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GUT SYMPTOMS LINKED WITH COVID-19: A SYSTEMATIC REVIEW

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Review



ABSTRACT

The most prevalent symptoms at the onset of COVID-19 are fever, cough, fatigue, myalgia, and dyspnea (shortness of breath). Initially, it was thought that the virus only causes respiratory distress in patients until the viral RNA has been detected in the patient's stool. Recently, several new studies have depicted that COVID-19 has impact on gut patients. We hypothesized that, there may have a link between gut symptoms and COVID-19. Therefore, the present study was reviewed to explore this study question; searches were conducted to identify the articles related to the association between gut symptoms and COVID-19, which were published between 2019 to 2020. Multiple searches were conducted in Google Scholar and ResearchGate using keywords. In this review, a total of 2639 cases of COVID-19 from 20 articles had been analyzed with special emphasize on gut symptoms. Among 20 studies, Diarrhea (highest 71.62% and lowest 2%) was the most prevalent symptoms, respectively, nausea (highest 17.1% and lowest 1%) & vomiting (highest 16.7% and lowest 1%), anorexia (highest 66.7% and lowest 17.9%), and abdominal pain (highest 8.8% and lowest 1.9%). Along with the main symptoms, we studied some commonly associated symptoms, such as, fever (highest 98.6% and lowest 55.6%) and coughing (highest 91.67% and lowest 35%) were heavily linked with COVID 19. Despite all the GI symptoms associated with COVID 19, there are currently no recommendations for a diagnostic approach in the presence of gastrointestinal symptoms associated with the corona virus, and there is no definitive knowledge of the role of COVID-19 in the gastrointestinal diseases. So, further studies are needed to identify the better relationship between gut symptoms and SARS-CoV-2 for suppressing the spread of COVID-19.

Keywords: COVID-19, gut symptoms, respiratory symptoms, gastrointestinal disease, SARS-CoV-2

INTRODUCTION

The first case of the ongoing COVID-19 pandemic was declared by WHO on 11th March 2020, was reported in Wuhan, Hubei Province, China, in December 2019. It was treated as a case of pneumonia of an unidentified causative agent which later on identified as novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). This virus has eventually spread almost throughout the globe affected millions of people and taken a death toll of a huge number of people implicating one of the important clinical features (Viana, Nunes, & Reis, 2020).

SARS-CoV-2 is a single-stranded RNA virus. It is an enveloped virus that contains crown-like spike (S) glycoproteins on the outer surface. The spike (S) protein is a trimeric protein having two functional subunits- S1 subunit and S2 subunit. The S1 subunit functions as a receptor-binding domain (RBD) and there are fusion proteins in the S2 subunit that aid viruses to transmit into host cells. (Viana, Nunes, & Reis, 2020). Phylogenetic analysis has revealed that SARS-Cov-2 has 79% similar nucleotide sequence identity with SARS-Cov from the same family and shares 96% and 89.6% sequence identities for the envelope and nucleocapsid proteins respectively with SARS-Cov. One important feature is shared by all of them which is the use of the cellular ACE-2 receptor for their entry into the host (Dhar & Mohanty, 2020). Researchers observed that ACE-2 was highly expressed in the proximal and distal enterocytes of the small intestine and also in the upper and stratified epithelial cells of the esophagus by analyzing single-cell RNA sequencing data (Ng & Tilg, 2020). Such information significantly triggered the researchers to sort out an association of SARS-CoV-2 with the lung-gut-brain axis, and microbiome symbiosis (Villapol, 2020).

However, the most prevalent symptoms at the onset of COVID-19 are fever, cough, fatigue, myalgia, and dyspnea (shortness of breath) (Lin et al., 2020). At the initial stage, because of these symptoms, it was thought that the virus only causes respiratory distress in patients until the viral RNA has been detected in the

patient's stool. The frequency of GI symptoms is low but significant in demonstrating the possibility of transmission via fecal-oral route causing viral GI infection (Lin et al., 2020; Viana, Nunes, & Reis, 2020). This virus negatively affects the major organ systems including- the respiratory system, cardiovascular system, central nervous system (CNS) and gastrointestinal system (Villapol, 2020).

Reports from Jin et al., (2020), Gou et al., (2020), and Villapol et al., (2020) indicated a possible association of gut symptoms with COVID-19. Although previous studies at the initial stage reported a small percentage of Covid-19 patients with GI symptoms such as diarrhea in the range of 1%–3.8% (Guan et al., 2020), another study demonstrated a higher incidence of GI symptoms such as diarrhea and nausea in 10.1% and vomiting in 3.6% (Ng & Tilg, 2020). Likewise, several related reports have been found from different studies on that subject (Nunes, & Reis, 2020). We hypothesized that there would be a holistic trend of respiratory and gastrointestinal symptomatic expression in COVID-19 patients. Hence, the aim of this study was to explore the major symptoms associated with COVID-19. Therefore, the present study reviewed research articles which are related to gut and associated symptoms with COVID-19, maintaining proper guidelines to explore the possible link between SARS CoV-2 with Gut symptoms for curbing the spread of COVID-19.

MATERIAL AND METHODS

Literature Search

The systematic review process was done according to the PRISMA guideline. A flow chart is included in figure 1. Searches were conducted to identify the articles related to the relationship between SARS CoV-2 and Gut symptoms, published between February 1 and August 30, 2020. We have searched articles on the Google Scholar and ResearchGate using different relevant keywords such

as relation between the gut symptoms, and COVID-19, gastrointestinal diseases, and SARS CoV-2 (also Coronavirus); Gut symptoms in COVID-19 patients. The use of those keywords assured inclusion of any study related to the Gut symptoms and COVID-19. Only peer-reviewed high-quality data were included in the present research for analysis, excluding preprint and other databases. All the referencing was done by using Mendeley referencing tools (https://www.mendeley.com).

From an underlying pool of 54 articles, 20 were chosen for data analysis. The selected articles had been picked on premise of the connection between COVID-19 and GI symptoms. All the investigations were led in China and distributed in the year of 2020.

Study Selection and Exclusion Criteria

According to the section 2.1, preprints were not used in this review and data was taken only from the peer-reviewed journal for analysis. **Figure 1** shows a diagram that demonstrates inclusion and exclusion criteria of searching databases. Articles reporting the clinical characteristics of COVID-19 patients with gastrointestinal symptoms and indicating the possible link with COVID-19 were included in this review. At the first screening phase, all duplicated works and those articles written in language except than English was excluded. And, finally, the studies which did not show any data of COVID-19 and GI Symptoms were removed.

Data Extraction and Analysis

All selected papers were assessed to accumulate data on publication year, study period, study location, and clinical syndrome. Quantitative data were also collected. Data extraction and management was performed independently by two researchers in Microsoft excel 2010 package to negate any possibility of error (Table.2). Finally, all the reviewers approved the data by reaching a consensus after screening the desirable studies.

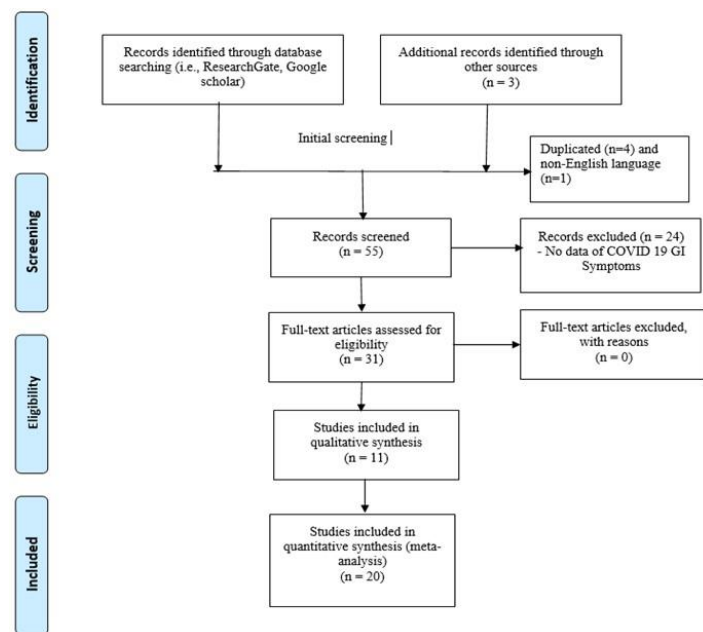


Figure 1 Prisma flow chart diagram demonstrates the database searches, number of articles identified, screened and exclusion, and final full texts included in the present systematic review.

RESULTS AND DISCUSSION

A total of 2639 COVID-19 positive patient’s report were archived in our entire review. We carefully tried to recapitulate the most significant information of the patients such as their gender distribution, median of age and different symptoms with corresponding references in the table (Table.1&2). According to the patient’s history, all the victims exposed gut symptoms. Here, we followed 20 published articles those were entirely conducted by the Chinese researcher during the study period as mentioned in the methods section. Among 20 studies, the fever as a symptom in COVID-19 patients was revealed in 19 articles, coughing as respiratory symptom was found in 15 studies. In case of gastrointestinal symptoms, all the articles explained regarding diarrhea while anorexia, nausea, vomiting, and abdominal pain were found in 05, 14, 13, and 03 article correspondingly (Table.1&2).

Table 1 Assembled of the entire published article to construct this present review

Characteristics	Frequency (%)	Reference
Publication Year		Zhou et al., 2020; An et al., 2020; Shi et al., 2020; Wu et al., 2020; Xiong et al., 2020; Xu et al., 2020; Y. Liu et al., 2020; Yang et al., 2020; Zhang et al., 2020; Zhiwei et al., 2020; D. Wang et al., 2020;
2020	20 (100%)	Zuo, Zhang, Grace C.Y. Lui, et al., 2020; Effenberger et al., 2020; Guan et al., 2020; Jin et al., 2020; K. Liu et al., 2020; L. Wang et al., 2020; Lin et al., 2020; N. Chen et al., 2020; Pan et al., 2020)

The highest median age patients - 57 (20-83) was reported by K. Liu et al., (2020), and the lowest median age 35.8 (28-45) was reported by An et al., (2020). In case of fever, more than 90% COVID-19 patients had a fever in the studies conducted by D. Wang et al., (2020a), Pan et al., (2020), and Jin et al., (2020) and the lowest 55.6% fever cases reported by An et al., (2020). In case of respiratory symptom, Y. Liu et al., (2020) reported 91.67 % COVID-19 patients had fever, which was highest and the lowest percentage was 35% reported by Wu et al., (2020). As common gastrointestinal symptoms, diarrhea was the highly reported symptoms compared to anorexia, nausea, vomiting, and abdominal pain, lowest reported symptoms (Table.2). The highest percentage of diarrhea (71.6%) was reported by Jin et al., (2020) and the lowest percentage (2%) was reported by N. Chen et al., (2020). Only 5 authors reported that COVID-19 patients had anorexia. Among them, the highest percentage likely 39.9% patients experienced anorexia in the study conducted by D. Wang et al., (2020), and the lowest percentage (1%) was reported by Shi et al., (2020). Nausea and vomiting were reported between 1-27% cases, in contrast, abdominal pain was between 1.9-5.8% common in patients (Table.2).

DISCUSSION

Since the 1918 influenza pandemic, the extreme acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered the largest worldwide pandemic. The coronavirus disease of 2019 (COVID-19) has catastrophic effects and is currently a major public health concern around the world. SARS-CoV-2 affects the respiratory system first because it is the key point of entry into the host, but it can also affect other organs. The present study analyzed a total number of 2639 patient’s data with COVID-19 those were directly lined with gut symptoms. The data showed, coughing and diarrhea are the predominant clinical symptoms of the COVID-19 patients among the other symptoms (including anorexia, nausea, vomiting, fever, and abdominal pain) (Table.1). Most of the plotted paper was published in 2020; our review accumulated all the data and presented the different symptoms of the COVID-19 patients in percentage. Moreover, in this analysis, we have tried to explore the association between the gut symptoms and COVID-19. Evidentially, these symptoms were heavily linked with COVID-19, thus, our report wanted to show in what degree and how these symptoms were related to COVID-19.

There are several suggested hypotheses, but the precise mechanism causing GI manifestation in COVID-19 are not entirely understood (Ramachandran et al., 2020). In this article, we provided evidence of SARS-CoV-2 related gastrointestinal infections and its potential fecal-oral transmission. Viral-specific target cells or organs determine the pathways of viral transmission as viruses spread from infected cells to non-infected cells. Entering the receptor-mediated virus into the host cell is the first stage of viral infection. (Xiao et al., 2020). According to (Cheung et al., 2020), ACE2 protein expression in human gastric, duodenal, and fecal epithelial cells and intracellular staining of viral nucleocapsid protein suggest that they serve as an entry point for the SARS-COV-2 virus in the intestinal tract. With more than 80% similarity to SARS-CoV. infection of the gastrointestinal tract by SARS-CoV-2 is not unexpected and supports the entry of SARS-CoV-2 into the host cells(Cheung et al., 2020; Xiao et al., 2020). In the gastrointestinal tract, especially proximal and distal enterocytes, ACE receptors are abundant and the strength of the ACE2 receptor association determines the path of infection. Because ACE2 modulates intestinal inflammation SARS CoV-2 can cause disruption of ACE2 activity and lead to diarrhoea, nausea and vomiting (Cheung et al., 2020; Zhang, T. et al., 2020).

Despite all the GI symptoms associated with COVID-19, there are currently no recommendations for a diagnostic approach in the presence of gastrointestinal symptoms associated with the corona virus, and there is no definitive knowledge of the role of COVID-19 in the gut. (Schmulson, Dávalos and Berumen, 2020). Again, further study was not conducted in our review, so the present study

suggests future studies are needed to identify a better relationship between the gut symptoms, microbiota, and SARS-CoV-2. Which may provide further insights for the development of new drugs, effective treatment, and therapies as well as to identify potential immunomodulatory biomarker.

Table 2 Symptomatic distributions of COVID-19

Article No.	Author name	N(total)	Male (%)	Age (median)	Fever (%)	Coughing (%)	Diarrhoea (%)	Anorexia (%)	Nausea (%)	Vomiting (%)	Abdominal pain (%)
1	(Lin et al., 2020)	58	46.6	48	-	-	24.2	17.9	17.9	4.2	-
2	(Jin et al., 2020)	74	37	46.14	85.14	-	71.62	-	13.51	14.87	1.9
3	(Zuo, et al., 2020)	15	47	55	60	73	7	-	-	-	-
4	(D. Wang et al., 2020)	138	54.3	56	98.6	59.4	10.1	39.9	10.1	3.6	2.2
5	(Effenberger et al., 2020)	40	24	*	85	-	55	-	27.5	12.5	-
6	(Pan et al., 2020)	204	52.45	52.91	92.23	-	34	-	-	3.9	1.9
7	(Guan et al., 2020)	1099	57.97	47	88.7	67.8	3.8	-	5	5	-
8	(Zhou et al., 2020)	191	62	56	94	79	5	-	4	4	-
9	(Zhang et al., 2020)	140	50.7	57	91.7	75	12.9	12.2	17.3	5	5.8
10	(Yang et al., 2020)	149	81	45.11	76.51	58.39	7.38	-	1.34	-	-
11	(K. Liu et al., 2020)	137	44.5	57	81.8	48.2	8	-	-	-	-
12	(N. Chen et al., 2020)	99	68	55.5	83	82	2	-	1	1	-
13	(Xu et al., 2020)	90	43	50	78	63	6	-	6	2	-
14	(Shi et al., 2020)	81	52	49.5	73	59	4	1	5	5	-
15	(Wu et al., 2020)	40	32.5	45	95	35	15	-	-	-	-
16	(L. Wang et al., 2020)	18	55.6	39	94.4	55.6	16.7	-	5.6	-	-
17	(Xiong et al., 2020)	42	60	49.5	86	64	24	-	-	-	-
18	(Y. Liu et al., 2020)	12	66.67	40	83.3	91.67	16.7	-	16.7	16.7	-
19	(An et al., 2020)	9	44.44	35.8	55.6	-	11.1	66.7	11.1	11.1	-
20	(Zhiwei et al., 2020)	3	66.7	*	66.7	-	66.7	-	-	-	-

* = undefined data

LIMITATIONS

Firstly, most of the studies included in this review were clustered in China. So, there might be a bias during selection and this review might not be an appropriate representation of the whole world. In addition, there is a possibility of biasness, regarding GI symptoms data selection, due to the presence of a small number of the related data, and scattered age groups. Moreover, the data was used and incorporated in this study was obtained by using different methodologies by the original researchers. Nevertheless, some of the data were so complex that it was difficult to extract them, unlike data from other studies. (some studies presented some symptoms together and some did not. i.e., nausea and vomiting).

CONCLUSION

In conclusion, this study revealed the major respiratory and gastrointestinal symptoms associated with COVID-19 disease occurrence. The predominant respiratory symptoms were coughing and diarrhea among the gastrointestinal symptoms. Other reported symptoms were anorexia, nausea, vomiting, and abdominal pain. This study would be very fascinating to the researcher who wants to study the association between gut symptoms with COVID-19, when the whole world is suffering from the corona pandemic and yet no successful remedy has come.

Author contributions: MRM, MA, MKU & MSH deigned the study, experimental work and MRM wrote the manuscript. SA, MSH, MMRS and MMI conducted data collection, and participated in the drafting manuscript. MA, MKU, MRM participated in the supervising and reviewing the draft and thoroughly checked and revised the manuscript for necessary changes in format. MRM also acted for all correspondences. All authors read and approved the final version of the manuscript.

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Conflicts of interest: Authors have no conflict of interest.

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