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GASTROINTESTINAL MANIFESTATIONS IN COVID-19 INFECTION

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Abstract

Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 originating from Wuhan, China, has caused an outbreak throughout the world and caused death. The severe acute respiratory syndrome coronavirus 2 enters the body via the angiotensin-converting enzyme 2 receptor, followed by priming by transmembrane serine protease 2 and provides an overview of the respiratory system's main clinical manifestations, such as shortness of breath, cough, and fever. The gastrointestinal tract also expresses angiotensin-converting enzyme 2 receptors so that it manifests in the gastrointestinal tract, namely decreased appetite, diarrhea, vomiting, and abdominal pain. Complaints in the gastrointestinal tract can appear first or together with complaints in the respiratory tract. Patients with gastrointestinal symptoms have a more severe disease degree than patients without gastrointestinal symptoms, and the majority have a high fever. When infected by Coronavirus disease 2019, there is a prolonged condition of dysbiosis even though the severe acute respiratory syndrome coronavirus 2 virus has been eliminated, and respiratory symptoms are not available. The expression and distribution of angiotensin-converting enzyme in the oral cavity and the discovery of the severe acute respiratory syndrome coronavirus 2 virus in the feces indicate a potential route of infection from Coronavirus disease 2019 through the fecal orally. Pathological findings in the gastrointestinal tract of Coronavirus disease 2019 patients are still limited and still require further research, especially concerning the association with the patient's previous history of the disease. For the treatment of Coronavirus disease 2019, so far, there has been no special therapy given. All treatments are supportive. In patients who experience diarrhea, evaluating their dehydration status, monitoring electrolyte abnormalities, antispasmodic drugs, and probiotics have been performed.

Keywords: *severe acute respiratory syndrome coronavirus 2, Coronavirus disease 2019, gastrointestinal, inflammatory bowel disease.*

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dan masuk dalam genus betacoronavirus [Gorbalenya A et al., 2020]. COVID-19 first reported in Wuhan, China, in December 2019 which then spread to other countries and causes global health problems. The World Health Organization (WHO) in March 2020 designated COVID-19 as a pandemic. Infection caused by the SARS CoV2 virus has infected nearly 6.2 million people and caused the death of nearly 400 thousand people worldwide. Indonesia is one of the countries infected with COVID-19 with a total of nearly 28,000 sufferers with a total of 1,500 more people who died [*WHO, 2020*]. The large number of infected patients, the rapid spread time, and the high mortality rate in a short time span not only cause problems in the health system but also have a negative impact on the world economy today [*Chakraborty I, Maity P, 2020*].

Coronavirus disease 2019 which is caused by the corona virus mainly provides a description of clinical manifestations in the respiratory system,

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such as shortness of breath, coughing, and fever. Manifestations of the respiratory system of patients infected with COVID-19 have a very varied picture, ranging from symptoms that are mild, moderate, and severe to cause severe hypoxia. The most frequent symptoms of SARS-CoV-2 infection are fever and respiratory disorders, such as coughing and shortness of breath [*Huang C et al., 2020*]. Although the SARS-CoV-2 virus attacks the airways more, about 11.4% of COVID-19 patients have gastrointestinal system disorders [*Jin X et al., 2020*]. Manifestations other than the respiratory system are suspected because the SARS-CoV-2 virus enters cells through angiotensin-converting enzyme 2 (ACE2) receptors. These receptors are located throughout the body, including esophageal epithelial cells and enterocytes in the ileum and colon so that this COVID-19 infection may cause gastrointestinal manifestations [*Tian Y et al., 2020*].

Gastrointestinal disorders accompany respiratory system disorders, and fever in COVID-19 patients, about 50.5%. It is very important to be vigilant for patients who show extrapulmonary symptoms because some COVID-19 patients may not be accompanied by respiratory symptoms to go undiagnosed and get the right treatment too late [*Pan L et al., 2020*]. Patients with gastrointestinal symptoms were associated with a longer duration of illness, but in the short-term observation of patients with gastrointestinal symptoms, the tendency to be admitted to the intensive care unit was reduced, and a lower mortality rate [*Nobel Y et al., 2020*]. Several recent studies have shown the discovery of ACE2 receptors on oral epithelial cells. This allows the oral cavity to be a way of transmission of the SARS-CoV virus. Besides, the results of examination on faeces also showed the presence of viruses [*Chen Y et al., 2020*]. Besides, the results of examination on faeces also showed the presence of viruses. These findings indicate the possibility of the spread of SARS-CoV virus through the faecal-oral route, so there is a need for action and prevention to avoid transmission [*Amirian E, 2020*]. Observing the problems above, a literature review was conducted to discuss gastrointestinal manifestations in COVID-19.

Coronavirus

COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this virus is included in the genus beta-coronavirus [*Gorbalenya A et al., 2020*]. Betacoronavirus is an enveloped, single-chain RNA virus. This virus can infect wild animals to humans and can cause outbreaks [*Xu X et al., 2020a*]. Coronavirus in humans was first discovered in the 1960s with common cold symptoms. This virus also causes Severe Acute Respiratory Syndrome (SARS) in 2003 and middle east respiratory syndrome (MERS) in 2016 [*Su S et al., 2016*].

The RNA genome of Coronavirus encodes polyproteins in both structural and non-structural proteins, including spikes (S), envelopes (E), membranes (M), and nucleocapsid proteins (N). These structural and non-structural proteins play a role in the pathophysiology and virulence mechanisms of SARS-CoV [*Du L et al., 2009*]. On genomic sequence examination, SARS-CoV-2 has similarities with SARS CoV and MERS CoV. The differences are mainly in ORF1a and spike [*Xu X et al., 2020a*]. Through phylogenetic mapping, it can be seen that there were mutations in the virus spike that occurred in November 2019 and then infected humans almost all over the world [*Angeletti S et al., 2020*].

Angiotensin-converting enzyme 2 (ACE2) is an enzyme that attaches to the outer surface (membrane) of cells in several organs, such as the lungs, arteries, heart, kidneys, and intestines. ACE2 works to catalyze the change in angiotensin II (a peptide vasoconstrictor) to angiotensin 1-7 (a vasodilator). ACE2 resists the activity of the angiotensin converting enzyme (ACE) by reducing the amount of angiotensin-II and increasing Angiotensin 1-7 [*Chappell M et al., 2014*]. Angiotensin 1-7 acts on its receptors and exerts vasodilation effects. Thus, the enzymes ACE and ACE2 work opposite in regulating blood pressure. Researchers have found that the SARS-CoV virus can enter its host cells by binding to ACE2 as its re-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

ceptor [*Du L et al., 2009*]. In comparison, the SARS-CoV-2 spike protein has 76.5% similarity in amino acid sequences with SARS-CoV and their homologous protein spike. This shows that both coronaviruses have the same way to infect their host cells [*Xu X et al., 2020b*]. Other findings prove that the SARS-CoV-2 virus can recognize human ACE2 receptors more efficiently than SARS-CoV, causing the higher ability of SARS-CoV-2 to transmit from humans to humans. This is proven by the ease with which the COVID-19 virus spread throughout the world to cause a pandemic compared to SARS-CoV [*Wan Y et al., 2020a*]. The presence of excessive ACE2 expression in humans will increase the severity of COVID-19 infection. Polymorphisms in the ACE2 gene, ACE2 mRNA expression, and ACE2 protein polymorphisms affect a person's susceptibility to SARS-CoV-2 infection and COVID-19 disease output [*Devaux C et al., 2020*].

ACE-2 can be found in oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, large intestine, skin, thymus, bone marrow, spleen, liver, kidney, brain, pulmonary alveolar epithelial cells, small intestinal enterocyte cells, endothelial cells venous arteries, and smooth muscle cells [*Hamming I et a., 2004*]. The discovery of ACE2 receptors in addition to the lungs is thought to be the cause of multi-organ failure in severe COVID-19 patients [*Devaux C et al., 2020*]. The human gastrointestinal tract that expresses the ACE2 receptor is the glandular cells in the gastric, duodenal, and rectal epithelium. The number of receptors in the gastrointestinal tract supports the entry of SARS-CoV-2 in the body [*Xiao F et al., 2020*]. The initial occurrence of infection by SARS-CoV-2 in the body occurs malfunctioning in ACE2. This is probably due to a binding with the virus causing steric hindrance or downregulation of the expression of ACE2 mRNA and ACE2 protein [*Devaux C et al., 2020*].

Pathophysiology

COVID-19 infection is not limited to the respiratory system, but the virus also replicates in enterocytes, causing diarrhea and shedding in feces, urine, and other body fluids [*Wang Z et al., 2020*]. The SARS-CoV-2 virus enters the body through the ACE2 receptor, followed by priming by TMPRSS 2. It is also suspected that FURIN in S SARS-CoV-2 protein also has the potential to increase the priming process against ACE2 receptor binding [*Lukassen S et al., 2020*]. The process of a virus infecting its host consists of 5 stages, namely attachment, penetration, biosynthesis, maturation, and release. Initially, the virus attaches to the host receptor. The process of endocytosis or penetration occurs. After that, the virus releases its viral content; then viral RNA enters the nucleus to replicate [*Yuki K et al., 2020*]. Replication and release of viruses cause body cells to undergo pyroptosis and release molecules that stimulate epithelial cells, endothelial cells, and alveolar macrophages to release pro-inflammatory cytokines and chemokines. The entry of the SARS-CoV-2 virus will activate the innate immune system, such as macrophages. In addition, T cells and B cells, which are adaptive immunity, are activated by APCs (dendritic cells) to eliminate viruses and stimulate the secretion of cytokines [*Zhang C et al., 2020*]. Cytokines and chemokines include IL-6, IP-10, and macrophage inflammatory protein 1α (MIP1α, MIP1β) and MCP1. This mechanism stimulates monocytes, macrophages, and T cells to trigger a wider inflammation [*Tay M et al., 2020*]. The existence of an imbalance of Th1 and Th2 in COVID-19 is thought to play a role in the severity of the disease, where Th2 is more dominant than Th1, which plays a role in eliminating viruses through the activation of macrophages and cytotoxic T cells. Dominant Th2 explains the onset of gastrointestinal symptoms in some COVID-19 patients who experience shortness of breath [*Roncati L et al., 2020*].

The mechanism of diarrhea in COVID-19 patients is not fully understood. It is suspected that viral infection can cause direct damage to the tissue given the discovery of ACE2 receptors in the gastrointestinal tract's epithelium, changes in intestinal permeability, impaired absorption of enterocytes, and inflammation of the intestine. When viewed from the pathophysiological process, if there is an infection by SARS-CoV-2, the inflammatory process occurs as a result of the infiltration of plasma cells and lymphocytes, lamina propria in the stomach, duodenum, and rectum, which experience edema, diffuse inflammation of the submucosa of the small blood vessels of the small intestine. In addition, mesenteric ischemia is suspected, which triggers a small bowel injury [*D'Amico F et al., 2020; Gupta A et al., 2020*].

ARDS caused by Cytokine Storm is the leading cause of death from COVID-19. Infection by SARS-CoV-2 triggers the emergence of a local immune response, activation of macrophages, and monocytes. Apart from cytokines, T and B cells are the main adaptive immune response [*Tay M et al., 2020*]. Cytokine storm occurs because of an uncontrolled systemic inflammatory response due to the release of large amounts of proinflammatory cytokines such as interferons, interleukins, chemokines, colony-stimulating factors, and TNF-alpha [*Coperchini F et al., 2020*]. Another study found that the severity of COVID-19 was related to TNF-α, IL-6, and IL-10. In addition, patients admitted to the ICU had decreased CD4 and CD8 T cells [*Chen Y et al., 2020*]. Through understanding the role of cytokine storm, specific immunotherapy can be a very important therapeutic modality [*Maggo S et al., 2020*].

Gastrointestinal Pathology in COVID-19

Information on pathological findings in COVID-19 patients is still limited. Pathological findings are more in the airway system, such as pleurisy, pericarditis, lung consolidation, and pulmonary edema [*Hanley B et al., 2020*]. Viral nucleocapsid proteins were detected in the cytoplasm of the stomach, epithelial cells of the duodenal and rectal glands, but not in the esophageal epithelium, suggesting that gastrointestinal symptoms of SARS-CoV-2 infection may be caused by the direct viral attack as well as tissue and organ damage due to immune response [*Tian Y et al., 2020*]. A study showed that on an electron micrograph examination, virus particles with a size of 70-100 nm were found in the lungs, trachea, kidneys, and large intestine. This study also found that the colon mucosal epithelial cells found in the virus particles were known to have degeneration, and of the 12 patients who had severe COVID-19, there was one patient (8.3%) who experienced multifocal gastric hemorrhage [*Bradley B et al., 2020*].

The liver histology shows moderate microvascular steatosis and a slight increase in lobular activity. However, it cannot be proven that this condition is caused by COVID-19 or a result of administering drugs [*Xu Z et al., 2020*]. Histology of the liver found sinusoidal dilatation, accumulation of glycogen in steatosis focal macrovesicular hepatocytes, and atypical lymphocytes in the portal tract. These findings are also atypical and following the basic disease description in the autopsy patient, namely chronic lymphocytic leukemia [*Tian S et al., 2020*]. In line with the previous findings, the pathological features show chronic changes in the liver following the features of preexisting comorbid diseases. Inflammation of the liver is mild, although some patients develop inflammation of the lymphocytic periportal [*Bradley B et al., 2020*].

Clinical Manifestations and Diagnosis

COVID-19 infection can cause mild, moderate, or severe symptoms. The main clinical symptoms that appear are fever (temperature >38°C), cough, and difficulty breathing. Moreover, it can be accompanied by heavy tightness, fatigue, myalgia, gastrointestinal symptoms, such as diarrhea, and other respiratory symptoms [*Huang C et al., 2020*]. Research conducted on 140 COVID-19 patients in Wuhan, China obtained clinical features, such as fever, cough, weakness, shortness of breath and gastrointestinal symptoms such as diarrhea, nausea, anorexia, abdominal pain, belching, and vomiting [*Zhang J et al., 2020*]. Patients can have mild, moderate, severe to acute symptoms. Based on previous studies, most of the patients treated had moderate symptoms, 63% [*Pan L et al., 2020*]. In severe cases, there are worsening rapidly and progressively symptoms, such as ARDS, sepsis, septic shock, acidosis, heart failure, and coagulation system dysfunction within a few days [*Zhou F et al., 2020*]. In some patients, the symptoms appear mild, even not accompanied by fever. Most patients have a good prognosis, with a small proportion in critical condition and even die. In previous studies, as many as 66.66% of patients did not need oxygen supplementation [*Young B et al., 2020*]. Physical examination with severe symptoms can be found in decreased consciousness, increased pulse frequency, increased breath rate, normal or decreased blood pressure, and increased body temperature. Oxygen saturation can be normal or decreased, as well as rales in both lungs [*Jin Y et al., 2020*].

Radiological examination can show a very varied picture and is very similar to infections caused by other corona viruses, such as SARS and MERS. Abnormal imaging features are found in 85% of patients and about 75% of both lungs (bilateral). The lung areas that are often affected initially are

the supleural and peripheral lungs. The picture of consolidation often occurs progressively, especially in the elderly [*Reddy S, 2020*]. Radiological features found were bilateral opacity, subsegmental consolidation, lobar or lung or nodule collapse, and groundglass appearance. At the initial stage, small multiple plaque shadows are seen with clear internal changes that show in the peripheral lungs and then develop into multiple ground-glass shadows and infiltrate in both lungs. In severe cases, pulmonary consolidation can be found, even "white-lung" and pleural effusion [*Xu X et al., 2020a*]. Some patients require a combination of CT scan, rapid test, and RT PCR because in some patients there is a false negative RT PCR result with CT scan leading to COVID-19 [*Xie X et al., 2020*]. A normal CT scan does not eliminate the possibility of a COVID-19 diagnosis because about 15% of COVID-19 patients give a normal radiological picture [*Reddy S, 2020*].

BLOOD CHEMISTRY TESTS: Complete peripheral blood (leukocytes can be found normal or decreased; lymphocyte counts decrease. The neutrophil-lymphocyte ratio (NLR) is related to the severity of the infection, which can be used as a prognostic biomarker for the patient [*Yang A et al., 2020*]. In most patients, LEDs and CRP increase), blood gas analysis, liver function (in some patients, liver and muscle enzymes are increased), kidney function, blood glucose, electrolytes, physiological hemostasis (PT/APTT, d Dimers) and procalcitonin [*Jin Y et al., 2020*]. An increase in D-dimer is a sign of a hypercoagulable state and can be a predictor of mortality in COVID-19 patients [*Zhang L et al., 2020*].

Detection of the airways can also be done to detect or rule out diagnoses caused by other pathogens, such as adenovirus, parainfluenza, respiratory syncytial virus (RSV), mycoplasmas, chlamydia, and influenza viruses A and B [*Jin Y et al., 2020*]. Zhang J. and co-authors (2020) reported from 140 patients who participated in their observations of the detection of pathogens carried out in COVID-19 patients, Mycoplasma pneumonia and RSV were also found.

Some cases of COVID-19 with gastrointestinal complaints such as diarrhea can occur with or without respiratory symptoms. Thus, patients who present with initial complaints of diarrhea who have previously been in contact with sufferers of COVID-19 should be suspected even though there are no symptoms of cough, shortness of breath, sore throat or fever. If possible, the patient is examined with samples taken from the airways and feces. It is of concern that gastrointestinal symptoms such as nausea, vomiting or diarrhea are symptoms that are also commonly seen by other diseases, but when there is a pandemic condition with a high prevalence of COVID-19, all patients with acute gastrointestinal symptoms accompanied by a history of contact should be considered infected with COVID-19. Failure to recognize these patients early can increase the risk of the spread of COVID-19 itself.

A study conducted in Wuhan, China, reported that 23% of patients had gastrointestinal symptoms, 34% had gastrointestinal symptoms, and respiratory symptoms, while 43% showed respiratory distress symptoms alone [*Han C et al., 2020*]. Gastrointestinal symptoms include decreased appetite, diarrhea, vomiting, and abdominal pain. As many as 50.5% of patients treated with gastrointestinal complaints [*Pan L et al., 2020*]. Diarrhea lasted an average of 5.4 days (± 3.1 days) with a frequency of bowel movements per day of 4.3 (± 2.2). This study also found the length of treatment of COVID-19 patients with longer gastrointestinal symptoms, i.e., for 16 days since the complaint first appeared. Researchers suspect the length of treatment required in patients with gastrointestinal symptoms has a higher viral load than patients with respiratory problems alone [*Han C et al., 2020*]. In the short-term observations, it was found that patients with gastrointestinal symptoms such as diarrhea and vomiting at the time of the PCR examination had a significantly higher probability of positive results, 61%, while only 39% had negative results [*Nobel Y et al., 2020*].

Out of total COVID-19 patients who had diarrhea symptoms, 19.4% of them actually complained of diarrhea first and then symptoms appeared in breathing, while the remaining patients got diarrhea symptoms after 10 days after the onset of respiratory symptoms appeared. Mostly, female sex complained of diarrhea (65.7%) compared to men (51.1%). Diarrhea experienced by COVID-19 patients was reported "watery" (52.2%), while complaints of discomfort and stomach pain were

rarely found [*Han C et al., 2020*]. Another study conducted in Wuhan, China, involving 1141 patients confirmed COVID-19 showed that as many as 16% of patients complained that there was a disturbance in their gastrointestinal system. The sex of patients who experience gastrointestinal symptoms is almost the same, 44% in women and 56% in men. The most common symptom found was a decrease in appetite as much as 98%. In addition, other gastrointestinal complaints such as vomiting (65%) nausea (73%), diarrhea (37%), nausea accompanied by vomiting (20%), abdominal pain (25%), abdominal pain accompanied by diarrhea (9%), and all the symptoms mentioned previously as much as 7% were also found. The study also reported that some patients showed more gastrointestinal symptoms than other manifestations, such as the respiratory system [*Luo S et al., 2020*].

Not all COVID-19 patients with gastrointestinal disorders showed fever. Only about 62.4% showed gastrointestinal symptoms accompanied by fever. Diarrhea in patients with COVID-19 occurred before fever in 20.4% of patients, and diarrhea that appeared after a fever occurred in 10.2% of patients, while the remaining showed initial onset of fever and diarrhea which appeared simultaneously [*Han C et al., 2020*]. Meanwhile, Jin-Wei Ai and co-authors showed that all patients who experienced gastrointestinal symptoms also had fever complaints, while not all respiratory complaints were obtained [*Jin-Wei Ai et al., 2020*]. Another study showed that of 204 patients with COVID-19 confirmed, 103 patients (50.5%) had gastrointestinal complaints. Of all these patients, 6 (3%) presented with gastrointestinal complaints alone without respiratory symptoms, while 97% had respiratory and gastrointestinal symptoms. Gastrointestinal symptoms that were often complained of are decreased appetite (78.64%), diarrhea (33.98%), vomiting (3.88%) and abdominal pain (1.94%) [*Pan L et al., 2020*].

Endoscopy found that the epithelium of the gastrointestinal tract of the COVID-19 patient, including the esophagus, stomach, duodenum, and rectum, was damaged [*Xiao F et al., 2020*]. Although COVID-19 can manifest in the digestive system, there are no guidelines for a diagnostic approach with endoscopy given the possibility of transmission of the virus through the faecal-oral [*Tian Y et al., 2020*]. Endoscopy is done very close to the patient, and the distance between officers is also very close. So that in areas with a high COVID-19 incidence, transmission is possible. However, studies in Italy showed the conclusion that the possibility of patients or health care workers contracting COVID-19 after endoscopy was very small. Researchers suspect this is due to the use of appropriate self-protection devices, so some guidelines have been issued to avoid such transmissions [*Repici A et al., 2020*].

Gastrointestinal symptoms as predictors of COVID-19 patients

Previous research investigated 74 patients infected with SARS-CoV-2 with gastrointestinal symptoms, such as diarrhea, nausea, and vomiting. The group of patients with gastrointestinal symptoms has a more severe degree of disease when compared to the group of patients without gastrointestinal symptoms. In the first group, patients experienced more fever >38.5°*C*, the degree of severe disease requiring ventilator, the formation of family clustering, and liver damage marked by the discovery of elevated levels of aspartate transaminase [*Jin X et al., 2020*]. Another study showed that the moderate category's gastrointestinal symptoms accompanied 63% of patients with COVID-19, 13.59% severe, and 22.33% critical. Although gastrointestinal symptoms are more evident in patients who experience worsening, there is no significant difference in length of treatment or mortality rates between groups with gastrointestinal symptoms or groups without gastrointestinal symptoms [*Pan L et al., 2020*]. A meta-analysis study found an association between gastrointestinal symptoms and disease severity, in which patients who had gastrointestinal symptoms were more likely to experience a more severe degree of disease at 17.1% [*Cheung K et al., 2020*].

Another study reported that patients who had symptoms of diarrhea showed more severe respiratory symptoms as many as 53%, whereas patients without symptoms of diarrhea who experienced worsening conditions were around 19%. About 31% of patients with diarrhea needed intensive care and 12% of patients needed ventilator assistance. Whereas in patients without diarrhea, 11% needed intensive care, and 2% needed ventilator

[*Wan Y et al., 2020b*]. Another study reported that there was an increase in gastrointestinal symptoms in patients with worsening of the condition. This result is presumably because the appearance of symptoms in the gastrointestinal tract indicates replication of the virus and viral load in the gastrointestinal tract, thus showing more severe manifestations [*Pan L et al., 2020*]. In contrast to what was reported by others, the study conducted by Lin L. and co-authors (2020) gave different results; there were no statistically significant differences in both general demographic conditions and clinical conditions of patients with gastrointestinal symptoms when compared with patients without gastrointestinal symptoms.

LABORATORY OF COVID-19 WITH GASTROINTESTINAL SYMPTOMS

COVID-19 patients with digestive symptoms on laboratory examination showed improved liver function and prolonged coagulation more frequently than patients without accompanying gastrointestinal symptoms. ALT and AST increased significantly by 21% and 17%, respectively, compared to patients without gastrointestinal symptoms of only 5.9% and 5%, respectively [*Pan L et al., 2020*]. Another study conducted by Yunle Wan and co-authors (2020) compared groups of patients with and without diarrhea. The results showed no significant laboratory value differences between the two groups, including AST, ALT, and activated partial thromboplastin time (APTT) values [*Wan Y et al., 2020a*]. Disorders of the liver are caused by infection with the SARS-CoV-2 virus and are associated with disease severity. Liver disorders in patients with mild symptoms can return to normal without special therapy, whereas liver disorders in patients with severe symptoms require protective liver therapy [*Wang H et al., 2020*].

In addition, a significant increase in prothrombin time of 13.1 seconds was also found. Whereas in patients without gastrointestinal symptoms, the increase was 12.5 seconds. For other indicators of coagulation function, there was no significant difference [*Pan L et al., 2020*]. Viral binding to the ACE2 receptor found in liver and bile duct epithelial cells causes liver damage and leads to increased aminotransferases, decreased albumin, and prolonged prothrombin time [*Aguila E et al., 2020*]. Monocyte counts were also found to be lower in patients with gastrointestinal symptoms with an average value of $0.39x10^9$/L. While for patients without gastrointestinal symptoms, the average monocyte value was $0.46x10^9$/L. Other laboratory values such as complete blood, electrolytes, and kidney function did not show any difference between the two groups [*Pan L et al., 2020*].

Further research still needs to be done to prove the relationship between COVID-19 and improvement in liver function, considering that several factors can still influence such as the use of drugs that can also improve liver function during treatment or the presence of patients with disorders of the liver before.

COVID-19 TRANSMISSION VIA FECAL-ORAL

The expression and distribution of ACE2 in the human body indicates a potential route of infection from COVID-19. Evidence is obtained that ACE2 is expressed in the oral cavity, especially in places with a high number of epithelial cells. Parts of the oral cavity with high ACE2 expression are the tongue then buccal and gingival. These findings support the oral mucosa as a potential route of entry or transmission of COVID-19 infection [*Xu H et al., 2020*]. A study in Singapore reported the first 18 patients diagnosed with COVID-19 who were treated between January and February. This research also conducted virus detection in feces. Of the 18 patients, as many as 8 patients had a virus in their feces. Although there was virus detected in the feces, of all these patients only 50% showed gastrointestinal symptoms, such as diarrhea [*Young B et al., 2020*]. More than 20% of patients infected with SARS-CoV-2 from fecal viral load testing still shows positive results even though examination of the airways has shown negative results. Thus, viral infections in the gastrointestinal tract and transmission through oral faecal transmission can still take place [*Xiao F et al., 2020*].

Although some feces examinations found the SARS-CoV-2 virus, to support the hypothesis of the transmission of the virus through the oral faecal, further research is still needed. Research on the possibility of oral fecal transmission from SARS-CoV-2 must include environmental studies to determine the environmental conditions that support the SARS CoV2 virus to survive and support the occurrence of such transmission. In addi-

tion, studies on enteric involvement and excretion of the SARS-CoV-2 virus in the feces are needed to investigate whether the concentration of SARS-CoV-2 RNA in the feces correlates with the severity of the disease and manifestations in the gastrointestinal system [*Yeo C et al., 2020*]. The presence of gastrointestinal symptoms and the discovery of the SARS-CoV-2 virus have an impact on the treatment and control of infections that prevent transmission. Feces that is not handled properly can be a source of transmission of the virus, especially when aerosols occur [*Wong S et al., 2020*]. Another implication of the possibility of transmission through the fecal-oral route is the need for education of cleaners about possible routes of transmission, training on best practices for sanitation and prevention, including good hand hygiene so as not to become infected with viruses and become carriers [*Amirian E, 2020*].

Gut-Lung Axis and microbiota

COVID-19 not only attacks the respiratory system, but also shows symptoms in the gastrointestinal. Complaints in the gastrointestinal include diarrhea. This diarrhea raises the hypothesis of a link between gut lung axis in COVID-19 patients who have diarrhea. As is known, the intestine has normal flora which has a very important function for the human body, among others as an immune system and metabolic functions. The SARS-CoV-2 virus is thought to cause an imbalance of normal flora in the gut, where there is an increase in the number of opportunistic pathogens and a decrease in beneficial pathogens commensalism [*Zuo T et al., 2020*]. Disturbances in the normal flora of the digestive system also affect the respiratory system through the common mucosal immune system. Vice versa, the disruption of the normal flora of the respiratory system will also affect the gastrointestinal system. Previous study has shown that infections of the airways affect the normal flora of the intestine [*Groves H et al., 2020*]. Previous studies have also shown that respiratory influenza virus and syncytial virus infection can affect the microbiota of the gut [*Yildiz S et al., 2018*]. The researchers suspect the same result occurs when there is an infection by the SARS-CoV-2 virus.

Dysbiosis is a state of imbalance in gut microbiota. This condition often occurs in old age, immunocompromised conditions, and patients with type 2 diabetes mellitus and cardiovascular disease. Patients with this condition are also known to have poor outcomes if infected with COVID-19 [*Dhar D, Mohanty A, 2020*]. When infected by COVID-19, a prolonged dysbiosis condition is obtained even though the SARS-CoV-2 virus has been eliminated, and respiratory symptoms are not obtained [*Zhan J et al., 2020*]. Previous studies have shown that the gut microbiota is an important factor in regulating Ace2 expression in the gastrointestinal tract and influences systemic inflammation in the host body. This is thought to contribute to the gut-lung axis pathology during COVID-19, possibly [*Yang T et al., 2020*].

COVID-19 and Inflmmatory Bowel Disease

Inflammatory bowel disease (IBD), a chronic inflammatory bowel disease, is an autoimmune disease consisting of Crohn's disease and ulcerative colitis, where the disease can occur in remission relapse [*Fakhoury M et al., 2014*]. Immunosuppressive conditions such as those in IBD patients often indicate that viral infection is not showing atypical symptoms [*Estevinho M, Magro F, 2020*].

As previously known, there are many ACE2 receptors in the intestine and colon. The presence of ACE2 receptors is thought to help the absorption of nutrients, where these receptors act as co-receptors. In patients with IBD, there was an increase in ACE2 expression. This is presumably because, in IBD, there is the release of cytokines such as IFN-gamma, which could potentially induce ACE2 expression. In addition, in IBD, mucosal inflammation found also plays a role in increasing ACE2 expression. Although the expression of ACE2 in IBD patients is higher, there is no evidence that IBD patients have a higher risk of suffering from COVID-19. Another aspect that needs to be investigated is whether infection by SARS-CoV-2 in IBD patients can trigger flares. So far, there is no strong evidence related to this [*Neurath M, 2020; Zuo T et al., 2020*].

Another thing that needs to be studied is related to the management of IBD patients during a COVID-19 pandemic, as it is known that IBD patients receive immunotherapy to achieve disease remission. The use of immunotherapy impacts suppressing the intracellular signaling cascade in the immune system, reducing the body's ability to fight pathogens [*Fak-*

houry M et al., 2014]. IBD patients infected with SARS-CoV-2 immunosuppressive use should be stopped first until the infection is resolved, but if based on clinical considerations, the patient must continue therapy with immunosuppressive, and IBD-specific therapy is still given [*Neurath M, 2020*].

Administration of systemic corticosteroids in IBD patients is also advised to gradually reduce the dosage to the smallest dose with optimal effects even if it is possible for patients without systemic corticosteroids. In IBD with flares, it can be considered giving budesonide or beclomethasone [*Al-Ani A et al., 2020*]. To date, there is no strong evidence to suggest stopping specific therapy for previous IBD patients, besides considering patients who have achieved remission if the drugs are previously discontinued, medication can cause flares in these patients and increase the chances of the patient being hospitalized in a pandemic condition. Furthermore, currently, the recommendation given is that IBD patients can continue with the specific therapy that was obtained previously [*Neurath M, 2020*].

COVID-19 THERAPY WITH GASTROINTESTINAL MANIFESTATIONS

For the management of COVID-19, so far no special therapy has been given, all treatments are supportive, so that until now there has been no special treatment for patients with gastrointestinal symptoms. One symptom that often appears in COVID-19 is diarrhea, patients who experience diarrhea in the first step are still evaluated for their dehydration status and if necessary, adequate hydration is given [*Doe W, Barr G, 1981*], monitoring of electrolyte abnormalities that occur such as hyponatremia is preferred in diarrhea patients [*Jin X et al., 2020*]. In patients who get abdominal pain, antispasmodic drugs can be given [*Tian Y et al., 2020*].

In recent study, more antibiotics and antiviral drugs were given to patients who had gastrointestinal complaints, although no further indications were given regarding the treatment [*Pan L et al., 2020*]. Another important thing to note is that antiviral and antibiotic administration can affect the balance of intestinal microbiota, bearing in mind that the lung-axis relationship does not rule out diarrhea [*Dhar D, Mohanty A, 2020*].

The existence of suspicion about the connection of the gut-lung axis in patients with COVID-19 with overcoming the condition of dysbiosis in patients using probiotics is thought to be able to overcome COVID-19 infection [*Kageyama Y et al., 2020*]. As we know, probiotics have a good effect on patients with pneumonia, in which the administration of probiotics decreases the need for ventilators. Although there is no direct evidence of the effectiveness of the use of probiotics in COVID-19, China provides probiotic therapy to patients treated with the critical category [*Gao Q et al., 2020*].

CONCLUSION

COVID-19 caused by SARS-CoV-2 enters the host via the ACE2 receptor. ACE2 receptors are widely expressed by body cells to cause extrapulmonary manifestations, one of which is in the gastrointestinal tract, causing manifestations such as diarrhea, nausea, vomiting, anorexia, and abdominal pain. The expression and distribution of ACE2 in the oral cavity and the discovery of the SARS-CoV-2 virus in the feces indicate a potential route of infection from COVID-19 through the fecal-oral. Patients who have a previous history of chronic inflammatory gastrointestinal diseases such as IBD are thought to have a higher risk of developing COVID-19 and flares but still need further research.

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