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Gastrointestinal Manifestations of COVID-19: An Evidence-based Review

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ABSTRACT

The first cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection were reported in December 2019, triggering a global health crisis with a coronavirus pandemic-19 (COVID-19). Fever, a dry cough, and shortness of breath are the most common symptoms. GI symptoms, on the other hand, have been found to be an essential clinical finding in the course of the disease. Furthermore, though the pathophysiology of these symptoms is still being researched, the relationship between SARS-CoV-2 and Angiotensin-Converting Enzyme type 2 (ACE2), which is expressed in both the respiratory and gastrointestinal systems, is implicated in viral pathogenesis as a key clinical finding in the progression of the disease. Gastrointestinal manifestations of disease has turned out to be a distinct entity and there is a need to update ourself on this issue as we need high index of suspicion to rule out this infection when patients initially present with gastrointestinal manifestations.

KEYWORDS: Coronavirus, Covid-19, SARS-CoV-2, Liver, Gastrointestinal tract, Pancreas.

Introduction

SARS-COV-2 infection which started in December 2019, caused by novel coronavirus, has had a worldwide reach and has already caused more than 0.5 million deaths in India till march 2022. It belongs to Coronaviridae family and is a spherical particle with crown like projection having an average diameter of 125nm. Viral envelope consists of lipid bilayer with attached proteins, Nucleocapsid – N protein and positive sense single stranded RNAgenome[1]. It is mainly a pulmonary infection; however gastrointestinal symptoms have also been increasingly shown to occur. It has appeared that up to 40% patients having COVID-19 may experience gastrointestinal symptoms like diarrhea, nausea, vomiting, anorexia and abdominal pain[2]. Various pathophysiological mechanisms have been proposed for gastrointestinal manifestations of COVID-19, including binding of corona virus spike protein to host Angiotensin- Converting Enzyme type 2 (ACE-2) receptor.

In this review, we summarize the pathogenesis, manifestations, mode of transmission, gastrointestinal complications, and discuss the effects on gastrointestinal diseases when the patient is suffering from COVID-19.

Pathophysiology

The pathophysiological instruments of this are multifactorial, and incorporate the virus attachment, recognition of receptor, protease cleaving and membrane fusion of its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS)[3].

SARS-CoV-2 enters cells primarily by protein S binding to ACE-2 receptors[4,5]. ACE2 receptors are found in a variety of human cells, including lung epithelial cells, brain neuronal and glial cells, and cardiomyocytes[6]. Furthermore, ACE2 is highly expressed in glandular cells of the gastric, duodenal, and rectal epithelia, as well as in the small intestinal endothelial cells and enterocytes[4,5]. SARS-CoV-2 also enters cells via receptors for transmembrane protease serine 2 (TMRPSS2), a cell surface protein expressed by epithelial cells in specific tissues, such as small intestinal epithelial cells, with co-expression of ACE2 and TMPRSS2 found in enterocytes and esophagus[6].

COVID-19 and Diarrhea

The diarrhea could be caused by direct invasion of intestinal epithelial cells by the virus, change in ACE2 function, and, as a result, interference in the gastrointestinal tract's equilibrium due to a change in the intestinal microbiota[7,8]. The virus's negative control of ACE2 may also limit the generation of key metabolites involved in intestinal homeostasis. As a result, bacteria with physiological functions are reduced, while pathogenic bacteria flourish[9]. The host immunological response, which is capable of causing damage to the intestinal epithelium due to the impacts of the cytokine storm, is another probable cause of diarrhea[8,9,10]. Many studies have found that patients with COVID-19 have higher levels of cytokines and chemokines, particularly interleukin-2, IL-6, IL-7, and IL-10. Furthermore, when compared to non-severe patients, Tumor necrosis factor (TNF)-alpha levels are much higher in individuals with severe illness[6,11,12]. Furthermore, when the intestinal microbiota is altered, the Th17 response is activated, resulting in the generation of IL-17A, which aids in the recruitment of neutrophils and can induce immunological damage in the GI tract[10,12]. There is an increase in faecal calprotectin as a result of the intestinal inflammatory response, which is directly connected with increase in IL-6[13]. Calprotectin and IL-6 levels were higher in COVID-19 patients who had diarrhea[6]. Intestinal symptoms during COVID-19 are also influenced by the so-called gut-lung axis. In addition to being an essential indicator of severity, pneumonia caused by the virus induces systemic tissue hypoxia, which can cause alterations in the intestinal microbiota and tissue damage (gut and liver, for example)[9,14]. Another etiology could be the activation of coagulation which promotes thrombin generation, activating complement system and inhibiting fibrinolysis, which triggers thrombo-inflammation, leading to deposition of microthrombi and microvascular dysfunction in the gastrointestinal system[14].

COVID-19 and Hepatobiliary Involvement

In some cases of SARS-CoV-2 infection, certain hepatic alterations are found, which can be due to direct damage to cholangiocytes and hepatocytes, as well as the cytokine storm, which causes systemic involvement and is implicated as a likely cause[12,14]. ACE2 is prominently found in bile duct cells and liver biopsies findings have confirmed the probable viral route in injured liver tissue[15,16]. Liver function abnormalities could be indicated by abnormal Aspartate aminotransferase (AST) values and Alanine aminotransferase (ALT)[15], accompanied by slightly raised bilirubin values. The gut-liver axis also plays a role, as a result of the modification of the intestinal microbiota and the inflammatory process, metabolites are produced and transported to the liver via the portal vein causing liver injury[12]. Cholangiocytes have high levels of ACE2 and are susceptible to SARS-CoV-2 infection; their impairment indicates yet another potential source of liver injury and dysfunction[17,18,19].

Hypoxemia due to ARDS, systemic inflammatory response syndrome, dysfunction of other organs can contribute to ischemia or reperfusion-induced liver dysfunction in patients with COVID-19. Hypoxia-induced hepatocyte death and production of inflammatory

cytokines can be found in hepatic ischemia/reperfusion models. Moreover, histopathological findings of the liver in COVID-19 patients showed the watery degeneration of a few hepatocytes, which was probably due to ischemia and hypoxia19.

COVID-19 is particularly dangerous in elderly people and persons with comorbidities[20,21]. One hypothesis is that ageing causes a reduction of microbial diversity, which leads to increased inflammatory vulnerability[6].

Gastrointestinal Manifestations

Interestingly, the first case of COVID-19 in United States reported nausea, vomiting and diarrhea on admission, after the patient returned from a trip to Wuhan, SARSCoV-2 was found in fecal sample after RT-PCR of respiratory samples revealed the virus[22]. As a result, it's worth noting that the most common gastrointestinal symptoms linked to SARS-CoV-2 include nausea, vomiting, abdominal discomfort, and diarrhoea[23].

According to a research conducted in California, 31.9 percent patients with COVID-19 experience GI symptoms, with anorexia, nausea/vomiting, and diarrhea being the most frequent and mild[24]. Other investigations have found cases of patients who solely had gastrointestinal symptoms as a result of COVID-19[23,25], highlighting the relevance of their awareness. Furthermore, in the Chinese province of Zhejiang, 11 percent of COVID-19 cases had gastrointestinal symptoms, with diarrhea being the most frequent, affecting roughly 70% of patients with gastrointestinal symptoms and 8% of all cases. Another significant factor was the 10.8% risk of liver problems associated with elevated AST) and/or ALT[26]. The other comorbidities of COVID-19 involving gastrointestinal tract include hypomotility-related complications, gastrointestinal bleeding, and bowel ischemia[26]. The presence of gastrointestinal symptoms was associated with a high risk of ARDS, noninvasive mechanical ventilation and tracheal intubation, but not with mortality in COVID-19 patients[26].

Anosmia and dysgeusia have been added to the COVID-19 core symptoms, with 52.7 percent reporting olfactory dysfunction and 43.9 percent reporting gustatory dysfunction[27]. These symptoms are most likely caused by COVID-19 neuropathy, which occurs due to SARS-CoV-2 entering the olfactory epithelium by ACE- 2 expressing cells and travels to the olfactory bulb by axons extending to the olfactory nucleus in the pyriform cortex[28,29].

When comparing adults and children, it was discovered that GI symptoms exist in both groups. However, children are more likely to present with vomiting, but adults are more likely to have diarrhea and abdominal pain. Further more, diarrhea may be the first sign of SARS-CoV-2 infection before a diagnosis is made[12,30]. Further more, while comparing critical patients to non-critical patients, it was discovered that critical patients were more likely to experience gastrointestinal symptoms[23]. As a result, even if gastrointestinal signs, whether simultaneous or isolated, are not significant, they are nevertheless valuable in identifying the COVID-19 spectrum. It can also be used as an alternate preventative and surveillance technique, resulting in more rapid and efficient care, as well as a lower rate of spread, complications, and mortality.

Laboratory Findings

SARS-CoV-2 infection has been linked to liver impairment in addition to lung and gastrointestinal problems, according to studies[31,32]. Despite the modest expression of the angiotensin II-converting enzyme (ACE2) in liver cells (approximately 2.6 percent of the total number), there is a significant expression of this receptor in bile duct cells (approximately 59.7% of the total number)[33]. This percentage is comparable to that of type 2 alveolar cells, implying that infection and viral replication are possible in these sites[31]. The bile duct is in control of the liver's regeneration and immunological response. As a result, the virus may infect bile duct cells, causing liver malfunction and damage[30]. These changes are suggested by increased quantities of ALT and AST, as well as a modest increase in total bilirubin and a drop in albumin levels[30]. A storm of pro-inflammatory cytokines is released at the site of viral infection in the hepatic duct, which results in a continual decline in lymphocyte count and an increase in neutrophil count in laboratory findings[33]. The amounts of IL-1, IL-6, and TNFα in the blood are also found to

be increased. Antibiotics, antivirals, and antipyretics, which are commonly used to treat COVID-19, may also cause liver damage, as measured by changes in AST/ALT levels[32]. All of these abnormalities were discovered in patients with severe infection stages.

Mode of Transmission

Feco-Oral transmission

SARS-Cov-2 virus has a resistant envelope, which allows it to withstand a wider range of adverse conditions, patients show a prolonged excretion of viral RNA in feces, raising the possibility of feco-oral transmission and retransmission via the formation of aerosols from infected feces, as well as the possibility of indirect contamination[34,35].

A research of 4,243 patients found that the SARS-CoV-2 RNA was present in stool of 48.1 percent of the patients during the disease's onset. After a negative respiratory test, 70.3 percent of faecal samples were found to be positive for viral RNA[36]. In another study, SARS- CoV-2 RNA was found in the faeces of 39 (53.42 percent) of the 73 patients studied, and the viral RNA was found in the faeces of 17 (23.29 percent) patients long after the virus had cleared the respiratory tract[37]. Another study of 4805 people found that 40.5 percent of patients had their viral genetic material retrieved from their feces[38]. In addition, a meta-analysis involving 95 studies found a prevalence of 51.8 percent of SARS-CoV-2 RNA positivity in faeces from infected individuals, with a mean persistence time of 12.5 days after negative results in respiratory tract samples. Nonetheless, the presence and persistence of viral genetic material in faeces, however, does not imply that the virus is infectious.

However, studies have found that cultures collected from the GIT contain live SARS-CoV-2, supporting the theory of viral feco-oral transmission[39]. Positive samples from toilets and sinks have been observed in some studies[40], which supports the notion of feco-oral transmission.

According to certain investigations, the SARS-CoV-2 RNA content in faeces is lower than that found in respiratory swabs shortly after symptoms appear[41]. These numbers, however, decline more quickly in the pulmonary site than they do in the stool. Patient's faecal samples remained positive on average for 27.9 days following the onset of symptoms, 11.2 days longer than respiratory samples[34], according to Wu et al. In terms of viral RNA content in faeces, Wolfel et al. found a range of 103-107 copies of RNA/g of faecal sample, depending on the day the sample was collected[39].

Nonetheless, the presence of viral RNA in faeces does not imply the presence of viable viruses, as evidenced by several studies which showed that despite the presence of RNA, positive cultures could not be obtained, with the exception of Wang et al, who found viable viruses in two of the four samples he cultured out of 44 faecal samples with SARS-CoV-2 RNA[17].

If oral-fecal transmission of SARS-CoV-2 is verified, other problems would arise, such as the virus spreading through waste water, especially in underdeveloped nations where cleanliness is lacking38. It's worth noting that the presence of the virus in sewers allows waste water epidemiology to be used in conjunction with other methods to determine the existence and prevalence of COVID-19 in the communities[42].

Furthermore, considering the risk to the health of professionals involved, prudence in handling the faeces of infected patients is highly recommended[43], as should appropriate preparation for procedures such as colonoscopy and physical examination itself. Even if the respiratory samples are negative, the prolonged time of viral elimination in faeces necessitates more attention to hand and sanitary cleaning, as well as the broadening of isolation and discharge criteria that now only consider the respiratory site[44].

SARS-COV-2 with Comorbidities

IBD and the SARS-CoV-2 Pandemic

Patients with IBD do not appear to be at an increased risk of infection with SARS-CoV-2 or the development of COVID-1945. Patients with IBD who do not have SARSCoV-2 infection should not stop taking their IBD medications and should continue to get infusions at appropriate infusion centers however drugs including

thiopurines, methotrexate, and tofacitinib should be avoided in patients with IBD who have been exposed to SARS-CoV-2 but have not acquired COVID-19[46].

Biological therapy administration should be postponed for two weeks while symptoms of COVID-19 are monitored. During the viral infection, patients with IBD who develop COVID-19 should avoid thiopurines, methotrexate, tofacitinib, and biological treatments[46]. These can be restarted after complete symptom clearance or, if available, when follow-up viral testing is negative or serologic tests show that the illness has progressed to the convalescent stage. The severity of COVID-19 and the severity of IBD should lead to thorough risk–benefit analyses of COVID-19 treatments and escalating IBD treatments[46].

COVID-19 and Hepatobiliary System

As we already know that ACE2 is found in biliary and liver epithelial cells, the liver is a possible infection target[47]. Coronavirus particles have been found in hepatocyte cytoplasm, together with typical histological signs of viral infection[48,49,50]. The prevalence of increased serum liver biochemistry in COVID-19-infected hospitalized patients ranges from 14 percent to 83 percent[51-60]. Early in the illness phase, AST and ALT levels are typically 1-2 times the upper limit of normal (ULN), with normal to mildly elevated total bilirubin. Direct viral infection of hepatocytes, immune-related damage, and medication hepatotoxicity could all be the factors[57-59,61].

Alkaline phosphatase and gamma glutamyl transferase levels are elevated in 6% and 21% of COVID-19 patients, respectively[62]. In severe COVID-19 cases, liver injury is more common than in moderate instances[56,58,63]. Patients with COVID-19 have reported a few instances of severe acute hepatitis[52,57,58,64]. Age, male gender, BMI, diabetes mellitus, medicines (e.g., ritonavir, hydroxychloroquine, remdesivir, tocilizumab), and inflammatory markers (IL-6, ferritin) are all predictors of peak abnormal liver tests >5x ULN[58,60]. In minor COVID-19 cases, liver impairment is usually transitory and does not require any therapy other than supportive care[65]. COVID-19 severity is indicated by a low serum albumin level on admission to the hospital[55,58,66-68]. AST is frequently higher than ALT and is linked to severe COVID-19 and mortality, which could indicate non-hepatic damage[54,58,59,63]. Baseline liver test abnormalities are linked to an increased likelihood of ICU admission and tend to recover over time[69]. They also are associated with a higher chance of death and severe COVID-19[62]. Peak levels of alkaline phosphatase are linked to the probability of death and may indicate a poor prognosis[69]. In children with COVID-19, serious liver injury is uncommon; when it does occur, elevations in ALT or AST are usually moderate (less than 2 times the ULN)[70,71].

COVID-19 has been associated to multisystem inflammatory syndrome in children (MIS-C), a post-infectious entity with overlapping symptoms of Kawasaki illness and positive COVID-19 antibody testing[72]. Histologic evaluation of the liver has been limited, but it has thus far been nonspecific, ranging from mild microvesicular steatosis with mixed lobular and portal activity to localized necrosis[49,73,74].

It is not contraindicated to start hepatitis B treatment in a patient with COVID-19, and it should be considered if there is a clinical suspicion of a hepatitis B flare or while starting immunosuppressive therapy. Initiating hepatitis C treatment in a patient with COVID-19 is not always necessary, and can be postponed until the patient has recovered from COVID-19[75].

SARS-COV-2 and Pancreas

Wang et al. in a study of 52 patients found that 17 percent of patients with COVID-19 pneumonia had pancreatic damage, defined as any abnormalities in amylase or lipase. They did not, however, show clinical signs of pancreatitis. Because the ACE2 receptor is extensively expressed in pancreatic islet cells, SARS-CoV-2 infection might hypothetically result in islet destruction and acute diabetes[76].

Other GI Manifestations

Bowel ischemia, transaminitis, gastrointestinal hemorrhage, pancreatitis, Ogilvie syndrome, and severe ileus may occur in critically ill COVID-19 patients[77]. Patients who have a severe case of COVID-19 are more likely to present with abdominal pain. According to a recent study, there is no substantial difference in appetite

loss, diarrhea, nausea, or vomiting between patients with severe and non-severe illness[78].

Conclusion

As a result, it's clear that SARS-CoV-2 infection can cause gastrointestinal symptoms in addition to respiratory symptoms, either before or during the disease. The ACE2 receptor appears to play an essential part in the infection's pathogenesis, which could explain the intestinal symptoms, as well as probable liver damage, adding to the list of COVID-19 symptoms. However, the feco-oral route as a possible route of SARS-CoV-2 transmission is controversial, particularly in poorer nations without proper sanitation facilities, necessitating further research into their true involvement in disease progression.

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