients with chronic inflammatory bowel diseases (IBDs) because they frequently are treated with immunosuppressive drugs and therefore potentially are exposed to a greater infectious risk than the general population.

Results

Our previous pooled analysis and 2 recent systematic reviews and 41 meta-analyses, showed a cumulative prevalence of diarrhea of approximately 7% to 10% in patients with COVID-19.

Patients may also present with gastrointestinal (GI) symptoms including diarrhea, nausea and vomiting, loss of taste and smell. The increased GI symptoms are thought to be angiotensin-converting enzyme-2 (ACE2) receptor mediated changes by the SARS-CoV-2 which is present throughout the gut mucosa in predominance. In the absence of typical symptoms, it is difficult to differentiate these GI symptoms due to COVID-19 infection or due to disease flare.

Patients with inflammatory bowel disease form a separate cohort, when it comes to the pathogenicity, severity, complication of COVID19. Their response to management, including vaccines might vary, due to the treatment patients might be undertaking. To better understand, fine tune the suggested treatments, there are many clinical trials, either ongoing or yet to begin (Table 1) (Table 2).

Table 1: Clinical trials in patients with Inflammatory Bowel disease with respect to the management of COVID-19

Reference number of trial	Objective of the trial	Method of Study	Population recruited	Exclusion	Results of the trial
NCT04818892	Immunogenicity of COVID-19 vaccines inpatients with Inflammatory bowel Disease	Case-Control Study	18 to 85 years old adults with IBD, on treatment for at least 2 months, and scheduled to receive COVID-	Patients who are allergic to COVID-19 vaccine components, or have previously received it. And	Ongoing

			19 vaccine, from University of Wisconsin Hospital and Clinics.	those with impaired decision making skills were also excluded.		
NCT04387279	Correlation between patient's perception of COVID-19 and medical use patterns during the pandemic period.	Cross-Sectional study	18 years or older, patients with IBD living in the Daegu city	Those who are unable to answer the questions.	Ongoing	
NCT04344249	Patients with IBD treated by Infliximab or Vedolizumab during COVID-19 pandemic.	Cohort Study	18 years or above patients with Crohn's or ulcerative disease treated by infliximab or vedolizumab	Not affiliated to a sanitary social insurance	Ongoing	
NCT04488471	Psychological impact of Isolation on IBD patients in Sheffield Teaching Hospital	Mixed Method Study	16 years or older patients with IBD treated in the clinics of Sheffield Teaching Hospital (NHS FT)	Patients who are not part of IBD clinics at STH NHS FT.	Ongoing	
NCT04492267	Retrospective study to analyse the severity and specific needs in cases of SARS-CoV-2 infection in IBD patients.	Retrospective observation Case only.	18 years or above, IBD patients infected with SARS-CoV-2	Patients under guardianship, safeguard of justice, or unable to understand questions due to language barrier.	Results posted.	not
NCT03944447	Study the role of Cannabis in prevention, treatment of covid-19 symptoms in patients taking it for another medical purpose.	Non Randomized Clinical trial.	18 years or above with a clinical diagnosis for medical cannabis.	Women who are pregnant, breast feeding, unable to provide informed consent, or participate by completing online questions	Ongoing	
NCT04798625	Assess the humoral and cellular immune response after COVID-19 vaccination in patients with inflammatory disease, using immunosuppressive medication.	Prospective Observational Study	> or equal to 18 years . With immune mediated disease :RA, SpA, PsA, UC, CD, AH or those who underwent liver transplantation	Individuals with allergy or intolerance of COVID-19 vaccine elements.	Ongoing	

Table 2: Understanding the study types and results (Supplementary table)

<i>Study Name</i>	<i>Study Type</i>	<i>Year of Study</i>	<i>Place of Study</i>	<i>Summary</i>
<i>Yang X et al</i>	Single-centered, retrospective, observational study	2020	China	The mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable. The survival time of the non-survivors is likely to be within 1–2 weeks after ICU admission. Older patients (>65 years) with comorbidities and ARDS are at increased risk of death
<i>Shah ED et al</i>	Systemic Review and Meta-analysis	2017	USA	Anti-tumor necrosis factor therapy but not anti-integrin therapy is associated with a greater infection risk than placebo in treating UC. Neither class of therapy is associated with increased infection risk over placebo in treating CD
<i>Bezzio C et al</i>	Observational study	2020	Italy	Active IBD, old age and comorbidities were associated with a negative COVID-19 outcome, whereas IBD treatments were not. Preventing acute IBD flares may avoid fatal COVID-19 in patients with IBD
<i>Abassi Z et al</i>	Review	2020	Israel	This review address the role of ACE2 within the RAS, and the inter-association of ACE2 and SARS-CoV-2, with their plausible combined impact on the clinical manifestations of COVID-19 disease
<i>Harmer D et al</i>	Case study	2002	UK	This study demonstrates the utility of QRT-PCR to assess the expression of mRNA transcripts in a wide range of human tissues. High expression of ACE2 was seen in cardio-renal tissues, in agreement with previous results. How-ever, the identification of ACE 2 at high levels in

<i>Neurath MF</i>	Review	2020	Germany	gastrointestinal tissues is a novel finding There is no evidence to suggest that patients with IBD should discontinue IBD-specific medications. However, older patients with IBD with comorbidities such as diabetes mellitus, obstructive lung disease, coronary heart disease and hypertension might have an increased risk for COVID-19 and further studies are urgently needed to address this point
<i>Jablaoui, A et al</i>	Report	2020	France	They used specific substrates to monitor fecal protease activities in a large cohort of healthy and IBD patients. Of interest, serine protease activity was 10-fold higher in IBD fecal samples compared to healthy controls. Moreover, functional analysis of these fecal proteolytic activities revealed that the most increased activities are trypsin-like, elastase-like and cathepsin G-like
<i>Sultan K et al</i>	Review	2020	Wuhan, China	Clinical observation/outcomes of the IBD population and perspectives on IBD management in the age of COVID-19
<i>Taxonera C et al</i>	Case series	2020	Madrid	IBD patients do not have an increased risk of COVID-19 and associated mortality compared with the general population
<i>Anikhindi SA et al</i>	Review	2020	India	Patients with IBD do not particularly appear to have increased susceptibility to COVID19 infection based on preliminary evidence
<i>Leon-Rendon JL de et al</i>	Review	2020	Spain	Systemic steroids should be avoided, The combined use of

<i>Allez M et al</i>	Practice guidelines	2020	N/A	thiopurines with steroids and/or tumor necrosis factor (TNF) monoclonal antibodies should also be avoided which could increase susceptibility to COVID-19 recommendations by the international membership of IOIBD regarding hospitalizations of IBD patients, either for active or complicated IBD or severe COVID-19, and for management of IBD patients according to SARS-CoV-2 status
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Tanenera et al. study conducted that 6.6 cases of COVID-19 infected patients with preexisting IBD per 1000 in general population in Spain during the peak of its pandemic; in comparison the crude incidence rate of COVID-19 in patients with IBD was lower at 6.2 cases per 1000 [13]. Data from the pediatric IBD Porto group of European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) reported only 8 known cases of children with pediatric IBD suffering from COVID-19 during the ongoing pandemic [12]. In addition, a meta-analysis study by Aziz et al reported only 0.3% incidence of COVID-19 infection in a pooled cohort of 9177 patients with IBD [12].

Discussion

Multiple studies showed how the mechanisms by which SARS COV2 may infect the human host, the entry of the SARS COV2 is mediated by surface glycoprotein binding to ACE receptor [1] which is expressed in pneumocytes in the lungs and also in duodenal, gastric, and rectal epithelium cells. [2] The S protein-driven viral entry is regulated by the cell surface-associated transmembrane protease serine protease 2 (TMPRSS2), a very crucial enzyme for cleavage and priming of protein S. [3] Then extracellular peptidase domain of ACE receptor recognizes the binding domain of S protein causing the infection.

As IBD patients are generally on immunosuppressive medicine, they are more prone to get any infection including COVID 19. Patients with IBD are traditionally treated with various immunosuppressant drugs, such as TNF combination therapies and mesalazine/5-aminosalicylic acid monotherapy to alleviate their symptoms.

Apart from making these patients more susceptible to infections per se,[4] on further analysis a study showed TNF monotherapy had protective effect against covid-19 while TNF combination therapies and mesalazine/5-aminosalicylic acid monotherapy may increase the risk of Covid 19 hospitalization and death [5]. In comparison, a study done in Bergamo demonstrates that immunosuppressive and biological therapies are associated with a significantly lower risk of covid-19[6].

Moreover, another study showed no increase in the positivity for Covid-19 after discontinuation of biological drugs like infliximab and immunosuppressive therapy. An (2020) et al. [7] SARS is a respiratory illness known for its life-threatening cytokine storm causing systemic inflammatory response syndrome, a study pinpointed that steroids treatment in Covid-19 patients' decreases mortality [8]. Although other study demonstrated that

using early steroids were associated with higher viral load of covid-19 in plasma compared to patients who did not receive any. [9]

Similarly, a previous study with a large sample of a total of 71,733 patients diagnosed with at least one IMID (1.6%) of them was positive with covid. (in comparison, the PCR positivity in the general population was 1.85%.) The study showed patients with IMIDs had more severe events with covid-19 due to the use of steroids. Attaubi (2021) et al. [10]

Beaugerie (2018) et al. [11] is a study worth mentioning that concluded accurate determination of the risk-benefit ratio of immunosuppressive drugs in IBD patients within this Covid pandemic is extremely vital for decision making.

Conclusion

It remains uncertain whether IBD patients are more susceptible to COVID-19 or more prone to severe disease. Consequently, there has been significant anxiety among IBD patients and clinicians regarding potential increased susceptibility. This is in part related to IBD management which involves immunosuppression, potentially placing patients at increased risk of opportunistic infections and respiratory illnesses. However, whether immunomodulators and biologics increase the risk of infection or of developing severe forms of COVID-19, is currently undefined.

Declarations

There is no conflict of interest. There are no ethical concerns. The study involves retrospective review of available data.

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