



Impact of Corona Virus Disease-19 (COVID-19) pandemic on gastrointestinal disorders

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Received: 13 May 2020 / Accepted: 29 June 2020 / Published online: 4 August 2020
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Abstract

Worldwide, several hospitals in different regions and countries have been affected with Corona Virus Disease-19 (COVID-19). All medical specialties including gastroenterology are impacted by COVID-19. Here, we review the bidirectional comorbidity of chronic gastrointestinal (GI) disorders and COVID-19, including the incidence and outcome of COVID-19 in individuals with various GI disorders and the impact of COVID-19 on the course and outcome of the underlying (or comorbid) GI disorders. Currently, there is no evidence that COVID-19 is more (or less) frequent in comorbid GI disorders. It is also reassuring that the outcome of COVID-19 is unaffected by the underlying GI disorder or its treatment, though potential concerns remain in regard to the use of immunomodulatory treatments in inflammatory bowel disease (IBD) and liver transplant recipients. Despite these concerns, there is now agreement among experts that ongoing immunomodulatory treatments may not be interrupted in individuals with IBD during the COVID-19 pandemic. Caution, however, may be exercised with the use of corticosteroids in the management of IBD. In addition, COVID-19 does not appear to impact the manifestations, course, outcome, and treatment of comorbid GI disorders, e.g. IBD. Decompensation of liver cirrhosis is, however, possible during COVID-19 episodes. A direct concern, however, might relate to the potential transmission of the virus through fecal microbiota transplants.

Keywords Comorbidity · Corona Virus · COVID-19 · Crohn disease · Diarrhea · Immunosuppression · Inflammatory bowel disease · Pandemic · Ulcerative colitis

Introduction

The occurrence of a large cluster of cases of pneumonia was first reported from Wuhan in Hubei Province, China, in early December 2019 [1]. Very rapidly, the outbreak metamorphosed into a local epidemic and eventually, a global pandemic and public health emergency [2]. The causative agent was found to be a novel beta coronavirus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as it shared considerable similarity to the SARS-CoV, responsible for the SARS syndrome in 2003. The WHO later renamed the infection as Corona Virus Disease-19 (COVID-19) [2]. The pathogenicity of COVID-19 is thought to be related to the

angiotensin-converting enzyme (ACE) type 2 receptor, expressed in the airway epithelium, vascular, kidney, and small intestinal cells [3].

As of May 29, 2020, the estimated number of positive patients is over 6 million with a mortality of 366,812. Within a relatively short period, there has been a surge of publications on the clinical, and imaging patterns, virus behavior, or biology. An initial PubMed search on April 07, 2020, using the terms COVID-19 and coronavirus yielded 2780 and 16,725 citations, respectively. A similar search on May 29, whilst revising this article, yielded 16,907 and 47,294 citations, respectively. Hence, we recognize the rapidity with which new information is being generated and acknowledge that the standpoints presented in this review might change in the times to come.

The cardinal manifestations of COVID-19 include fever, dry cough, fatigue, and myalgias [4]. Gastrointestinal (GI) manifestations are not uncommon and rarely might be the sole presenting manifestation of SARS-CoV-2 infection [5–8]. These have been systematically reviewed elsewhere, and an updated meta-analysis of the gastroenterological

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manifestations of COVID-19 appears in this very issue of the Indian Journal of Gastroenterology [9]. Hence, we choose not to discuss GI manifestations of COVID-19 here and the reader is referred to the accompanying paper for further information. On a different note, there is concern that the course, outcome, and treatment of certain GI disorders, e.g. inflammatory bowel disease (IBD), are modified by COVID-19 [10]. Lastly, the flood of COVID-19 to hospitals in several locations has had implications on the operation of several GI procedures and treatment and in a larger unforeseen manner of routine GI practice [11]. Here, we review published literature from PubMed to address the following two concerns: (i) Are people with GI disorders at an altered risk or severity of developing COVID-19? and (ii) Does the occurrence of intercurrent COVID-19 impact the manifestations, course, outcome, and treatment of premorbid GI disorders? Also, we chose not to address the feasibility, indication, and adaptations to GI endoscopic procedures as several professional bodies across different countries and regions have proposed interim guidelines, largely based on expert consensus, and the reader is referred to these for detailed understanding and adherence [12, 13].

Are people with GI disorders at an altered risk or severity of developing COVID-19?

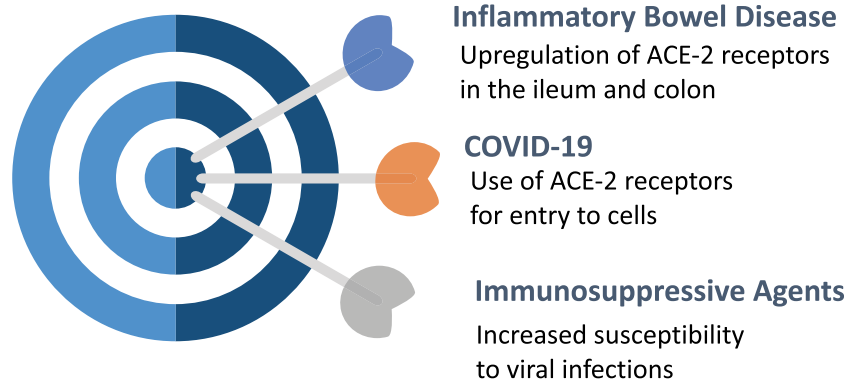
SARS-CoV-2 RNA has been isolated from stool specimens [5, 14, 15]. The isolation of viral RNA from stool samples correlates with abdominal pain but not to other GI symptoms [16]. Anecdotally, the virus isolation from feces follows isolation from the throat or the respiratory tract by 2–3 days but more experience is required to confirm this observation. In convalescent individuals, i.e. those in whom fever has resolved with two consecutive nasopharyngeal swabs negative for reverse transcriptase polymerase chain reaction (RT-PCR), the virus might persist in stool specimens for several days [17, 18]. The familial clustering of cases, observed anecdotally, adds support to and might indeed be the result of transmission by the fecal route [19]. Transmission by the fecal route might be more important in infected children, particularly those who have not acquired bowel control [20, 21]. Virus isolation from stool specimens raises several issues: (1) it opens up the possibility of diagnosis using fecal samples, thereby potentially reducing false-negative results if nasal and throat swabs are negative; (2) it also opens up the possibility of transmission via the fecal route; (3) it also precludes the potential of contamination and spread of infection during colonoscopic and proctoscopic examinations [18]; and (4) it raises the speculation that certain inflammatory bowel disorders might alter the risk of acquiring or the severity of COVID-19. Below, we discuss the clinical implications of the fourth concern.

The pathogenicity of COVID-19 agent in relation to the GI tract has been recently reviewed elsewhere [22]. Briefly, an S protein component of the virus interacts with cell surface angiotensin-converting enzyme type 2 (ACE-2) receptors to enter human host cells [23]. The ACE-2 receptors are expressed abundantly in the nasal epithelium and upper and lower respiratory tract epithelial cells [3]. In addition, ACE-2 receptors are also highly expressed in the human GI tract epithelium, particularly the terminal ileum and fairly in the colon [24]. Studies have documented an increased expression of ACE-2 in histological samples of IBD [25]. Lastly, there is an upregulation of trypsinases, which might aid the solubilization of viral S protein to aid the assimilation of the virus in the human host cells [22]. The findings have stirred speculation that individuals with IBD might be more prone to COVID-19 and, when infected, more likely to have severe manifestations, e.g. requirement for intensive care, mechanical ventilation, and even death (Fig. 1). Alternatively, studies have demonstrated a massive increase in the expression of several cytokines in individuals with severe COVID-19, referred to as the cytokine storm [26]. It has been, therefore, surmised that immunomodulatory agents used in the treatment of IBD might favorably modulate the cytokine expression and shield COVID-19 infected individuals from serious manifestations.

The use of angiotensin-converting enzyme–blocking agents, e.g. for the control of hypertension, is thought to upregulate the expression of ACE-2 receptors and may predispose individuals with COVID-19 to more severe manifestations with poor outcome [27, 28]. Anecdotally, the occurrence of hemorrhagic colitis in an individual with COVID-19, who was previously using lisinopril, has been described [29].

Initial reports of a large number of cases from Wuhan and other locations in China did not identify IBD as one of the predisposing conditions for COVID-19 or its more severe manifestations [5, 30]. Likewise, IBD did not figure in a systematic review of premorbid conditions associated with COVID-19 [31]. The concern of an altered risk, however, fueled investigators from different parts of the world to join hands to initiate a collaborative voluntary online registry, known as the Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion-inflammatory bowel disease (IBD) database (<https://covidibd.org>) (SECURE-IBD). As of May 31, 2020, 1302 cases of COVID-19 in IBD have been registered from 46 countries, though most cases have been volunteered from the USA. Of them, 30% required hospitalization, 6% required intensive care, 5% required mechanical ventilation, and 3% died. Overall, therefore, the need for mechanical ventilation and mortality due to COVID-19 does not seem to be increased among individuals with IBD. To date, three cases in the registry have been contributed from India, of whom one died. Interestingly, in

Fig. 1 Cartoon depicting the possible relationship between inflammatory bowel disease and Corona Virus Disease-19 (COVID-19). *ACE-2* angiotensin-converting enzyme type 2



contrast to the bimodal peak of the age distribution of IBD, over 57% of the patients in the SECURE-IBD registry are younger than 50 years of age [32]. Individuals over 60 years represent only 21% of the global cohort. In contrast, 46% of those who died in the registry were over 60 years of age. These data are consistent with the age trends on mortality associated with COVID-19 [33]. Preliminary data gathered from the website depicts the high case fatality rates (of 10%) among users of oral or parenteral corticosteroids. A sizable proportion of the cohort was on anti-tumor necrosis factor with or without other immunosuppressive agents and the case fatality rate in this subgroup was less than 2%.

Once published, the SECURE-IBD data are likely to drive treatment recommendations for IBD during the COVID-19 pandemic. Currently, however, most scientific bodies recommend the continuation of ongoing therapies including immunosuppressants as well as biological agents during the period of COVID-19 pandemic [34–36]. If an individual with IBD requires new treatment/s (e.g. due to a flare-up or new-onset disease), then the risks and benefits of the treatments, especially corticosteroids, should be carefully discussed in order to arrive at a mutual decision between the physician and patient. If an individual with IBD develops COVID-19, immunosuppressants may be carefully withheld during the period of active infection and reinstated as soon as microbiological clearance has been demonstrated. Surgical treatments with the exception of emergent procedures are best deferred until after the pandemic wanes [37]. Needless to add, all individuals with IBD should maintain high levels of safety precautions required in general for the prevention of COVID-19, including the use of masks, hand washing, social distancing, and avoiding face-to-face visits to hospitals. Physicians involved in IBD care should be mindful of the high mortality risks associated with older age and other comorbidities, e.g. hypertension and diabetes, and should likewise advise their patients.

Other than IBD, data on the comorbidity of COVID-19 and GI disorders are limited [5, 30]. Preliminary data from China pointed towards an increased likelihood of comorbid chronic

liver disease in COVID-19-infected individuals with GI symptoms and signs [15, 16]. The National Health Commission study of 1099 COVID-19-infected individuals from China found that the frequency of HBsAg positivity in this population was 2.1% [30]. The SECURE registries invited data collection for celiac disease, eosinophilic gastroenteritis, chronic liver disease, and liver transplant in association with COVID-19 (<https://covidibd.org/other-registries/>). The data for each of these conditions are sparse in comparison with IBD. The SECURE-Cirrhosis collects data on chronic liver disease (both cirrhotic and non-cirrhotic; liver transplant included) from the Americas, Japan, Korea, and China and works in tandem with the European Association for the Study of the Liver COVID-Hep registry, which likewise collects data from the rest of the world. A combined up-to-date dataset can be accessed at <https://covidcirrhosis.web.unc.edu>. Towards the end of May 2020, there is information on 710 cases including 124 liver transplant recipients (<https://covidcirrhosis.web.unc.edu/updates-and-data/>). Case fatality rates have been the highest (over 30%) in those with hepatic cirrhosis and hepatic transplant recipients (17%) but low in those with non-cirrhotic chronic liver disease (7%) (<https://covidcirrhosis.web.unc.edu/files/2020/05/Weekly-Data-Update-26-May-2020-1.png>). The current issue of the journal presents a single-center study on COVID-19 from Delhi, India on this issue [38].

Hepatic transplant recipients present special concerns from the standpoint of vulnerability to COVID-19 (see Table 1 for mortality outcomes in different centers). A single-center report described 6 COVID-19 infection episodes among 150 transplant recipients, of whom 3 died [39]. Those who died were over 65 years of age and had undergone transplant over 10 years ago. Early data from the two combined international registries (up to April 20, 2020) included 39 individuals with 9 (24%) deaths [40]. Age, duration of transplant, and treatment agents used did not appear to influence mortality risk. More data from the registry accrued over time would, however, clarify the issue.

Table 1 Mortality outcomes in reported cases of Corona Virus Disease-19 (COVID-19) among liver transplant centers in different countries and the combined international registries*

Author/s	Country	Number of cases	Mortality (%)
Gruttadauria et al. [47]	Italy	24	5 (21%)
Fernandez-Ruiz et al. [48]	Spain	6	2 (33%)
Pereira et al. [49]	USA	13	NA
Tschopp et al. [50]	Switzerland	5	0
Bhoori et al. [39]	Italy	6	3 (50%)
Webb et al.**	Multicenter registry	122	23 (19%)

* Isolated case reports are excluded from this Table

**The multicenter international registry is updated up to May 26, 2020 (<https://covidcirrhosis.web.unc.edu/>)

Does the occurrence of intercurrent COVID-19 impact the manifestations, course, outcome, and treatment of premorbid GI disorders?

Theoretically though, even with the pathophysiological inter-relatedness of COVID-19 and other GI disorders through the ACE-2 receptors, there are scanty evidence to suggest that the occurrence of intercurrent COVID-19 influences the manifestations of pre-existing chronic GI disorders [41, 42]. In the two combined international registries of the 288 cases with hepatic cirrhosis included until May 26, 2020, 43% experienced decompensation in the form of increased ascites, spontaneous bacterial peritonitis, or worsening encephalopathy grades during COVID-19 episodes. Variceal hemorrhage was reported in only about 1%. Worsening jaundice was reported in nearly 18% of patients in the registry. A preliminary analysis of the registry data (until April 20, 2020) demonstrated an association between decompensation of liver cirrhosis and mortality [43]. Most deaths in individuals with liver cirrhosis and COVID-19 episodes were still attributed to respiratory failure with only 12% of deaths being liver-related. Nonetheless, treating physicians should be mindful of the possibility of decompensation of liver cirrhosis during COVID-19 episodes. In the current issue of the journal, a single-center study from Delhi, India showed poor outcome of cirrhosis patients with COVID-19 [38].

An isolated case of hemorrhagic colitis in an individual with COVID-19, who was previously using lisinopril, has been described [29]. It would be expected that some individuals with IBD might experience flare-ups as natural events during their disease course [44]. These should, however, not be attributed to co-incident COVID-19. Lastly, however, the isolation of the virus from fecal samples has implications for fecal microbiota transplants [45, 46]. Although presently undocumented, COVID-19 might potentially spread during fecal microbiota transplants, and hence, it might be prudent to demonstrate negative viral RT-PCR multiple times in donor samples before accepting fecal samples for transplant.

Our understanding of the manifestations and comorbidities of COVID-19 are rapidly evolving and are likely to advance as more data emerge. At the moment, however, healthcare

systems across the world are overwhelmed by care provision to critically ill individuals with COVID-19. This precludes systematic analyses of clinical manifestations especially in relation to comorbid conditions. The creation of web-based international platforms by GI specialists to pool in rare presentations and the effect of COVID-19 on rare premorbid GI disorders will be immensely useful in sorting out some of the issues and is a welcome step. Many unanswered questions will perhaps be suitably addressed with time.

Compliance with ethical standards

Conflict of interest ANSB, VM, RM, and AS declare that they have no conflict of interest.

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