

Potential of Fecal-Oral Transmission and Gastrointestinal Manifestation of COVID-19

Randy Adiwinata*, Visakha Revana Irawan*, Jonathan Arifputra*,
Bradley Jimmy Waleleng**, Fandy Gosal**, Luciana Rotty**, Jeanne Winarta**,
Andrew Waleleng**, Marcellus Simadibrata***

*Department of Internal Medicine, Faculty of Medicine,

Universitas Sam Ratulangi/Prof. dr. R. D. Kandou Hospital, Manado

**Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine,

Universitas Sam Ratulangi/Prof. dr. R. D. Kandou Hospital, Manado

***Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine,

Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:

Randy Adiwinata. Department of Internal Medicine, Faculty of Medicine, Universitas Sam Ratulangi/Prof. dr. R. D. Kandou Hospital Manado Indonesia. Phone: +62-431-7283949. Email: randyadiwinata@yahoo.com

ABSTRACT

The World Health Organization have declared COVID-19 as a pandemic. The COVID-19, caused by SARS-CoV-2, is spreading at an alarming rate and creates a significant worldwide burden to the economy while increasing morbidity and mortality. While COVID-19 was primarily considered as a respiratory-infection disease, several reports have shown that many COVID-19 infected patients have presented or developed some digestive symptoms. Many studies also demonstrated, using reverse transcriptase-polymerase chain reaction method, that SARS-CoV-2 are present in stools or other gastrointestinal tract secretions. All these reports raised the possibility of COVID-19 transmission via the fecal-oral route and the involvement of the gastrointestinal-liver system. Until further studies are available, physicians should be aware of the digestive manifestation of COVID-19 and use universal precautions to avoid the transmission of COVID-19 via the fecal-oral route.

Keywords: COVID-19, Coronavirus, gastrointestinal, liver, pandemic, infection

ABSTRAK

Badan Kesehatan dunia (World Health Organization/WHO) telah menyatakan COVID-19 sebagai suatu keadaan pandemi. COVID-19, disebabkan oleh SARS-CoV-2, menyebar dengan cepat dan memberikan dampak beban ekonomi akibat tingginya angka kesakitan dan kematian. COVID-19 diketahui sebagai penyakit pernafasan, akan tetapi beberapa laporan menunjukkan bahwa pasien COVID-19 juga mempunyai gejala gangguan pencernaan. Beberapa studi menunjukkan bahwa dengan penggunaan metode reverse transcriptase-polymerase chain reaction, SARS-CoV-2 juga ditemukan pada faeces atau sekret saluran cerna lainnya. Laporan tersebut menimbulkan hipotesa terkait kemungkinan penularan COVID-19 melalui jalur fecal-oral dan keterlibatan sistem pencernaan dalam patogenesisnya. Hingga dibuktikan dengan penelitian lebih lanjut, para praktisi kesehatan hendaknya waspada mengenai kemungkinan manifestasi pencernaan pada pasien penderita COVID-19 dan menegakkan kewaspadaan universal selalu untuk menghindari kemungkinan transmisi COVID-19 melalui fecal-oral.

Kata kunci: COVID-19, Virus Corona, Pencernaan, Hati, Pandemi, Infeksi

INTRODUCTION

The novel Coronavirus (COVID-19) has been declared as a world pandemic. It is caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), genus β Coronavirus. COVID-19 was first identified in Wuhan, China, at the end of 2019.^{1,2} By the end of March 2020, COVID-19 had spread to 202 countries and had infected 634,835 people and caused 29,891 deaths worldwide.¹ Fever and respiratory symptoms are the major symptoms of COVID-19 infection, but digestive symptoms are also present in some of the patients.

Based on recent studies, SARS-CoV-2 ribonucleic acid can be found in fecal specimens, which leads to the idea that SARS-CoV-2 can infect the gastrointestinal tract and transmit via the fecal-oral pathways.³ This review article will discuss the manifestations and infection of COVID-19 in the digestive tract.

Evidence of SARS-CoV-2 Traces in Saliva and Feces

Several studies have shown the detection of SARS-CoV-2 in the gastrointestinal secretion products, mainly saliva and stool. Detection of SARS-CoV-2 in the saliva has raised the possibility of virus transmission and awareness among dentists when performing dental procedures. A study has shown that selected strains of SARS-CoV-2 have remain detected in saliva for 29 days after infection. SARS-CoV-2 may be present in saliva, through (1) the liquid droplets frequently exchanged between the upper and lower respiratory tract; (2) SARS-CoV-2 accessed the oral cavity through the crevicular fluid; (3) SARS-CoV-2 directly infects major-minor salivary gland.⁴ To et al. have discovered that SARS-CoV-2 could be detected in salivary specimens from 20 of 23 subjects included in their study. The highest salivary viral load was detected during the first week when the symptoms occurred. The SARS-CoV-2 detected viral load declines gradually after the first-week onset.⁵ Further studies are still required to both characterize the SARS-CoV-2 viral load in the saliva and to validate the diagnosis of COVID-19 using salivary samples.

Previous studies have concluded that the SARS-CoV-2 RNA remained present in both stool specimens and anorectal swabs of COVID-19 patients, even after the swab result from upper respiratory tract was already negative. These findings may indicate that the COVID-19 virus was persistent in shedding on the gastrointestinal tract even after viral clearance in the respiratory tract.⁶ Both the first COVID-19 cases

reported in the United States and Europe turned up positive for the detection of SARS-CoV-2 in their stools.^{7,8} The first COVID-19 patient in the United States was tested positive for SARS-CoV-2 in his stool using the reverse transcriptase polymerase-chain-reaction (RT-PCR) on the seventh day of illness.⁷ Two of the first five cases in Europe had positive stool detection in the first few days of illness, while they did not have any digestive symptoms.⁸

Zhang et al conducted a retrospective analysis of 14 laboratory-confirmed cases of COVID-19 pneumonia. They found that 35.7% of the patients had positive stool samples for SARS-CoV-2 nucleic acid. They demonstrated that the accuracy of detection using either the stool or the oropharyngeal swab was similar.⁹ Xu et al presented other evidence that further raised the possibility of virus shedding in the gastrointestinal tract and the possibility of fecal-oral transmission. They found that 8 among ten pediatric COVID-19 patients aged 2 months to 15 years old were positive for COVID-19 based on RT-PCR results from rectal swabs. After follow-up, those patients remained positive, even after the nasopharyngeal swab turned negative.¹⁰ Xiao et al observed 73 COVID-19 patients. About 39 (53.4%) patients were found to be positive for COVID-19 in their stool, with the duration ranging from one to twelve days. Moreover, 17 (23.3%) patients remained positive for COVID-19 in stool after being negative in their respiratory samples.¹¹ All those evidence have demonstrated that COVID-19 can be present in the stools of some COVID-19 confirmed cases, and that viral shedding on the gastrointestinal tract may last longer compared to the respiratory tract. There is also a lack of correlation between the presence of digestive symptoms and the presence of positive tests from stool samples.^{3,8-11}

Gastrointestinal - related COVID-19 Pathophysiology

Coronaviruses are a family of single-stranded enveloped DNA viruses that consists of four major genera. SARS-CoV-2 have an almost identical genome sequence with SARS-CoV. Structurally, the SARS-CoV has a well-defined composition comprising 14 binding residues with human angiotensin-converting enzyme 2 (ACE-2). It was reported that the coronavirus S protein is a significant determinant of virus entry into host cells. In the case of SARS-CoV-2, the spike glycoprotein (S protein) on the virion surface mediates receptor recognition and membrane fusion. The cleavage of the SARS-CoV S protein is facilitated by cathepsin L in endosomes, indicating a mechanism of

receptor-mediated endocytosis. During viral infection, the trimeric S protein is cleaved into S1 and S2 subunits. S1 subunits contain the receptor-binding domain (RBD), which directly binds to the peptidase domain (PD) of ACE-2, whereas the S2 is responsible for membrane fusion and viral infectivity.^{3,11-14} Aside from membrane fusion, the clathrin-dependent and independent endocytosis also mediated SARS-CoV entry. After the virus enters the cells, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are then inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by combining the genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment. Finally, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.^{3,11-14}

The mechanism for gastrointestinal tract infection of SARS-CoV-2 is proposed to be related to the ACE-2 cell receptor. The binding affinity of ACE-2 receptors is one of the most important determinants of infectivity. Some cells in the human body have ACE 2 receptors such as AT2 lung cells, upper esophagus, glandular cells of gastric, stratified epithelial cells and enterocytes of the ileum and colon. The interaction of the claw-like ACE2-PD in complex with the RBD or the S protein of SARS-CoV is a crucial molecular detail. Esophageal epithelium is composed mostly of squamous epithelial cells, which express less ACE-2 than glandular epithelial cells. Thus, ACE-2 staining in the esophageal mucosa is very unlikely to bear desired results. After SARS-COV-2 binds to ACE2 receptors via glycoprotein S, the endocytosis process begins. Then, virus-specific RNA and proteins are synthesized in the cytoplasm to assembly new virions, which can be released to the gastrointestinal tract. When a virus infects, enterocyte cells increases the gastrointestinal wall permeability to foreign pathogens, producing enteric symptoms such as diarrhea.^{3,13,14}

Reported Gastrointestinal Manifestation of COVID

COVID-19 infection is mainly regarded as a respiratory infection, which affects the respiratory tract with common manifestations such as dry cough, running nose, shortness of breath, and fever.¹² However, several published case reports have shown that many COVID-19 patients had gastrointestinal manifestations (Table 1) and signs of liver injury. Holshue et al. reported the first case of COVID-19 in the United States of which the patient came with a complaint of persistent dry cough and a 2-day history of nausea and vomiting, followed by abdominal discomfort and diarrhea during admission. His stool was tested positive for COVID-19 using RT-PCR.⁷

Pan et al have released a report regarding the characteristics of COVID-19 patients in Hubei with digestive symptoms. This study has revealed that among 204 COVID-19 patients, there are 103 patients (50.5%) with digestive symptoms of which a lack of appetite was most common (78.6%), followed by diarrhea (34%), vomiting (3.9%), and abdominal pain (1.9%). There were 6 patients with only gastrointestinal symptoms without respiratory symptoms. They also found that COVID-19 patients with digestive symptoms have demonstrated a higher level of liver enzymes and a worse clinical course.¹⁵

Another descriptive study was conducted by Zhang et al., which found that up to 39.6% of 140 COVID-19 patients in Wuhan had GI symptoms. Nausea was the most common GI symptom (17.3%), followed by diarrhea (12.9%), anorexia (12.2%), abdominal pain (5.8%), belching (5.0%), and vomiting (5.0%).¹⁶

Yu et al. found that among 10 COVID-19 pediatric patients, three patients had symptoms of diarrhea without other GI symptoms.¹⁰ Qiu et al. also found that 6% among 36 COVID-19 infected children in Zhenjiang had either a diarrhea or vomiting symptom.¹⁷ Contrast findings was reported by Guan et al., who analyzed 1099 positive COVID-19 hospitalized patients. They found that diarrhea (3.8%) and nausea or vomiting (5.0%) were uncommon manifestations.¹²

Table 1. Presentation of gastrointestinal symptoms in Coronavirus infection^{10-12,15-20}

Study	Subject (n)	Age (years old)	Male (%)	Lack of appetite	Nausea	Vomiting	Diarrhea (%)	Abdominal pain
Xu et al	10	0-15*	60	NA	NA	NA	30	NA
Xiao et al	73	0-78*	56.2	NA	NA	NA	35.6	NA
Guan et al	1099	47 (35-58)**	58.1	NA	5%	5%	3.8	NA
Pan et al	204	52,9±16***	52.5	78,6%	NA	3.9%	34	1.9%
Zhang et al	140	25-87*	50.7	NA	17,3%	5%	12.9	5.8%
Qiu et al	36	1-16*	63.9	NA	NA	6%	6	NA
Luo et al	183	53,8***	55.7	98%	73%	65%	37	25%
Zhou et al	254	15-87*	45.3	NA	8.3%	5.9%	18.1	1.2%
Jin et al	74	46,1±14,2***	50	NA	13.5%	14.7%	71.6	NA

NA: Data not available, *Presented as range, ** Presented as Median (Interquartile range), *** Presented as Mean ± Standard Deviation

A recently published review article by Wong et al. has described several published studies regarding the digestive manifestation of COVID-19, of which they found that diarrhea was a complaint among 2.0-10.1%, while nausea and vomiting were found in 1.0-10.1% COVID-patients. The variable-frequency number of reported GI symptoms between the studies is an indication for the need for further study to identify the exact cause of said variations and determine whether digestive symptoms are specific for COVID-19 or not.³

Elevated Liver Enzymes among COVID-19 Patients

Several studies have shown that the liver may be affected by COVID-19 infection. While jaundice or ascites is not commonly reported as a clinical manifestation of COVID-19, laboratory result has commonly shown elevations of liver enzymes. Pan et al. reported that patients with digestive symptoms had significantly higher elevated AST and ALT compared to those without digestive symptoms.¹⁵ Wong et al. have found that elevated liver enzyme levels were reported 14.8-53.1% among COVID-19 patients based on several published reports.³ Severe liver injury is more commonly found in a severe condition of COVID-19. Mild bilirubin levels elevation and decreased albumin levels can also be present.^{3,21-23}

The exact mechanism of liver injury in many COVID-19 patients was still unclear. Liver injury may be caused by several mechanisms such as possible direct liver injury by COVID-19 or related to COVID-19 management. The use of high-level positive end-expiratory pressure during mechanical ventilation may lead to hepatic congestion. Ischemic hepatitis due to the hypoxic condition in the acute respiratory distress condition may also serve as a possible explanation.²¹⁻²³ The use of several drugs during COVID-19, such as: chloroquines; macrolides; quinolones; and lopinavir/ritonavir may also lead to drug-induced liver injury. However, all those probable mechanisms require further study, as many elevated liver enzymes were present without any previous treatment, nor are they severely hypoxic.²² Other explanation may be related to the dysregulated innate immune response, which leads to liver injury. The role of cytotoxic T cell in response to COVID-19 infection should be further evaluated. Dysregulated immune system in response to SARS-CoV-2 infection may lead to the cytokine-storm and multiple organ damage. Interleukin-2, interleukin-6, interleukin-7, tumor necrosis factor- α , Th17, macrophage inflammatory protein 1- α were some significantly elevated pro-inflammatory cytokines in

severe COVID-19 patients. Based on the common sepsis model, hypoxic liver injury affects the bile metabolism leading to cholestasis. That, and the cytokine-storm condition altogether may play a part in liver injury.^{3,21-23}

Nowadays, it is postulated that the ACE-2 serves as the entry point of COVID-19. Direct liver injury may be explained by the detection of ACE-2 receptor in bile duct cells and epithelial cell of the liver, which is minimal in hepatocytes. During the acute phase of liver injury, the proliferation of hepatocytes may increase to restore liver function. This compensatory mechanism may lead to an upregulated ACE-2 expression in the liver.²³ Xu et al. have conducted pathological examinations of the liver of deceased COVID-19 patients, demonstrating moderate microvesicular steatosis and mild lobular activity.²⁴ Other autopsy reports by Liu et al have shown lobular focal necrosis with infiltration of neutrophils, hepatic sinuses congestion with microthrombosis, and monocytes and lymphocytes in the portal area.²⁵

The Implication of Gastrointestinal and Liver Involvement related to COVID-19 Prognosis

Regarding infection-related markers for COVID-19 patients, there were no significant differences in both procalcitonin and C-reactive protein (CRP) between patients with and without GI-related symptoms. Of COVID-19 patients with GI symptoms, acute respiratory distress syndrome (ARDS), liver injury, and shock occurred as a complication in 6.76%, 17.57%, and 1.35% of cases, respectively. ARDS occurs significantly more common in COVID-19 patient groups with GI symptom compared to the non-GI symptoms (6.76% vs. 2.08%, $p = 0.034$). The liver injury also significantly occurs more commonly among COVID-19 patients with GI symptom (17.57% vs. 8.84%, $p = 0.035$).²⁰

About 6.76% of COVID-19 patients with GI symptoms were transferred to and managed with mechanical ventilation in the ICU, which was significantly higher than 2.08% in COVID-19 patients without GI symptoms ($p = 0.034$).²⁰ COVID-19 patients without GI symptoms were more likely to be cured and discharged from the hospital than COVID-19 patients with GI symptoms (60% vs. 34.3%). This may be caused by a more severe disease course, as patients who initially do not have typical respiratory symptoms may suffer from later stages of the disease down the line or may suffer from viral replication in the digestive tract, which causes more severe illness.²⁶

Higher body temperature (more than 38.5°C) indicates a higher severity in COVID-19 patients with GI symptoms when compared with those without GI symptoms. GI symptoms may cause COVID-19 patients to be more susceptible to electrolyte disturbances, such as decreased in serum sodium levels significantly ($p = 0.016$). Symptoms of fatigue, shortness of breath, and headaches are also significantly higher in COVID-19 patients with GI symptoms. It was due to higher fever and increased electrolyte imbalance.²⁰

As outlined before that, liver injury in COVID-19 patients may be caused due to the sepsis condition. Cai et al have reported that, at admission, severe COVID-19 patients in Zhenzhen had significantly higher level of ALT, AST, total bilirubin, and gamma GT level compared to non-severe patients. Liver injuries also more commonly found among severe COVID-19 patients compared to non-severe patients (36.2% vs. 9.6%).²⁷ A cohort study involving 1099 COVID-19 patients by Guan et al have shown that liver injury has more commonly occurred in severe and critical cases.¹² Wang et al have discovered that ALT, AST, and total bilirubin levels are significantly higher among COVID-19 patients that require ICU admission.²⁸ Several other reports with similar findings had also been published.^{29,30} All this evidence may point out the possible relationship of liver injury with the severity of the COVID-19 condition.

Current and Future Direction with Gastrointestinal Issue Related with COVID-19

On March 15, the Joint GI society in America released recommendations regarding endoscopy and outpatient GI services regarding the COVID-19 pandemic. They recognized that the virus may be present in stools and that a potential fecal-oral transmission must be considered. Liver injuries, which are marked by elevated liver enzymes, were found in 20-30% of COVID-19 infected patients. They strongly recommend rescheduling elective non-urgent endoscopic procedures. Patients with GI symptoms should be screened for respiratory symptoms, fever, travel history, and recent contact with COVID-19 patients. All patients should have their body temperatures checked-up upon arrival at the endoscopy unit. Always equip adequate protective equipment and dispose of them accordingly. Physical-distancing between patients in the endoscopy unit should also be emphasized.³¹

The Indonesian Society for Digestive Endoscopy (ISDE) has also released a protocol regarding

endoscopic procedures in Indonesian endoscopic centers related with the COVID-19 pandemic, which are mainly emphasizing the need to sort candidate patients to undergo endoscopy and maintain the hygiene of the endoscopic room. Practitioners should always be aware of the potential fecal-oral transmission route of COVID-19 and consider GI manifestations as the sign of COVID-19 infection. Future research should be conducted to prove the transmission. More evidence regarding the COVID-19 detection in GI secretion products, epidemiological models for transmission, and cohort with larger sample sizes regarding GI manifestation in COVID-19 positive patients are needed.

CONCLUSION

Several published reports have demonstrated that COVID-19 can be detected in stools. Positive stool samples are not correlated with the presence of digestive symptoms that might otherwise be present in some COVID-19 patients. Several mechanisms have been proposed to explain the occurrence of liver injury in COVID-19 patients. Further studies are needed to confirm the possibility of fecal-oral COVID-19 transmission.

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