Systematic Review: Intestinal Symptoms in Patients with COVID 19 Infection

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Abstract: <u>*Background*</u>*: Coronavirus Disease 2019 (COVID - 19) infection first time reported in Wuhan, China in December 2019 become global health burden until now. Clinical manifestation of this disease similar with severe acute respiratory syndrome (SARS), so it also called SARS - CoV - 2. Gastrointestinal (GI) symptoms also experienced almost by all patients with COVID - 19, like nausea, vomiting, abdominal pain, diarrhea, and anorexia. From all of this background, the writer wants to evaluate the gastrointestinal symptoms that often happen in patient with COVID - 19.* <u>*Methods:*</u> *This research aims to determine gastrointestinal (GI) symptoms that often found in patient with COVID - 19. This type of research is a literature review using Google Scholar, Pubmedand Clinical Key using time span from 2020 - 2021, with writing keywords ("Covid" AND "gastrointestinal symptoms") according to inclusion and exclusion criteria.* <u>*Results:*</u> *The results of this study found 10 literature that met the inclusion and exclusion criteria. From that literature found the most common gastrointestinal symptoms are nausea/ vomiting (14.88 %), followed by diarrhea (13.39%), abdominal pain (12.21%), and the last is anorexia (9.43%). Gastrointestinal symptoms also associated with impaired liver function.* <u>*Conclusion:*</u> *Gastrointestinal symptoms often occur in COVID - 19 patients, there are nausea/vomiting, diarrhea, abdominal pain and anorexia. Some of these symptoms are associated with the course of the severe COVID - 19 also accompanied by impaired liver function which contributes to severity of these symptoms and become a marker of a poor clinical course of COVID - 19.*

Keywords: COVID - 19, gastrointestinal symptoms, SARS - CoV - 2

1. Introduction

Infection of Coronavirus Disease 2019 (COVID - 19) has become a serious health problem for the world public health in January 2020 until now. This disease was first reported as a viral outbreak of pneumonia in Wuhan, China, in December 2019, and its spread rapidly into a pandemic affecting the entire continent, and the World Health Organization (WHO) declared the disease potentially fatal. COVID - 19 infection is caused by a new pathogen, identified as a new family of the genus Betacoronavirus.[1, 2] The manifestations of COVID - 19 infection involve the respiratory tract and the clinical presentation is very similar to the recorded symptoms during the Severe Acute Respiratory Syndrome (SARS) outbreak, there are fever, cough, sore throat, shortness of breath, fatigue, malaise, thus known as SARS - CoV - 2.[1, 3]

Based on report of World Health Organization (WHO) report in August 2021, there are nearly 214 million cases of infection and 4.46 million deaths have been reported globally. Indonesia reported its first case on March 2, 2020.4The cases are increasing and spreading rapidly throughout Indonesia. As of August 20, 2021, the Indonesian Ministry of Health reported 3, 930, 300 confirmed cases of COVID - 19 and 122, 633 deaths (CFR 3.1%). In Bali alone, there were 100, 708 confirmed cases of COVID - 19 with 10, 387 active cases and 3, 006 deaths (CFR 2.9%).[5]

Gastrointestinal (GI) symptoms are also experienced by some patients with COVID - 19. The first case of COVID - 19 (in Seattle, Washington) manifested as cough and fever, followed by nausea, vomiting, and diarrhea. The individual initially experiences malaise and gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), and does not experience respiratory distress until later in the course of day 9 of the illness, which tends to lead to a diagnosis of

gastrointestinal infection.[6] Many studies report the virus can actually involve various organs that contain angiotensin - converting enzyme 2 (ACE2) receptors. The virus will penetrate into the organ through these receptors expressed in epithelial cells of the small intestine and actively infect and replicate in the gastrointestinal tract.[2, 7] Therefore, COVID - 19 infection in the intestinal tissue can cause problems in digestion system. In addition, SARS - CoV - 2 RNA was also found in the feces of some COVID - 19 patients even after clearance of the virus in the upper respiratory tract.[1, 8] Based on that background, there are various factors related between COVID - 19 and gastrointestinal symptoms so the authors want to evaluate gastrointestinal symptoms that often occur in patients with COVID - 19.

Research Methods

This study is a literature review with literature search using Google Scholar, Pubmed, and Clinical Key databases, the available filters are filters for the time range from 2020 - 2021 by writing keywords ("Covid" AND "gastrointestinal symptoms"). Inclusion and exclusion criteria are determined before t the literature search. Inclusion criteria must be met for research to be conducted, including: (1) confirmed RT - PCR cases of COVID - 19; (2) age >18 years; (3) features of clinical symptoms; and (4) data on the number of people with GI symptoms. The exclusion criteria are as follows: (1) research that does not meet the inclusion criteria; (2) there is no data on GI symptoms; (3) age <18 years; (4) patients with other SARS - like diseases; and (5) case reports. Studies that have one of these exclusion criteria excluded from our research.

The literature obtained from the three databases total 1, 747 from PubMed, 1, 011 from Clinical Key, and 30 from Google Scholar (n = 2, 788) that matched these keywords. The search results that have been obtained then filtered based on the appropriate abstracts, then obtained 115 literatures. Furthermore, the literature was filtered again

based on inclusion and exclusion criteria, and 10 literatures were obtained to be used in this research.

2. Research Results

Searches of the article searches are collected from online journal databases there are Google Scholar, PubMed, and Clinical Key. Based on the search process, 2, 788 articles were obtained. The articles obtained were then re - selected, and 10 articles were analyzed in depth. Table 1 shows the results of a review of the articles used in this study.

Table 1: Results of literature review used in research

No	Journal title and author	Research methods	Research results
1	Yusuf et al., 2021. Global prevalence of prolonged gastrointestinal symptoms in COVID - 19 survivors and potential pathogenesis: A systematic review and meta - analysis.[9]	*Systematic review* without meta - analysis	• 3, 19% (95% CI: 1, 62% - 6, 17%) from patients experiencing continuous nausea • 4, 12% (95% CI: 1, 07% - 14, 64%) the patient has prolonged diarrhea • 4, 41% (95% CI: 1, 91% - 9, 94%) patients decreased and loss of appetite • 1, 68% (95% CI: 0, 84% - 3, 32%) patients have abdominal pain • 7, 04% (95% CI: 5, 96% - 8, 30%) prolonged dysgeusia
2	Shehab et al., 2021. Gastroenterological and hepatic manifestations of patients with COVID - 19, prevalence, mortality by country, and intensive care admission rate: systematic review and meta - analysis.[10]	*Systematic review* with meta - analysis	• Prevalence mortality GI 3, 5% (95% CI: 3, 1% - 6, 2%) • 16, 5% (95% CI: 14, 2% - 18, 4%) patients have diarrhea • 9, 7% (95% CI: 9, 0% - 13, 2%) patientshave nausea • 1, 6% (95% CI: 1, 2% - 5, 1%) patients have decreased and loss of appetite • 1, 5% (95% CI: 5, 1% - 8, 0%) patients have vomit • 4, 5% (95% CI: 3, 1% - 7, 3%) patients have abdominal pain • 1, 3% (95% CI: 1, 1% - 4, 1%) patient have the loss of tasting • 5, 6% (95% CI: 4, 2% - 9, 1%) patients have increased in liver enzyme
3	Zeng et al., 2021. Gastrointestinal symptoms are associated with severity of coronavirus disease 2019: a systematic review and meta - analysis.[11]	Systematic review with meta - analysis	• 41, 1% (95% CI: 31, 0–51, 5%) patients have diarrhea • 59, 3% (95% CI: 41, 3–76, 4%) patients have abdominal pain • 41, 4% (95% CI: 23, 2–60, 7%, I2=46.6%, P=0.112) patients have nausea with severe disease • 51, 3% (95% CI: 36, 8–65, 8%, I2=0%, P=0, 450) patients have vomit with severe COVID – 19
4	Dorrell et al., 2021. Gastrointestinal and hepatic manifestations of COVID - 19: A systematic review and meta - analysis.[12]	Systematic review with meta - analisis	• Prevalence of all GI Symptoms in COVID - 19 are 20% (95% CI: 15–24%, I2=94%) • 1% (95% CI: 0 - 6%, I2=88%) have GI symptoms without fever • 13% (95% CI: 11 - 16%, I2=94%) patient positive COVID - 19 have diarrhea • 4% (95% CI: 3 - 6%, I2=83%) patients have nausea and vomit • Abdominal pain happens in 4% of the patients (95% CI: 2 - 6%, I2=93%) • 21% (95% CI: 15 - 27%, I2=97%) patients have anorexia
5	Dong et al., 2021. The Prevalence of Gastrointestinal Symptoms, Abnormal Liver Function, Digestive System Disease and Liver Disease in COVID - 19 Infection A Systematic Review and Meta - Analysis.[13]	Systematic review with meta - analysis	• 7% (95% CI: 0, 04 - 0, 09, P<0, 0001, I2=85, 8%) patients have nausea and vomit • 8% (95% CI: 0, 06 - 0, 11, P<0, 0001, I2=86, 4%) patient have diarrhea • 3% (95% CI: 0, 01 - 0, 05, P=0, 005, I2=73, 4%) patient have abdominal pain • 17% (95% CI: 0, 06 - 0, 27, P<0, 0001, I2=95, 6%) patient have anorexia • 24% (95% CI: 0, 16 - 0, 32) patient have increased in AST • 25% (95% CI: 0, 16 - 0, 33) patient have increased of ALT • 13% (95% CI: 0, 05 - 0, 20) patient have increased oftotal bilirubin
6	Merola et al., 2020. Prevalence of gastrointestinal symptoms in coronavirus disease 2019: a metaanalysis.[14]	Systematic review with meta - analysis	• The combined prevalence of GI symptoms are 11, 51% (95% CI: 8, 16 - 15, 35) • 7, 78% (95% CI: 5, 05 - 11, 04, I2=91, 85%, p<0, 01) patients have diarrhea • 3, 57% (95% CI: 1, 87 - 5, 80, I2=90, 82%, p<0, 01) patients have vomit • 2, 39% (95% CI: 0, 55 - 5, 46, I2=96, 22, p<0, 01) patients have loss of appetite • 0, 78% (95% CI: 026 - 1, 57, I2=80, 10%, p<0, 01) patients have abdominal pain
7	Puli et al., 2020. Gastrointestinal Symptoms and Elevation in Liver Enzymes in COVID - 19 Infection: A Systematic Review and Meta - Analysis.[15]	Systematic review with meta - analysis	• 7% (95% CI: 6, 00 - 8, 00) patient have nausea/vomit/both of them • 6% (95% CI: 5, 00 - 7, 00) patients have diarrhea • Increased average amount of AST in all patients COVID - 19 20, 54 U/liter (95% CI: 19, 95 - 21, 13) • Increased average of ALT level in all patients COVID - 19 by 21, 38 U/liter (95% CI: 20, 92 - 21, 84) • Bilirubin total found increased by 7% (95% CI: 6, 00 - 9, 00) patients positive COVID – 19
8	Zarifan et al., 2020. Gastrointestinal and hepatic	Systematic review with	• 10, 2% (95% CI: 6, 2% - 16, 4%) patients have anorexia • 8, 4% (95% CI: 6, 2% - 11, 2%) patients have diarrhea

	abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis.[16]	meta - analysis	• 5, 7% (95% CI: 3, 7% - 8, 6%) patients have nausea • 39, 8% (95% CI: 15, 3% - 70, 8%) patients have decreased albumin level • 22, 8% (95% CI: 18, 1% - 28, 4%) patients have increased of AST and 20, 6% (95% CI: 16, 7% - 25, 1%) have increased of ALT
9	Ghayda et al., 2020. Correlations of Clinical and Laboratory Characteristics of COVID - 19: A Systematic Review and Meta - Analysis.[17]	Systematic review with meta - analysis	• 6% (95% CI: 0, 05%–0, 08%) patients have diarrhea • 5% (95% CI: 0, 03–0, 06) have nausea and vomit
10	Aziz et al., 2020. Gastrointestinal predictors of severe COVID - 19: systematic review and meta - analysis.[18]	Systematic review with meta - analysis	• Total prevalence of all diarrhea is 13, 0% (95% CI: 10, 8 - 15, 5%; I2=95, 1%) • Total prevalence of nausea/vomit are 9, 5% (95% CI: 7, 9 - 11, 4%; I2=92, 6%)

The presence symptoms of diarrhea and nausea / vomiting obtained in ten research report and analyzed in percentage form. Symptoms such as abdominal pain and anorexia have found in some of the research.

Table 2: Percentage of GI symptoms in Covid - 19 patients

Research	Diarrhea (%)	Nausea/ vomit (%)	Abdominal pain (%)	Anorexia (%)
Yusuf (2021) [9]	4, 12	3, 19	1, 68	4, 41
Shehab (2021) [10]	16, 5	11, 2	4, 5	1, 6
Zeng (2021) [11]	41, 1	92, 7	59, 3	-
Dorrell (2021) [12]	13, 0	4, 0	4, 0	21, 0
Dong (2021) [13]	18, 0	7, 0	3, 0	17, 0
Merola (2020) [14]	7, 78	3, 57	0, 78	2, 39
Puli (2020) [15]	6, 0	7, 0	-	-
Zarifan (2020) [16]	8, 4	5, 7	-	10, 2
Ghayda (2020) [17]	6, 0	5, 0	-	-
Aziz (2020) [18]	13, 0	9, 5	-	-
Average	13, 39	14, 88	12, 21	9, 43

Liver function disorders were obtained in three research reports analyzed in percentage form.

Table 3: Percentage of impaired liver function in COVID - 19 patients

Research	Increased of AST (%)	Increased of ALT (%)	Decreased of Albumin (%)
Shehab (2021) [10]	5, 6		-
Dong (2021) [13]	24	25	-
Zarifan (2020) [16]	22, 8	10, 6	39, 8

3. Discussion

Based on 10 research reports, there are two research reports that report the cumulative prevalence of GI symptoms in Covid - 19 patients. Research conducted by Dorrell et al.[12] obtained a prevalence of 20% of all Covid - 19 patients and 1% of GI symptoms in patients without fever. Not much different from the research of Merola et al[14] said that the prevalence was 11.51% of all Covid - 19 patients. The study of Shehab et al[10] showed a GI mortality prevalence of 3.5% (95% CI: 3.1% - 6.2%).

All studies show the same GI symptoms appear in COVID - 19 patients there are diarrhea and nausea/vomiting. Other symptoms include abdominal pain and anorexia. According to these results, the research of Zeng et al[11] has the highest percentage of diarrhea (41.4%) and nausea/vomiting (92.7%). This happened in the course of severe COVID- 19 disease. The lowest percentage in the research of Yusuf et al[9] where the percentage of diarrhea was 4.14% and

prolonged nausea/vomiting was 3.19%. The average percentage of gastrointestinal symptoms was nausea/vomiting 13.39%, followed by diarrhea 14.88%, abdominal pain 12.21%, and anorexia 9.43%.

Even tough the low percentage of abdominal pain symptoms, they have a significant correlation with severe Covid - 19.[11] Some gastrointestinal symptoms caused by SARS - CoV - 2 infection in patients ranging from nausea, vomiting, diarrhea to loss of appetite and abdominal pain due to the presence of angiotensin - converting enzyme 2 (ACE2) receptors as receptors enter SARS - CoV - 2 into digestive system organs such as the esophagus, small intestine, and colon.

After occupied by the virus, ACE2 becomes not functional, resulting in decreased protective activity in the axis of ACE2/Ang - (1 - 7) /Mas, while activity of ACE/AngII/AT1R axis increases. Following this condition, nicotinamide adenine dinucleotide phosphate oxidases are over activated leading to oxidative stress that are that induced inflammation and finally make the tissue damage.[9]

Previous research stated that there is high ACE2 expression in absorptive enterocytes and low in progenitor absorptive cells in ileum epithelial cells. In the colon, ACE2 expression is found high in enterocytes and low in immature enterocytes. Enterocytes function as barriers, can be present as antigen - presenting cells and also have an absorptive function. Absorptive enterocytes make up >80% of all epithelial cells of the small intestine. Enterocyte abnormalities can cause malabsorption. This leads to decreased absorption of NA+, water, and mucosal disaccharidase. As a result, the colon will not be able to absorb enough water, and will causing diarrhea.[19]

Gastrointestinal symptoms are also associated with impaired liver function. High levels of ALT and/or AST cause various GI symptoms, such as nausea/vomiting and anorexia. The percentage of impaired liver function in COVID - 19 patients is relatively high. Impaired liver function is also associated with a poor clinical course of COVID - 19.8

4. Conclusion

Gastrointestinal (GI) symptoms in COVID - 19 patients vary from nausea/vomiting, diarrhea, abdominal pain, and anorexia have a relatively high prevalence. Impaired liver function also exacerbates these symptoms as well as being a marker of a poor clinical course of COVID - 19.

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