Review Article

Association between COVID-19 and Gastrointestinal Manifestations and Available Treatment Options

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Abstract

Background & Objective: Corona virus disease 2019 (COVID-19) is an emerging outbreak which has involved almost all of the countries of the world now. While the main symptoms of the disease are known to be respiratory symptoms like coughing and shortness of breath, extrapulmonary symptoms have also been reported in many cases of COVID-19. Gastrointestinal (GI) manifestations including diarrhea, nausea and vomiting, abdominal pain and liver injury are amongst the most common extrapulmonary symptoms in COVID-19 patients.

Materials & Method: We used Scopus, PubMed, and Google scholar databases for this review. The last search was run on November 21, 2020

Results: Liver injury is mostly accompanied by an elevation in AST and ALT levels and a slight increase in serum billirubin levels that is observed in approximately 14.8-53.1% of COVID-19 patients.1-29% of COVID-19 patients present nausea and vomiting and 2 to 10% develop diarrhea. Abdominal pain is seen in about 2.2-6% of COVID-19 patients and most frequently seen in severely ill patients.

Conclusion: Diarrhea, nausea, and vomiting and liver injury are the most common GI symptoms in COVID-19 patients while abdominal pain is not pretty common. There are no medications of proven efficacy to treat COVID-19 or its GI manifestations so far.

Keywords: COVID-19, gastrointestinal manifestations, treatment protocols, extra pulmonary

Introduction

Coronavirus disease 2019 (COVID-19), a major pandemic, has infected millions of people worldwide. The latest update on18 June, more than 8.400.000 cases and 451000 deaths have been reported (1). Members of Coronaviridae family are RNA viruses with a large genome and a great capability for mutations which makes them very potent to initiate new epidemics (2). Like other members of the family, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is morphologically known by a crown-like protein spike on envelope (3). SARS-CoV-2 enters target cells using angiotensin-converting enzyme 2 (ACE 2) which is expressed on the surface of certain cells (4, 5).

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The most common clinical manifestations of COVID-19 infection are cough, fever, myalgia, fatigue, and dyspnea. Gastrointestinal symptoms such as nausea and vomiting, diarrhea and abdominal pain are also reported (3, 6-18). ACE 2 is overexpressed in gastrointestinal tract cells including epithelial cells of the esophagus, enterocytesin ileum and colon. This fact brings the idea of possible fecal shedding and transmission of the virus through fecal-oral transmission (3). The mortality rate of COVID-19 infection is estimated at about 6 % globally (6). The main causes of death during COVID-19 infection are due to acute respiratory distress syndrome (ARDS), cardiac and renal failure (19).

Since gastrointestinal symptoms are common during COVID-19 infection, it is very important to manage them effectively. In addition, there is limited data available on how to treat COVID-19 patients with gastrointestinal symptoms; therefore, the aim of this study is to review COVID-19 associated gastrointestinal manifestations and available treatment options.

Material & methods

Sources of Information

Studies were identified by searching through electronic databases and scanning the reference lists of articles. The sources of the literature review encompassed Scopus, PubMed, and Google Scholar. The last search was run on November 21, 2020.

Search

The following terms were used to search all the trials, registers, and databases: COVID-19 AND Gastrointestinal AND (manifestations OR complications OR treatment protocols)

Study Selection and Data Collection Procedure

We included original and review articles that had been designed for COVID-19 GI manifestations and possible treatment protocols. A number of 121 articles were found in primary search. Then we evaluated the eligibility of the articles by looking at the titles, abstracts, and full-text reports to make inclusion and exclusion decisions and delete duplicates. To ascertain the validity of studies, pairs of reviewers worked independently. Finally, 52 articles were reviewed.

Gastrointestinal manifestations of COVID-19

Nausea and vomiting

Nausea and vomiting are frequent symptoms observed among COVID-19 patients. The first COVID-19 confirmed case who was a 35 years old man presented a history of nausea and vomiting for two days (20). In this regard, a Chinese study on 1099 confirmed COVID-19 cases showed that 5% of the cases presented nausea and vomiting (9). Another study on 140 COVID-19 patients in Wuhan, China reported that 17.3% and 5% of the patients suffered from nausea and vomiting respectively (21). In an Iranian review study by Aghdam et al (17) nausea and vomiting were demonstrated as the most common GI symptoms of COVID-19. Another Iranian study demonstrated that nausea and vomiting are the most common GI symptoms of COVID-19 with a prevalence of 18.8%. (22) Another review study showed that vomiting was more common in children (6.5-66.7%) than in adults (3.6-15.9%). The same study reported nausea in 1-29.4% of COVID-19 patients (23). Another review study in the U.S showed that 1-29% of COVID-19 patients presented nausea and vomiting (24). Moreover, different numbers of studies are reported about nausea and vomiting prevalence in COVID-19 patients from about 4 to 20% (7, 9, 21, 25-30). Another Iranian study by Omidi A et al discussed anorexia and nausea as common GI symptoms of COVID-19 (31). The largest study of gastrointestinal symptom of COVID-19 so far which is done in China on 1099 confirmed cases suggests that nausea and vomiting were seen in 5% of the study population (9).

Diarrhea

Diarrhea is a common gastrointestinal symptom in COVID-19 patients. A comprehensive study on 1099 confirmed COVID-19 cases demonstrated that 3.8% of patients had diarrhea (9). Another study on 140 COVID-19 cases showed that 12.9% of patients suffered from diarrhea (21). In addition, a smaller cohort on 73 COVID-19 cases reported 35.6 % of patients had diarrhea (32).

Several other studies have reported the frequency of diarrhea from 2 to 10% in COVID-19 patients (7, 13, 26, 29, 33-36). Two review studies also revealed that diarrhea is the most common gastrointestinal (GI) manifestation both in children and adult cases of COVID-19 (23, 24). Wei et al showed that COVID-19 patients with diarrhea presented myalgia, headache, cough, nausea and vomiting, sputum production and fatigue more common in comparison with patients without diarrhea, while they rarely experienced abdominal pain and tenesmus (37). In another study conducted in China, Huang et al. found that 3% of COVID-19 patients developed diarrhea all of whom experienced mild to moderate symptoms without need for intensive care unit (ICU) admission (33). A similar study in Singapore showed that 25% of COVID-19 cases had diarrhea none of whom needed oxygen supplementation which can indicate that diarrhea often occurs in mild to moderate cases (38). The largest cohort on GI symptoms of COVID-19 so far which is done in China demonstrates that diarrhea is seen in 3.8% of the studied patients (9).

Abdominal pain

Abdominal pain is an unusual common GI symptom in COVID-19 patients (39). Two studies showed abdominal pain in about 2.2-6% of COVID-19 patients that were more frequent in severely ill patients (21, 35). A review study confirmed that abdominal pain is rarely seen among COVID-19 patients (2.2-6%)(23).

A similar result was observed in the study conducted by Pan et al. They reported that abdominal pain occurred in 0.4% (/204) COVID-19 patients as a rare GI finding, which is inconsistent with literature (40). Wang et al showed that abdominal pain can be indicative of severe disease among COVID-19 patients. They showed that 8.3% of ICU admitted patients had abdominal pain while 0% of non-ICU admitted patients showed this symptom (35). Lie et al also showed that abdominal pain was more observed in critical COVID-19 patients (8.7%) compared to non-critical cases (0%)(40).

Liver injury

Liver injury is mostly accompanied by an elevation in AST and ALT levels and a slight increase in serum billirubin levels that is observed in approximately 14.8-53.1% of COVID-19 patients (7, 9, 26, 29, 33, 35, 36). To date, several studies have reported the proportion of liver injury in COVID-19 patients. In a cohort study, 56 COVID-19 patients were investigated. Gamma-glutamyl transferase (GGT) was considered to be elevated in about 54% of COVID-19 patients (41). According to literature review, most cases of liver injury occur in severe COVID-19 patients (9, 33). In an Iranian study by Nouri-Vaskeh M et al, elevation in aminotransferase levels was common among fatal COVID-19 cases (42). In a meta-analysis that investigated the incidence of liver injury among 4191 COVID-19 patients, the prevalence of liver injury was reported at 19.5%. Moreover, the pooled prevalence of liver injury was 22.8% among dead patients (43). However, contrary to these results, a study showed up to 78% of liver injury in severe COVID-19 patients (44). Furthermore, out of 138 COVID-19 hospitalized patients, 3% of them had an underlying chronic liver disease that none of these patients needed ICU admission (35). The same study showed that in comparison with patients admitted in ICU whose mean levels of AST and ALT had been increased (52 and 35U/L respectively), the mean levels of AST and ALT in non-ICU admitted patients were normal (29 and 23 U/L respectively). According to a meta-analysis consisting of 10 studies on COVID-19 cases, aminotransferase elevation was reported in 17-37% of COVID-19 patients (45). Alkalin phosphatase elevation is not common among COVID-19 patients and reported in only 1-2 % (41). Acute liver failure or acute fulminant liver injury is not accounted for a COVID-19 complication but different degrees of ischemic liver injury are seen in COVID-19 cases with shock (24). Guan et al's (9) study with 1099 COVID-19 patients from 552 hospitals in 30 provinces in China indicates that abnormal ALT and AST are seen in 21.3% and 22.2% of the studied population respectively.

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However, the main mechanism of liver injury during COVID-19 infection is unclear. Literature review demonstrated that the majority of COVID-19 cases experienced psychological stress, the use of antibiotics, antivirals, steroids and pneumonia-associated hypoxia that may contribute to liver injuries. Gastrointestinal manifestations of COVID-19 are shown in figure 1. These manifestations are sorted by the article discussing them and the country in which the studies were done in table1.

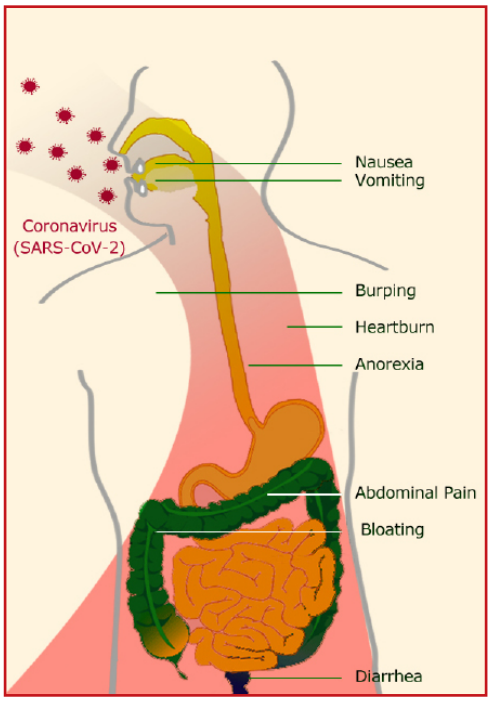


Figure 1. COVID-19 gastrointestinal manifestations

Treatment of GI manifestations and complications of COVID-19

There are available few studies about treatment of COVID-19 GI manifestations (30, 46). In this regard, in a study on 74 confirmed COVID-19 cases, all patients were treated with supportive and empiric medication and added antiviral treatment including interferon-a sprays, arbidol hydrochloride capsules (2 tabs 3 times a day) and lopinavir-ritonavir (2 tabs 500mg twice a day) to the medication of 66 (89.19%) patients. Nevertheless, in that study, a patient died (47). Two studies suggested treating GI symptoms with symptomatic, antiemetic and supportive treatments (48, 49). Use of antibiotics is indicated only if bacterial co-infection of GI is present (48).

Recently, there are some medications used in the treatment of COVID-19 most of which can be effective in gastrointestinal adverse reactions.

Chloroquine and hydroxychloroquine should be used with caution in patients with liver injury or in patients who are already on a hepatotoxic medication because it can aggravate the situation (50, 51). The use of Lopinavir-ritonavir as a treatment for COVID-19 can cause some side effects in GI such as diarrhea, abdominal pain, nausea and vomiting and an increase in amylase, lipase, AST and ALT serum levels. It can also aggravate chronic liver disease (24, 38). Use of Lopinavir-ritonavir has been decreased after a paper's failure to show its efficacy (52). Some monoclonal antibodies including tolicizumaband sarilumab can also increase AST and ALT levels. They can be effective even in the increased risk of acute liver failure. Remdesivir and favipiravir are also known to have GI adverse reactions like abnormalities in liver function tests although data about them is not sufficient (24).

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Recent studies suggest that probiotic treatment may have good results in treating COVID-19 induced diarrhea. (53-55).

Some novel treatment options are discussed recently which need more investigation to be considered as possible therapeutic candidates (56, 57).

Table 1. Gastrointestinal symptoms in COVID-19

	Number of cases	nausea	vomiting	diarrhea	Abdominal pain	Abnormal Liver profile	Country that performed the study
Guan W et al(9)	1099	5%	5%	3.8%	NA	22.2%	China
Chen N et al(7)	99	1%	1%	2%	NA	43%	China
Lu X et al(34)	171	4.9%	4.9%	8.8%	NA	NA	China
Liu K et al(13)	137	NA	NA	8%	NA	NA	China
Huang C et al(33)	38	NA	NA	2.6%	NA	31%	China
Shi H et al(26)	81	4.9%	4.9%	3.7%	NA	53%	China
Zhou F et al(27)	141	3.7%	3.7%	4.7%	NA	NA	China
Zhang et al.(44)	82	NA	NA	NA	NA	78%	China
Zhang JJ et al(21)	140	17.3%	5%	12.9%	5.8%	NA	China
Yang X et al(29)	52	3.8%	3.8%	NA	NA	29%	China
Xu XW et al(36)	62	NA	NA	4.8%	NA	16%	China
Xiao F et al(32)	73	NA	NA	35.6%	NA	NA	China
Wang D et al(35)	138	10.1%	3.6%	10.1%	2.2%	NA	China
Haytham M.A.Kaafarani et al(58)	141	17.3%	42.3%	28.8%	14.4%	67.3%	United states of America
M M Khalil et al(59)	226	22.6	NA	35%	NA	NA	Bangladesh
Moura DT et al(60)	400	13.75%	7.5%	17.25%	6%	NA	Brazil
Montazeri et al(22)	611	18.8%	18.8%	NA	NA	NA	Iran

Discussion

Although the main symptoms of COVID-19 patients are associated with the common cold and respiratory manifestations, gastrointestinal symptoms have been severally reported in patients with COVID-19. Diarrhea, nausea and vomiting, and liver injury are common GI manifestations of COVID-19 while abdominal pain is uncommon. The fact that abdominal pain is seen in severe-critical patients only can suggest that it is a potential predictor of the severity of the disease.

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We found that the liver injury seen in COVID-19 patients does not involve bilirubin levels much and it is often accompanied by elevation of AST and ALT enzymes plus a slight elevation of bullirubin. On the other hand, according to Zhang.C et al's study, elevation of glutamyl transferase (GGT) was pretty common among COVID-19 patients (41). We also found that most cases of liver injury are seen among severe cases of COVID-19 and about 20% of COVID-19 cases develop liver injury (43). We also determined that there are neither any medications of proven efficacy to treat COVID-19 nor any specific medication to treat GI symptoms of it so far. However, a recent paper suggests that using probiotics can be effective in the treatment of those patients presenting diarrhea (53). Most of GI manifestations of COVID-19 can be treated symptomatically. There are some drugs used to treat COVID-19 right now which are of unknown efficacy and need more investigation. It is worth mentioning that most of these drugs like Chloroquine, Lopinavir-ritonavir, tocilizumab, Remdesivir and favipiravir have different GI adverse effects which physicians should pay attention in choosing treatment options for COVID-19 patients.

Conclusion

Diarrhea, nausea and vomiting, and liver injury are the most common GI symptoms in COVID-19 patients while abdominal pain is not pretty common. There are no medications of proven efficacy to treat COVID-19 or its GI manifestations so far.

Conflict of Interests

None.

Acknowledgments

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