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MINI-REVIEW

Gastrointestinal and Hepatobiliary Manifestations of Coronavirus Disease-19: Potential Implications for Healthcare Resource-Deficient Countries

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Abstract: It is believed that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved and developed with broad tissue tropism as hospitalized coronavirus disease (COVID)-19 patients have been showing non-respiratory manifestations. As evidenced in recent clinical studies, even if the results of oral or nasal swab test were negative, the tests on rectal swab, feces, and blood samples in recovered patients could still be positive. The viral shedding in these specimens provides a cautionary warning that fecal-oral route may represent a hidden trigger of rampant spread of COVID-19 in developing countries with poor sanitization. In addition, the presence of SARS-CoV-2 in rectal, fecal, and blood samples endorses gastrointestinal and hepatic origins for the pathogenesis of COVID-19. These observations highlight the importance for the infected patients to obtain accurate and timely diagnosis as well as the treatment of COVID-19 and its associated non-respiratory symptoms to reduce the risk of spreading the infection through unexpected routes. This review also discusses the potential implications of fecal-oral transmission of COVID-19 for healthcare resource-deficient countries.

Keywords: COVID-19, SARS-CoV-2, Gastrointestinal manifestations, Hepatobiliary manifestations

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1 Introduction

In general, the introduction of novel pathogenic viruses into a population often causes highly contagious infection and devastating epidemics. The ongoing pandemic of coronavirus disease (COVID)-19, which at the time of writing has affected over 5.1 million and killed approximately 330,000 million people has taken a toll on the health and lives of human[1,2]. Although the origin and source of its transmission still remain unclear, genetic analysis showed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, shares a very close similarity (~96%) with horseshoe bat SARS-like coronavirus, indicating potential zoonotic origin of this virus in bats[3,4]. Due to its zoonotic origin, the lack of natural immunity makes SARS-CoV-2 aggressively pathogenic in humans[4]. SARS-CoV-2 has an incubation period of 2 – 14 days, and the infected individuals will manifest symptoms such as fever, cough, headache, and breathlessness[5]. The severity of the disease can range from mild pneumonia to severe illness and death[5].

Scientists have confirmed that COVID-19 can be transmitted among humans through multiple modes, such as nasal droplets and aerosols[5]. Deprivation of pre-existing, natural

immunity to fight the virus is an important reason why the development of adaptive immune responses against SARS-CoV-2 is delayed in humans. In addition, COVID-19 patients in old age or with pre-existing chronic conditions such as respiratory, cardiac, kidney, and liver conditions are associated with higher mortality rate[5]. In the absence of an approved antiviral drug or vaccine, healthcare agencies have to provide supportive care to the patients, and government authorities are enforcing safety guidelines to thwart the spread of the infection. In addition to this, several non-respiratory symptoms have also been observed in COVID-19 patients. The present article discusses the gastrointestinal symptoms and hepatobiliary manifestations of COVID-19, and how the potential gastrointestinal and hepatic origin of the virus is implicated in the increasing burden on healthcare resource-deficient countries.

2 Biology of SARS-CoV-2

The SARS-CoV-2 is the seventh known human coronavirus with positive-sense single-stranded RNA genome (~2.9 kb), classified within the genus *Betacoronavirus*[6]. The viral RNA consists of twelve open reading frames, which code for its two non-structural polyproteins in the 5'-end and four structural polyproteins as well as six accessory proteins in the 3'-end[7].

The non-structural replicase polyproteins pp1a and pp1b undergo proteolytic processing to further produce eleven (nsp1–nsp11) and five (nsp12–nsp16) smaller proteins, respectively. These proteins are necessary for viral mRNA synthesis and replication and involved in the modulation of host innate immunity. Of the structural proteins, the crown-shaped spike (S), envelope (E), and membrane (M) glycoproteins form the outer shell of SARS-CoV-2, while the nucleocapsid (N) contains the viral genomic RNA. The "S" protein contains a structural subunit called "S1" that binds to the human cell-receptor angiotensin-converting enzyme 2 (ACE2). The "M" is a transmembrane glycoprotein that is crucial for cell membrane fusion, whereas the "E" protein is required for virion assembly and morphogenesis in infected cells[7]. Although the "N" protein of SARS-CoV-1 is known to be highly antigenic and used as a serological marker, its serological application for virus detection still remains to be established in SARS-CoV-2-infected individuals[8]. The six accessory proteins are involved in the interaction with host factors and the modulation of innate immune system. Unlike other betacoronaviruses that have seven accessory proteins, SARS-CoV-2 owns six and lacks an accessory protein called the "3b"[9].

3 Gastrointestinal symptoms of COVID-19

In general, among the patients with COVID-19, ~80% of them remain asymptomatic or show very mild flu-like symptoms, ~15% are the severe cases that require hospitalization, and remaining 5% develop respiratory failure, septic shock, and even multiorgan failure[10]. Several clinical studies reported that a proportion of COVID-19 patients manifested gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and abdominal pain within 1–2 days before the onset of fever and dyspnea[11-17]. In a recent study, more than 60% of COVID-19 patients showed gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abnormal liver function[12]. More importantly, endoscopy results demonstrated the presence of SARS-CoV-2 RNA in esophagus, stomach, and duodenum in the biopsies of three patients.

In another study, detection of SARS-CoV-2 RNA in anal or rectal swabs and blood of hospitalized COVID-9 patients has been also reported, and a higher proportion of positive results in anal swab test than oral swab test suggested the possibility of SARS-CoV-2 transmission through fecal-oral route[13]. Furthermore, in a clinical investigation of COVID-19 confirmed cases, a persistent observation that rectal swabs were viral RNA positive even after the results of nasopharyngeal swab test became negative was made, presenting the evidence of viral shedding through the gastrointestinal tract[14]. In further clinical studies, stool specimens of COVID-19 patients have also been found positive for SARS-CoV-2, even after the clearance of the virus[15-17]. In spite of these findings, it is still not known that whether the presence of SARS-CoV-2 RNA is a proof of shedding of live viruses and supports their infectious nature in the specimens from where they were derived.

In view of these recent observations, however, we should still be alarmed about the possibility that SARS-CoV-2, similar to some well-known enteric viruses, can be transmitted through contaminated water or food in countries with inadequate sanitation facilities. Furthermore, these findings also showed us that the pathogenesis of COVID-19 may have gastrointestinal and hepatobiliary origins based on the presence of SARS-CoV-2 RNA in rectal, fecal, and blood samples. Therefore, with accurate and timely diagnosis and treatment of COVID-19 pneumonia as well as other non-respiratory symptoms, the spread of the infection through unknown routes and fatality rate can be reduced efficiently.

4 Hepatobiliary manifestations and inflammation of COVID-19

Moreover, SARS-CoV-2 has been linked to mild-to-moderate liver injury as indicated by changes of parameters such as elevated levels of serum aminotransferases (alanine aminotransferase and aspartate aminotransferase) and bilirubin, hypoproteinemia, and prothrombin time prolongation, which are supported by liver histopathology[18-21]. Molecular analysis of COVID-19 patients has shown elevated expression of ACE2 in cholangiocytes as compared to hepatocytes, suggesting that SARS-CoV-2 might directly affect intrahepatic bile ducts[22]. A recent study also showed that 15.46%

of COVID-19 patients manifested liver dysfunction[23]. Moreover, in severe cases of COVID-19, liver dysfunction is also observed in company with greater activation of coagulative and fibrinolytic pathways as well as altered profiles of platelets, neutrophil, and lymphocytes[16].

Notably, among the known human coronaviruses (HCoVs), the HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1 cause respiratory infections in immunocompromised individuals, infants, and the elderly, while SARS-CoV-1 and Middle-East respiratory syndrome (MERS-CoV) cause respiratory, gastrointestinal, and hepatic diseases[24]. SARS-CoV-1-infected individuals showed mild-to-moderate increase in aminotransferases and serum albumin or sometimes, decrease in serum albumin levels, which are possibly caused by cytotoxic T-cell-induced liver inflammation or hepatocyte damage as a result of activation by cytokines[24-26].

Previously, higher levels of serum cytokines such as interleukins (IL-1, IL-6, and IL-10) have been reported in patients infected by SARS-CoV-1, along with abnormal liver function, suggesting a possible correlation between liver damage and inflammatory responses[27]. IL-6 is an important inflammatory cytokine that plays a central role in the development and progression of liver diseases. Significantly higher levels of serum IL-6 have been detected in alcoholic or non-alcoholic cirrhosis, toxin-induced hepatitis, and viral hepatitis patients[28]. In line with this, it is possible that SARS-CoV-2 is able to cause viral hepatitis while inducing a dysregulated innate immune response in the infected individuals. Considerable release of cytokines, such as IL-6 that binds to its receptor on the lungs and other cells, would cause severe inflammatory responses in SARS-CoV-1- or MERS-CoV-infected patients[29,30]. Consistent with this finding, activated T lymphocytes and mononuclear macrophages have been reported to produce IL-6 in SARS-CoV-2-infected patients[31], possibly giving rise to IL-6-mediated inflammatory responses in COVID-19. Very recently, treatment with tocilizumab, an antagonist to IL-6 receptor has been shown to restore peripheral lymphocytes counts in critically ill COVID-19 patients without obvious adverse reactions[32].

5 Current diagnostic and treatment options

The World Health Organization (WHO) has recommended case definitions for COVID-19 where the suspected cases are those with SARS requiring hospitalization and/or a recent history of visiting infected population before the appearance of clinical manifestations[1]. Meanwhile, probable cases of COVID-19 refer to the individuals whose routine test is inconclusive or those who are tested positive, but negative for laboratory evidence of other respiratory viruses. In short, the identification of a COVID-19-positive case requires a laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical manifestations. Plasma- or antibody-based rapid test kits and reverse transcription-polymerase chain reaction are the diagnostic tools to detect SARS-CoV-2, whereas chest X-ray and computed tomography scan are the routine clinical methods for non-invasive pulmonary assessment.

As part of Solidarity Trial, hundreds of treatment and intervention strategies, including antiviral drugs, cytokine antagonists, convalescent plasma therapy, and vaccine candidates, have been registered worldwide[33]. In the United States, an anti-Ebola drug called remdesivir has been granted approval for emergency use, and tocilizumab, an IL-6 antagonist, has entered a Phase 3 clinical trial for assessing its efficacy in hospitalized COVID-19 patients[32,33]. Among eight leading vaccine candidates, mRNA-1273 which is an mRNA vaccine against SARS-CoV-2 is ready for Phase 2 trial in humans[33].

6 Implications of COVID-19 for healthcare resource-deficient countries

The current pandemic is taking a toll on the public healthcare systems of some developing countries as they are unable to support the increasing number of COVID-19 cases. What makes the current plight even worse is that the inadequate sanitation conditions in some resource-poor countries will further aggravate the epidemic. With the latest findings on the positive detection of SARS-CoV-2 RNA in stool samples, it is possible that poor sanitation will fuel the spread of SARS-CoV-2 in any communities, not least the highly dense populations. One possible consequence would be the tremendous increase in the incidence of COVID-19, which eventually places a huge burden on the fragile healthcare systems in some developing countries.

Although SARS-CoV-2 RNA has been detected in stools of infected individuals, it is still not clear whether the virus remains viable and infectious after defecation. Nonetheless, a recent *in vitro* study has reported that the stool-derived SARS-CoV-2 can infect Vero E6 cells, indicating the possibility of its fecal-oral or fecal-respiratory transmission through aerosolized feces[34]. This is supported by a piece of evidence derived from a study on hundreds of SARS-CoV-1-infected residents living in a private housing estate which is located in Hong Kong[35]. Later, investigation of the residence building's structure showed that high concentrations of coronavirus in the feces and the aerosolization due to hydraulic action inside the drainage pipes contributed to the generation of virus-laden aerosols, indicating aerosolization of feces-derived virus as a possible source of infection. Therefore, poor hygienic practices and insufficient maintenance of sewage or drainage pipelines may render more people vulnerable to the infection. While this putative route of infection remains to be elucidated, more studies are still required to show that whether infectious amounts of viable SARS-CoV-2 can be found in the stool samples.

Developing countries generally have populations with relatively younger age structure, and the older populations

account for a lesser proportion. Despite that, the elderly groups can hardly escape from the perils of COVID-19 if they live in high-density populations such as those in the developing countries. Hence, in the conventional sense, the demographic structure and poor sanitation may put the healthcare resource-deficient countries at the disadvantage in face of the new pandemics, like COVID-19.

7 Conclusion

The infection of SARS-CoV-2 is associated with aggressive clinical manifestations, including non-respiratory manifestations such as gastrointestinal symptoms and hepatic manifestations. The detection of viral RNA in rectal swabs, stool, and blood samples implies that fecal-oral route could be a potential transmission mode of SARS-CoV-2. This finding may raise concerns that incomplete sewage system and poor sanitation practices might contribute to worse COVID-19 outbreaks which further encumber the frail healthcare systems in some regions.

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Conflicts of interest

None.

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