Gastrointestinal Symptom with COVID-19 Infection

Subjects: Others

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In this highly populated and comprehensive systematic review and meta-analysis study, we reported high PPE rates of anorexia, diarrhea, nausea/vomiting, and abdominal pain. The PPE rates of diarrhea, nausea/vomiting, and abdominal pain were significantly higher in non-Chinese studies compared to Chinese studies. We also observed a higher prevalence of GI symptoms for the Chinese studies than what was reported previously. Non-respiratory symptoms including those related to the GI tract should be more carefully evaluated and reported in future studies.

Keywords: COVID-19 ; GI symptoms ; diarrhea

1. Introduction

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in the Wuhan region of China and spread across the world [1]. The causative virus was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The infection is spread by droplets, aerosols, and direct contact with contaminated surfaces. As of 2 October 2020, there have been over 33,842,281 confirmed cases of COVID-19, including 1,010,634 deaths, reported to WHO [3]. Although respiratory symptoms such as fever and cough are the most common findings in patients with COVID-19, GI tract involvement has been identified by endoscopic biopsies. In addition, the presence of several GI symptoms, including diarrhea, nausea/vomiting, and abdominal pain, has been reported [4]. COVID-19 uses an ACE2 protein to gain entry into cells [5]. ACE2 receptors are widely distributed in the human body, including in the lung, liver, stomach, ileum, colon, and kidney, allowing COVID-19 to infect many different organs.

Human coronaviruses are known to cause respiratory and enteric symptoms. During the SARS outbreak in 2002–2003, 16–73% of patients with SARS had diarrhea [6]. Early reports of COVID-19 may not represent the actual rate of GI symptoms, because in the early times of the outbreak the most notable symptoms were severe respiratory symptoms. Viral RNA has been detected in GI epithelial cells and stool of COVID-19 patients, pointing to a possible fecal–oral transmission of the SARS-CoV-2 infection [7].

2. Discussion

The novel SARS-CoV-2 is currently causing a major pandemic that constitutes a world health crisis. COVID-19 patients commonly have fever and respiratory illness. However, some patients also complain of GI symptoms such as diarrhea, nausea/vomiting, and abdominal pain. Fecal–oral transmission of COVID-19 infection has been confirmed by the fact that the virus can replicate in both the respiratory and digestive tracts [8]. The first step of viral entry into enterocytes occurs via angiotensin-converting enzyme 2 (ACE2) binding to ACE2 receptors on the surfaces of enterocytes, similarly to SARS-CoV [4]. After entry into the host cell, viral RNA and proteins are produced by ribosomes. Viral capsids, RNA, and proteins combine to form multiple new copies of COVID-19. These viral particles lead to cytokine release (interleukin (IL)-2, IL-7, tumor necrosis factor (TNF)-α, and macrophage and monocyte products), which mediate various effects on organs. The virus can then spread to other digestive organs, such as the liver using the same ACE2 enzyme [9].

Patients with metabolic conditions such as obesity, diabetes, cardio-metabolic problems, and liver diseases were repeatedly reported to have higher rates of COVID-19 related morbidity in various studies [10][11][12]. Gut microbiota can influence the immune response via affecting disease progression. Not only over-active but also a hypo-active immune response possibly mediated by gut microbiota may lead to severe clinically adverse events. The colon includes a large density of bacteria in the families of Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae, and Ruminococcaceae [13], while Bacteroidetes, Firmicutes, and Proteobacteria are more preponderate in the lung [14]. The gut microbiota may affect pulmonary health through interactions between the gut microbiota and the lungs, named the "gut–lung axis" [15]. The gut–lung axis is reciprocal, so endotoxins, microbial metabolites, can affect the lung through the blood and inflammation of the lungs can affect the gut microbiota as well [16]. Several studies have shown that respiratory infections are associated with a change in the composition of the gut microbiota [17]. Multiple data suggest that the gut

microbiota play a key role in the pathogenesis of sepsis and Adult Respiratory Distress Syndrome (ARDS). Loss of gut bacterial diversity may lead to dysbiosis that can be associated with many diseases [18]. As many elderly and immune-compromised patients progress to serious adverse clinical consequences in Covid-19, possible cross-talk may be occurring between the lung and intestinal microbiota, which may affect the outcome of the disease's course.

To the best of our knowledge, this systematic review and meta-analysis presents the largest patient population involving COVID–19 infection and GI symptoms. We used prepublication repositories medRxiv and bioRxiv that enabled us to search and include unpublished manuscripts from gray literature and enlarge our study population drastically. Most of the studies outside of China began reporting in May 2020, especially those from Western countries. We included 31 Chinese studies with a total of 12,798 patients and 13 non-Chinese studies with a total of 50,094 patients. Therefore, we were able to effectively compare Chinese and non-Chinese COVID-19 infection studies according to their GI manifestations. Currently, the majority of original studies, systemic reviews, and meta-analysis studies are from China with a few exceptions and are mostly limited to the "inpatient-only" clinical setting [19]. We included clinical settings of both mixed studies ("inpatient together with outpatient" plus "outpatient-only") and "inpatient-only" studies.

2.1. Diarrhea

In our meta-analysis the overall prevalence of diarrhea was 15%. The rate of diarrhea was significantly higher in non-Chinese studies (24%) compared to Chinese studies (12% and $p < 0.001$). Similar but lower prevalence rates have been reported in a recent meta-analysis [19]. The pooled prevalence estimate (PPE) of diarrhea was 7.7% in the overall population, 18.3% in non-Chinese studies, and 5.8% in Chinese studies.

In this study, the occurrence of diarrhea was similar for the "inpatient-only" study group (14%) and mixed patient study group (16% and $p = 0.795$). The meta-analysis by Sultan et al. [19] included 39 "inpatient-only" studies with a total of 8521 patients, and the PPE for diarrhea was 10.4%, which was lower than the corresponding PPE of 14.4% in this study.

We detected a total of four studies (three Chinese and one USA study), which tailored the clinical setting as "outpatient-only." Since there was a low number of patients ($n = 951$) we could not compare the "outpatient-only" study group with the "inpatient-only" study group. However, a meta-analysis for these four "outpatient-only" studies was conducted. The PPE of diarrhea was 10%. On the other hand, the meta-analysis by Sultan et al. [19] analyzed three "outpatient-only" studies, including 1701 patients. In that meta-analysis, the PPE value for diarrhea in "outpatient-only" studies was 4%.

In a recent and large comprehensive meta-analysis about general evaluations of patients with COVID-19 infection included 59,254 patients mostly from China but also including 10 other countries, reported a PPE of 9% for any type of GI symptoms [12]. However, subgroups of GI symptoms were not given in that meta-analysis.

The inception studies from China mostly reported low incidence of diarrhea and other GI symptoms [20]. In an earlier meta-analysis including 6686 patients from 35 Chinese studies, which compromised "inpatient-only" studies, a PPE value of 9% for diarrhea was reported [21]. In contrast with low prevalence reports, in a study from Taizhou, China and another one from Shanghai, China in which 212 mild COVID-19 patients were included, the rates of any GI symptoms were reported as high as 42.8% and 43.8%, respectively [22][23]. More recent reports from China claimed even higher rates of diarrhea (49.5%) and any GI symptoms (79%) [24]. Interestingly, a Chinese study including 232 hospitalized patients from Wuhan compared the rate of diarrhea between a group of patients who were admitted from January 19 to February 11, 2020 with that of another non-overlapping group of patients who were admitted from February 12 to March 2020 at the same hospital setting [25]. They concluded that as the COVID-19 infection outbreak progressed, the rate of diarrhea increased from 19% up to 43% ($p = 0.022$) in these two distinct groups of hospitalized patients.

The increase in the reported rates of GI symptoms from Chinese studies needs further explanation. Possible explanations may include increased awareness of non-respiratory symptoms, increased documentation, and re-infection as the outbreak progressed. Re-infection is common for "seasonal" coronaviruses 229E, OC43, NL63, and HKU1 [26]. COVID-19 can also reoccur after the first infection. It was confirmatively reported that one patient had a re-infection instead of persistent viral shedding from the first infection, by the epidemiological, clinical, serological, and genomic analyses [27]. These results showed that SARS-CoV-2 may continue to circulate among human populations.

2.2. Nausea/Vomiting

The PPE of nausea/vomiting for the whole study population was 10%, which included 44 studies with a total of 46,390 patients. The PPE of nausea/vomiting was significantly higher in non-Chinese studies (17%) than in Chinese studies (7% and $p < 0.001$).

In a recent meta-analysis by Sultan et al. [19], the overall PPE of nausea/vomiting was reported to be 7.8%. It was also noted that nausea/vomiting PPE in non-Chinese studies had a higher value (14.9%) than Chinese studies (5.2%). These results are in line with the current study results but have lower rates.

In this study, we reported the PPE for of nausea/vomiting for 22 "inpatient-only" studies was (12%). The PPE was (6%) for nausea/vomiting in an earlier Chinese meta-analysis that included 6686 hospitalized patients from 35 studies [21]. In this study, PPE of nausea/vomiting in the 22 mixed studies was (8%). Still, the difference was not statistically significant between "inpatient-only" and mixed-study groups.

2.3. Abdominal Pain/Discomfort

In the whole study population, the overall PPE of the abdominal pain/discomfort symptom was 6%. The abdominal pain/discomfort symptom was significantly higher in non-Chinese studies (9%), compared to Chinese studies (4% and $p < 0.001$). In a recent meta-analysis by Sultan et al. [21], the overall PPE of the abdominal pain/discomfort symptom was reported as 3.6%. Sultan et al. reported that non-Chinese studies had a PPE value of 5.3%, which is higher than that of Chinese studies (2.7%) and is in line with our results, but still has lower rates than what we have seen. The occurrence of the abdominal pain or discomfort symptom was significantly higher in the mixed-patient study group (7%) when compared to the "inpatient-only" study group (4% and $p = 0.032$).

2.4. Anorexia

The overall PPE of anorexia was 18% in the whole study population and was the most prevalent GI symptom. The anorexia symptom was higher in Chinese studies (21%) when compared to non-Chinese studies (17%), but the difference was not statistically significant (p: 0.783). In a Chinese meta-analysis including 6686 patients, the reported PPE of the anorexia symptom was the same as that in this study, 21% [21]. Usage of experimental drugs and herbal medicine against COVID–19 infections might be a possible explanation for the higher rate of anorexia symptom PPE values [28].

3. Conclusions

In this highly populated and comprehensive systematic review and meta-analysis study, we reported high PPE rates of anorexia, diarrhea, nausea/vomiting, and abdominal pain. Although healthcare providers and patients are well aware of the common symptoms of COVID-19 such as fever, cough, and shortness of breath, there is a need to raise awareness about the fact that not all individuals present with these symptoms, as gastrointestinal symptoms are relatively common with this disease. The PPE rates of diarrhea, nausea/vomiting, and abdominal pain were significantly higher in non-Chinese studies compared to Chinese studies. We also observed a higher prevalence for GI symptoms in Chinese studies than what was reported previously. Non-respiratory symptoms, including those related to the GI tract, should be more carefully evaluated and reported in future studies.

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