

CLINICAL MANIFESTATIONS OF THE GASTROINTESTINAL SYSTEM IN PATIENTS WITH SARS-COV-2 INFECTION

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ABSTRACT

SARS-CoV-2 infection was declared as a pandemic by the WHO since March 11, 2020, with confirmed cases increasing every year. SARS-CoV-2 is one of the variants of coronavirus that has a higher transmission rate, where it is transmitted through infected droplets. SARS-CoV-2 can manifest in the digestive tract. This descriptive study uses a literature study method. Diarrhea was a common symptom of gastrointestinal manifestations in COVID-19 patients. Apart from diarrhea, other symptoms are anorexia, nausea, vomiting and abdominal pain. Gender prevalence varies. The average age of patients exposed to COVID-19 was over 50 years with hypertension as the most common comorbidity. SARS-CoV-2 are associated with Gastrointestinal manifestations which binds to ACE2 on gastrointestinal epithelial cells. SARS-CoV-2 infection causes an imbalance in the gut microbiota that can trigger secondary infections and multiple organ disorders and affect the severity of COVID-19.

Keywords: COVID-19, Gastrointestinal Symptoms, ACE2, Gut Microbiota, Gut-Lung Axis

INTRODUCTION

SARS-CoV-2 infection was declared a global pandemic by WHO since March 11, 2020 with confirmed cases that continued to increase in 1 year. According to WHO as of March 11, 2020, more than 118,000 confirmed cases of COVID-19 and 4,291 deaths worldwide (WHO, 2020). 1 year later, on July 15, 2021, there were 180 million confirmed cases of COVID-19 and 4 million deaths (WHO, 2021). The elderly and those with comorbidities are at high risk of being exposed to SARS-CoV-2. The symptoms of COVID-19 are characterized by febris, cough and fatigue. There are also gastrointestinal symptoms such as

diarrhea, nausea, vomiting, abdominal pain, loss of appetite to anorexia. SARS-CoV-2 manifests in gastrointestinal tract because gastrointestinal epithelial cells expresses ACE2 as a SARS-CoV-2 receptor (Woo, 2020).

Clinical manifestations of the gastrointestinal system in COVID-19 occur through direct infection of the epithelial cells of the digestive tract. ACE2 are used as a transport of membrane-bound amino acids B0AT1. B0AT1 functions in the exchange of amino acids in cells. SARS-CoV-2 which binds to ACE2 can affect B0AT1 so that amino acid transport in the intestine stops. Deficiency of an

amino acid, namely tryptophan, in the small intestine causes impaired activation of mTOR which results in impaired secretion of antimicrobial peptides by paneth cells so that the gut microbiota becomes abnormal. In addition, the cytokine storm that occurs due to the massive release of cytokines in ACE2-expressing cells in the digestive tract can attack healthy body tissues, resulting in primary damage. SARS-CoV-2 that infects the lungs can also cause inflammation and trigger pro-inflammation. As a result, cytokines are released in the lungs and increase CCR9+CD4+ T cells. Furthermore, CCL25 in the small intestine causes changes in flora, causing damage to the immune system in the small intestine and gastrointestinal symptoms (Wang, 2014). Despite the significant insights gained regarding gastrointestinal manifestations in COVID-19 patients, there remains a notable gap in understanding the precise mechanisms by which SARS-CoV-2 induces gut microbiota imbalance and its subsequent impact on the development of secondary infections and multi-organ disorders. Further research efforts are warranted to address this knowledge gap and enhance our comprehension of the complex interplay between viral infection, gut microbiota dysbiosis, and disease severity in COVID-19.

The objective of the research is to comprehensively investigate and describe the gastrointestinal manifestations associated with SARS-CoV-2 infection, including common symptoms such as diarrhea, anorexia, nausea, vomiting, and abdominal pain, while also examining demographic factors such as gender prevalence and prevalent comorbidities. Furthermore, the study aims to elucidate the underlying mechanisms of gastrointestinal involvement in COVID-19, particularly focusing on

the interaction between SARS-CoV-2 and ACE2 receptors in gastrointestinal epithelial cells, as well as the potential impact of gut microbiota imbalance on disease severity and the development of secondary complications.

LITERATURE REVIEW

In humans, it usually causes respiratory tract infections, from the common cold to serious diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The new type of coronavirus is named Severe Acute Respiratory Syndrome Coronavirus (SARS-COV2), and causes Coronavirus Disease-2019 (Covid-19). This disease caused by Coronavirus was unknown before the outbreak in Wuhan, China in December 2019 (Nasution, 2021).

Coronavirus is a zoonosis (transmitted between animals and humans). Research explains that SARS is transmitted from civet cats to humans and MERS from camels to humans. Meanwhile, the animal that is the origin of the transmission of Covid-19 is still unknown. The incubation period for Covid-19 is on average five to six days, with a range between 1 and 14 days but can reach 14 days. The highest risk of transmission is obtained in the first days of the disease due to the high concentration of the virus in secretions. Infected people can be directly contagious up to 48 hours before the onset of symptoms (presymptomatic) and up to 14 days after the onset of symptoms (Anggraeni, 2020). The symptoms experienced are generally mild and arise gradually. Some infected people do not show any symptoms and still feel healthy. The most common symptoms of Covid-19 are fever, fatigue, and dry cough. Some patients may experience aches and pains, nasal congestion, runny nose,

headache, conjunctivitis, sore throat, diarrhea, loss of smell and smell or skin rash (Sibero, 2023).

METHODOLOGY RESEARCH

This descriptive study uses a literature study method. The scientific research articles are reviewed from PubMed, Google

Scholar and ScienceDirect. The search results from the three databases will go through a process of identification, screening, eligibility and inclusion based on inclusion criteria, namely articles at least from 10 international journals indexed by Scimago or national journals indexed by SINTA in the 2016 to 2021 range.

RESULTS RESEARCH

Table 1. Incidence of Gastrointestinal Manifestations in COVID-19 Patients

Article	Subject	Sex	Average age	Comorbidity	Common symptoms	Gastrointestinal symptoms
Zhang et al. ⁵	N= 140 Hospital No. 7 Wuhan	M = 50,7 % W = 49,3 %	57 years (25-87) 70% > 50 years	Hypertension = 30.0% Diabetes mellitus = 12.1%	Fever = 91.7% Cough = 75.0% Fatigue = 75.0% Dyspnea = 36.7%	N = 39.6% Nausea = 17.3% Diarrhea = 12.9% Anorexia = 12.2% Abdominal pain = 5.8% Burping = 5.0% Emesis = 5.0%
Zhang et al. ⁶	N= 164 Wuhan Central Hospital, Tongji Medical School, HuaZhong University of Science and Technology	M = 44,5 % W = 55,5 %	53.0±18 .3 years	38,4%	Fever = 83.5% Dry cough = 36% Fatigue = 62.8% Myalgia = 30.5% Expectation = 25% Dizziness = 14%	Loss of appetite = 56.7% Diarrhea = 37.8% Nausea = 16.5% Abdominal pain = 10.4% Vomiting = 7.9%
Cholankeiril et al. ⁷	N= 166 California	M = 53,4 % W =	50 years (35-67)	Hypertension = 27.8% Chronic lung	Cough = 94.8% Fever = 76.7%	Loss of appetite = 25.3% Diarrhea = 10.3%

			disease = 20.7%	Dyspnea = 58%	Nausea or vomiting = 10.3%
			Diabetes = 16.4%	Myalgia = 52.2%	Abdominal pain = 8.6%
Ramachandran et al. ⁸	N= 31 Brooklyn Tertiary Hospital, New York	W = 57.6 38,7 years %	Hypertension = 71%	Cough = 74.2%	Diarrhea = 14.7%
			Diabetes Mellitus = 38.7%	Fever = 71%	Nausea or vomiting = 10.7%
			Dyslipidemia = 32.3%	Dyspnea = 54.8%	Abdominal pain = 2%
				Fatigue = 61.3%	
				Myalgia = 38.7%	
Huang et al. ⁹	N= 41 Wuhan, China	M = 49.0 73% years W = (41.0-58.0) 27%	Diabetes = 20%	Fever = 98%	Diarrhea = 3%
			Hypertension = 15%	Cough = 76%	
			Cardiovascular disease = 15%	Myalgia/fatigue = 44%	
Jin et al. ¹⁰	N= 74 Zhejiang, China 17 January - 8 February 2020	M = 46.14±1 50,0 4.19 years W = 50,0 %	Hypertension = 16.22%	Fever = 85.14%	Diarrhea = 71.6%
			Diabetes = 9.46%	Cough = 71.62%	Vomiting = 14.9%
			Chronic liver disease = 10.81%	Sputum production = 39.19%	Nausea = 13.5%
			Heart disease = 1.35%	Fatigue = 31.08%	
				Headache = 21.62%	
				Shortness of breath = 10.81%	
Wang et al. ¹¹	N= 138 Wuhan, China	M = 56 years 54,3 % W = 45,7 %	Hypertension = 31.2%	Fever = 98.6%	Diarrhea = 10.1%
			Cardiovascular disease = 14.5%	Fatigue = 69.6%	Nausea = 10.1%
			Diabetes = 10.1%	Dry cough = 59.4%	Vomiting = 3.6%
					Abdominal pain (2.2%)

Aumpan et al. ¹²	N= 40 30 mild 10 severe Thailand	Mild W = 53,3 % Sev ere W = 60,0 %	Mild 29.7±8. 7 years Severe 33.0±10 .8 years	Mild 10.0% Severe 40.0%	Mild Fever 13.3% Cough 66.7% Sore throat = 53.3% Fatigue 0% Dyspnea 3.3% Severe Fever 40.0% Cough 70.0% Sore throat = 30.0% Fatigue 60.0% Dyspnea 60.0%	Mild Anorexia = 16.7% Nausea/vo miting = 0% Diarrhea = 6.7% Abdominal pain = 3.3% Severe Anorexia = 20.0% Nausea/vo miting = 20.0% Diarrhea = 40.0% Abdominal pain = 10.0%
Xu et al. ¹³	N= 62 Zhejiang , China	M = 56% W = 44%	41 years (32-52)	Liver disease = 11% Hypertens ion = 8%	Fever = 77% Cough = 81% Myalgia/fa tigue = 52%	Diarrhea = 8%
Wang et al. ¹⁴	N= 28 Wuhan, China	M = 75% W = 25%	68,6 ± 9,0 years	Hypertens ion = 53,6%	Fever = 92.9% Dry cough = 82.1% Fatigue = 64.3% Dyspnea = 57.1% Expectatio n = 25.0%	Anorexia = 57.1% Diarrhea = 42.9% Nausea = 21.4% Vomiting = 10.7%
Papa et al. ¹⁵	N= 34 Rome, Italy	M = 64,7 %	71 years (64-82)	Hypertens ion = 8%	Fever = 85.3% Dypsnea = 55.8% Cough = 32.35%	8,8%
Cholanke ril et al. ¹⁶	N= 207 Stanford Hospital	M = 50,2 % W = 49,8 %	49 years (34-65)	Hypertens ion 25.5% Chronic lung disease = 20.3%	Fever = 68.6% Cough = 85.4% Shortness of breath = 52.2%	Diarrhea = 10.8% Nausea/vo miting = 10.8% Nausea/vo miting and

			Diabetes = 16.0%	Sore throat = 26.2%	diarrhea = 4.9%
			Cardiovascular disease = 11.7%	Myalgia = 51.0%	Abdominal pain = 7.1%
			Metabolic syndrome = 9.2%		
			Chronic kidney disease = 4.4%		
			Chronic liver disease = 2.7%		
	N= 206	M = 62.5 44,1 % W = 55,8 %	Hypertension = 27.2%	Fever = 67.0%	Loss of appetite = 34.0%
			Diabetes = 10.2%	Cough = 25.7%	Vomiting = 11.7%
			Cerebrovascular disease = 8.3%	Chest pain = 23.8%	Diarrhea = 32.5%
			Chronic lung disease = 3.9%	Shortness of breath = 14.6%	Abdominal pain = 4.4%
	Union Hospital, Tongji Medical University	M = 52.21±1 53,4 % W = 46,6 %	Diseases of the cardiovascular system = 22.3%		Loss of appetite = 78.6%
			Endocrine system disease = 9.71%		Diarrhea = 34%
			Malignant tumors = 7.77%		Vomiting = 3.9%
			Diseases of the respiratory system = 6.80%		Abdominal pain = 1.9%
			Digestive system disease = 3.88%		

Han et al.¹⁷

Pan et al.¹⁸

				Diseases of the nervous system = 0.97%	
Graham et al. ¹⁹	N= 161 Royal Liverpool Universit y Hospital, UK	M = 68 years 54.0 %			Diarrhea = 17.4% Anorexia = 13.8% Vomiting = 13% Nausea = 7.5% Abdominal pain = 7.3%
Buscarini et al. ²⁰	N= 42 Crema General Hospital 21 February -13 March 2020	M = 68,2±14 ,2 years 64,3 % W = 35,7 %			Mual = 4,3% Muntah = 3,8% Diare = 3,6% Nyeri perut = 1,2%
Guan al. ²¹ et	N= 1099 552 Hospitals in Mainland China	W = 47 years 41,9 % (35.0- 58.0)	Hypertens ion = 15% Diabetes = 7.4%	Fever = 43.8% (hospital admission) 88.7% (hospitaliz ation) Cough = 67.8% Fatigue = 38.1%	Nausea/vo miting = 5% Diarrhea = 3.8%
Lu et al. ²²	N= 171	M = 6.7 60,8 % (1 day - W = 15 39,2 % years)			Cough = 48.5% Diarrhea = 8.8% Pharyngeal Vomiting = erythema = 6.4% 46.2% Fever = 41.5% Fatigue = 7.6% Rhinorrhea = 7.6%
Sun al. ²³ et	N= 8 Wuhan Pediatric Hospital January 24-	M = 2 75% months W = - 15 years			Polypnea = 100% Diarrhea = 37.5% Fever = 75% Constipati on = 12.5% Cough = 75%

	February 24				Expectatio n = 50%	
					Nausea/vo miting = 50%	
					Fatigue = 12.5%	
					Headache = 12.5%	
Aquino- Matus et al. ²⁴	N= 108 Medica Sur Clinic and Foundati on, Mexico	M = 53±14 68,5 %	years	Hypertens ion = 42%	Cough = 72.2%	Diarrhea = 28.7%
					Fever = 69.4%	Hyporexia = 9.3%
					Dyspnea = 48.1%	Nausea = 8.3%
						Vomiting = 4.6%
Lin et al. ²⁵	N= 58 The Fifth Affiliate d Hospital of Sun Yat-sen Universit y, Zhuhai China	M = 48.0±17 46,6 %	.1 years	Hypertens ion = 17.2%		Diarrhea = 24.2%
		W = 53,4 %		Diabetes mellitus = 5.2%		Anorexia = 17.9%
				Cardio- cerebrova scular disease = 5.2%		Nausea = 17.9%
				Malignant tumors = 6.9%		Vomiting = 4.2%
				Chronic lung disease = 1.7%		Acid reflux = 2.1%
				Chronic kidney disease = 1.7%		Epigastric discomfort = 2.1%
						Upper GI bleeding = 2.1%
Redd et al. ²⁶	N= 318 9 hospitals in Massachu setts				Fever = 81.3%	Loss of appetite =
					Cough = 77.7%	34.8%
					Fatigue = 57.5%	Diarrhea = 33.7%
					Dyspnea = 60.1%	Nausea =
					Myalgia = 38.7%	Vomiting = 15.4%
					Sore throat = 17.0%	Abdominal pain = 14.5%

Ghoshale et al. ²⁷	N= 26 Universit y Hospitals in North India April- May 2020	M = 40 years 65,4 %	53,8% (DM, COPD, CKD)	Fever 42.4% Cough 34.6%	= Vomiting = 61.5% = Anorexia = 53.8% = Nausea = 53.8%	Abdominal pain = 23% Diarrhea = 11.5%
Giacomet et al. ²⁸	N= 127 Italy	W = 4.8 34,9 %	Chronic heart disease = 3.9% Gastrointe stinal disorders = 3.1% Obesity = 2.4% Chronic kidney disease, chronic neurologic al disorders and immunolo gical conditions = 1.6%	Fever 82.7% Cough 48% Rhinorrhea = 3.8%	= Diarrhea = 22% = Vomiting = 9.6% = Abdominal pain = 6.3%	
Bialek et al. ²⁹	N= 291 (pediatri c) N= 10944 (adult) USA 12 February -12 April 2020	< 18 years (pediatr ic) 18-64 years (adult)		Pediatic Fever = 56% Cough = 54% Shortness of breath = 13% Myalgia = 23% Sore throat = 24% Headache = 28% Mature Fever = 71% Cough = 80%	Pediatic Diarrhea = 13% = Nausea/vo miting = 11% = Abdominal pain = 5.8% Mature Diarrhea = 31% = Nausea/vo miting = 16% = Abdominal pain = 12%	

Shortness
of breath =
43%
Myalgia =
61%
Sore throat
= 35%
Headache
= 58%

Incidence of Clinical Manifestations of the Gastrointestinal System in COVID-19 patients

The most common gastrointestinal symptoms that occur based on the results of research by Lin et al. was diarrhea as much as 24.2% of 58 patients. Apart from diarrhea, other gastrointestinal symptoms were also present, including anorexia (17.9%), nausea (17.9%), vomiting (4.2%) and upper gastrointestinal bleeding (2.1%). In stool samples from 65 patients, SARS-CoV-2 was found, of which 42 patients had gastrointestinal symptoms and 23 patients without gastrointestinal symptoms. Endoscopy revealed esophageal bleeding accompany with erosions and ulcers in one patient. SARS-CoV-2 RNA was also found in specimens of the esophagus, gut, duodenum and rectum in both severe patients. As for the four severe patients, SARS-CoV-2 RNA was found in the duodenal area only (Lin, 2020).

A study in Liverpool United Kingdom by Graham et al., where 161 patients with SARS-CoV-2 infection have a mean age of 68 years had gastrointestinal symptoms such as diarrhea (17.4%) as the most common symptom, anorexia (13.8%), nausea (13%), vomiting (7.5%) and abdominal pain (7.3%) (Zhang, 2020).

Cholankeril, Podboy, Aivaliotis, Pham, et al., also reported that diarrhea had a seven-fold higher chance of being hospitalized while nausea or

vomiting had a higher chance of fourfold higher (OR=4.39, 95% CI: 1.61-11.4, p=0.005). A significantly increased risk of hospitalization was found in patients with gastrointestinal symptoms (corresponding to OR 4.84% 95% CI: 1.68-13.94) (Pan et al., also describes that COVID-19 patients with gastrointestinal symptoms had a longer duration than patients without gastrointestinal symptoms of 9.0 days and 7.3 days, respectively and required antimicrobial treatment than patients without gastrointestinal symptoms (Graham, 2021).

Rather than the consequences of exploration by Han et al. reports that loss of appetite was the highest gastrointestinal symptom as was the case in the studies of H. Zhang et al (56.7% of 164 patients) and Pan et al. (73.64% of 103 patients) with score 34.0%¹⁷. Research by Redd et al. at 9 hospitals in Massachusetts also noted that 34.8% of 318 COVID-19 patients had symptoms of loss of appetite, followed by other gastrointestinal symptoms such as diarrhea (33.7%), nausea (26.4%), vomiting (15.4%) and abdominal pain (14.5%). Study in Thailand by Aumpan, Nunanan and Vilaichone involving 40 people who were confirmed positive for COVID-19 has been classified into groups with moderate symptoms and severe symptoms (Cholankeril, 2020) In the moderate and severe symptom groups, the most experienced gastrointestinal symptoms such as anorexia (16.7% and 20.0%) and

diarrhea (6.7% and 40.0%). In addition, diarrhea was significantly connected with cases of severe COVID-19.

Not only is diarrhea a common gastrointestinal symptom, a study at a University Hospital in North India by Ghoshal et al. show that 61.5% from 26 COVID-19 patients with gastrointestinal symptoms experienced vomiting. Likewise with research by J. jin Zhang et al. that nausea (17.3%) occurred more than diarrhea (12.9%) and anorexia (12.2%). Research by Buscarini et al. involving COVID-19 patients treated at Crema Hospital mostly have nausea (4.3%) as gastrointestinal manifestations, followed by other symptoms such as vomiting (3.8%), diarrhea (3.6%) and pain. stomach (1.2%). 42 COVID-19 patients with gastrointestinal symptoms required CPAP/NIV, 2.3% were admitted to the ICU and 9.5% died and 10% proved that the prevalence of gastrointestinal symptoms could not be ignored. Symptoms such as nausea or vomiting (5%) which were more common than diarrhea (3.8%) were also noted in the study by Guan et al., which involved 1099 patients in several hospitals in Mainland China²¹. Diarrhea and nausea or vomiting were also experienced simultaneously in 4.9% of 207 patients.

Incidence of Gastrointestinal System Clinical Manifestations by Age and Comorbidities in COVID-19 Patients

Research that was held in Hubei, China by Pan et al., reported that the number of men (53.4%) who were confirmed for COVID-19 followed with gastrointestinal manifestations was more than women (46.6%). The average age of the 103 COVID-19 patients who experienced gastrointestinal symptoms was 52.21 ± 15.92 years.

Comorbidity was reported starting from the highest, namely cardiovascular system disease (22.3%), endocrine system (9.71%), malignant tumor (7.77%), respiratory system (6.80%), digestive system (3.88%) and nervous system (0.97%). In contrast to other studies, the most common gastrointestinal symptoms found in this study were loss of appetite (73.64%), followed by other symptoms such as diarrhea (33.98%), vomiting (3.88%) and abdominal pain (1,94%).

Research by J. jin Zhang et al. and Pan et al. conducted in China stated that men experience more gastrointestinal symptoms than women. Likewise, in the study by D. Wang et al., said that 54.3% men and 45.7% women patients were found from 138 patients with an average age of 56 years and hypertension (31.2%) was recorded as the highest comorbidity.

Based on the findings on January 2, 2020 by Huang et al., 41 confirmed COVID-19 patients were found, most of which occurred in men with a total of 73% and women 27% with an average age of 49.0 years (41.0-58.0). 13 of them had certain medical conditions such as diabetes (20%), hypertension (15%) and cardiovascular disease (15%).

Research at Stanford Hospital noted that the prevalence by sex was dominated by 104 men from 207 patients with an average age of 49 years and the highest comorbidity was found, namely hypertension as many as 52 patients.

A female-dominated prevalence was also reported in the study by Han et al., where 55.8% of the 206 patients were women. It was noted that the mean age of 206 patients was 62.5 years with a range of age from 27 to 92 years. The history of accompanying disease was dominated by hypertension with the acquisition of 27.2% and diabetes

10.2%. In this study, women had a higher chance of experiencing diarrhea than men, respectively, it was found to be 65.7% and 51.1% ($p=0.048$).

In a study by Jin et al., the number of COVID-19 patients with gastrointestinal manifestation in men contrast to women was the same (50.0% vs. 50.0%). Of the 74 patients it was reported that the mean age was 46.14 ± 14.19 years. The most commonly reported comorbidities were hypertension (16.22%) and diabetes (9.46%). Comorbidities such as moderately high hypertension (71%) and diabetes mellitus (32.3%) were also found in a study by Ramachandran et al., at Brooklyn Tertiary Hospital, New York.

Manifestations of the gastrointestinal in COVID-19 patients were not only experienced by adults. A study by Bialek et al., that was held in the USA, characterized the manifestation in

COVID-19 patients into two groups, namely the adult group (10,944 patients) and pediatric (291 patients). In addition to general symptoms such as fever (56%), cough (54%) and shortness of breath (13%), gastrointestinal symptoms were also experienced by both groups. Gastrointestinal symptoms found in the pediatric and adult groups were diarrhea (13% and 31%), nausea or vomiting (11% and 16%) and abdominal pain (5.8% and 12%).

A study by Giacomet et al., in Italy consisting of 127 patients with an average age of 4.3 years reported that as many as 22% of patients had diarrhea, vomiting (9.6%) and abdominal pain (6.3%) (24). Diarrhea (37.5%) and constipation (12.5%) also occurred among 8 pediatric patients aged 2 months to 15 years (19). Gastrointestinal symptoms such as diarrhea (8.8%) and vomiting (6.4%) also occurred among 171 pediatric patients aged about 6.7 years .

DISCUSSION

Mechanism of SARS-CoV-2 Infection on Clinical Manifestations of the Gastrointestinal System of COVID-19 Patients

The phenomenon of the emergence of gastrointestinal manifestations in COVID-19 patients raises the question, is there an association between SARS-CoV-2 infection and clinical manifestations of the gastrointestinal system in COVID-19 patients. SARS-CoV-2 must bind to the ACE2 receptor in order to infect host cells. Apart from pulmonary alveolar cells, ACE2 was also expressed highly in small intestinal enterocytes.

There are 6 factors that can affect the intestinal flora of COVID-19 patients that are causing gastrointestinal manifestations. First, the release of

proinflammatory cytokines such as IL-2, tumor necrosis factor and cytokine storm due to the infection of SARS-CoV-2 which is common in COVID-19 patients can alter the gut flora. Second, the side effects of antimicrobial drug therapy, both antibiotics and antivirals, can affect the composition of the intestinal flora, resulting in decreased antimicrobial activity and susceptibility to infection. Third, the gut-lung axis factor is the result of changes in the flora in the lungs that have the potential to cause changes in the intestinal flora. Fourth, changes in intestinal flora can result in an imbalance in the ratio of pathogenic organisms. Fifth, enteral nutrition and the last factor is SARS-CoV-2 which binds to the ACE2 receptor affects the aberrant mTOR

activity, which can change intestinal flora (Ramachandran, 2020).

The mechanism of SARS-CoV-2 infection in the gastrointestinal system is supported by Devaux, Lagier and Raoult in their research, where SARS-CoV-2 can cause direct and indirect infections. Direct infection occurs because the SARS-CoV-2 spike protein binds to ACE2 which is expressed on small intestinal enterocytes. In addition to ACE2, the serine protein TMPRSS2 also plays an important role in separating the SARS-CoV-2 spike protein into S1 and S2 so that they can attach efficiently so that more effective endocytosis occurs. S1 will help the virion to attach to the ACE2 receptor, while S2 is attached to the cell membrane. The ACE2 receptor is located near B⁰AT1 which acts as an amino acid transporter. Because ACE2 is an amino acid transporter companion (Papa, 2020), tryptophan absorption is impaired. If it persists tryptophan deficiency and decreased production of antimicrobial peptides through activation of the mTOR pathway by Paneth cells. Imbalance of gut microbes can trigger enteritis and cause diarrhea.

According to the findings of Mönkemüller, Fry and Rickes, there are several possibilities of SARS-CoV-2 contamination associated with the onset of gastrointestinal symptoms, namely SARS-CoV-2 infection in the small intestine can occur primarily because of the presence of ACE2 receptors. Second, SARS-CoV-2 infection which interferes with amino acid transport can cause malnutrition which is prone to occur in elderly and malnourished patients. Third, disorders of the small intestine that cause inflammation and changes in intestinal flora can affect intestinal permeability which can trigger the entry of bacterial antigens and other

toxins. In addition, a cytokine storm can occur when lymphocytes, dendritic cells and macrophages in the small intestine are activated.

Direct infection of SARS-CoV-2 with ACE2 present in the ileum can trigger the release of proinflammatory cytokines such as monocyte chemokine-1 (MCP-1), IL-1 and IL-6 (30) (Xu, 2020). The release of proinflammatory cytokines causes a cytokine storm that can cause damage to organs in the gastrointestinal tract by attacking the surrounding healthy tissue. Cytokines from the gut can also enter the bloodstream and cause systemic inflammation in COVID-19 patients (Huang, 2019).

Other evidence showing that SARS-CoV-2 infection is related with gastrointestinal symptoms is by indirect viral infection through the gut-lung axis. SARS-CoV-2 is apically released into the gastrointestinal tract via mucociliary clearance. This is supported by the statement that tracheal and lung cells originate from the intestinal endoderm (Aumpan, 2020). The epithelium of the respiratory tract and intestines is also included in the mucosal immune system, where influenza infection can cause the lungs to mediate CCR9 to the intestine, thereby disrupting the balance of the gut microbiota. Similarly, the opinion of Fanos et al. that the respiratory tract and intestines can modulate immune cells, on the other hand, an imbalance of gut microbiota triggers secondary infection. Another opinion also states that SARS-CoV-2 infection can strike out intestinal cells through the systemic circulation, causing damage to the digestive tract (Jin, 2020).

Digestive tract organ damage was found on endoscopic examination where esophageal bleeding was accompanied by

erosions and ulcers in serious COVID-19 patients. Furthermore, SARS-CoV-2 RNA was found in the esophagus, stomach, duodenum and rectum. The severity of COVID-19 patients with gastrointestinal symptoms was confirmed by the findings by Jin et al., which occurred in 22.97% of patients. In addition, gastrointestinal symptoms are significantly associated with severe COVID-19. Severe or critical conditions were not uncommon in patients with significant gastrointestinal symptoms ($p=0.029$) in the study of Giacomet et al (Wang, 2020).

There are no studies that mention the relationship between COVID-19 patients who have hypertension directly with gastrointestinal symptoms. It is possible that cases of COVID-19 patients who have a history of certain medical conditions such as hypertension are due to the presence of ACE2 in the heart muscle, which is a SARS-CoV-2 receptor, which can have an effect on excessive RAAS. Increased accumulation of Angiotensin II which is not converted by ACE2 bound to SARS-CoV-2 can produce a blood pressure-raising effect because Angiotensin II binds to AT1R (Han, 2020); (Pan, 2020).

Men are more at risk of infection with SARS-CoV-2 because plasma levels of ACE2 are higher in men than women. In addition to an unhealthy lifestyle in men, a study states that there is a relationship between increased free androgen hormones with the seriousness of COVID-19 illness. TMPRSS2, a serine protein that also plays a main role in SARS-CoV-2 attachment, is regulated by androgen hormones in the prostate gland, thus supporting that men are more at risk of contracting COVID-19. The ACE2 gene found on the X chromosome is widely

expressed in the testes, which are the male reproductive organs. This is supported by the research of Chen et al., that ACE2 is widely in the gut, testes and kidneys. Research by Fan et al., also found that renal tubular cells, Sertoli cells, Leydig cells and cells in the seminiferous ducts express ACE2.

CONCLUSIONS

Gastrointestinal symptoms in COVID-19 disease include diarrhea as the most frequent symptom, nausea, vomiting, loss of appetite, abdominal pain, and anorexia. Incidence of gastrointestinal symptoms is mostly experienced by COVID-19 patients whose average age is over 50 years. Prevalence by sex in COVID-19 patients with gastrointestinal manifestations has different findings.

The most commonly reported comorbidity was hypertension. The occurrence of gastrointestinal symptoms in COVID-19 patients is induced by the presence of ACE2 as a SARS-CoV-2 receptor on epithelial cells of the ileum, colon and rectum. The mechanism of infection of SARS-CoV-2 can occur directly and indirectly.

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