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Gastrointestinal Coronavirus disease 2019: epidemiology, clinical features, pathogenesis, prevention and management

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Abstract

Introduction: The new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiologic agent of coronavirus disease 2019. Some authors reported evidences that patients with SARS-CoV-2 infection could have a direct involvement of the gastrointestinal tract, and in symptomatic cases, gastrointestinal symptoms (diarrhea, nausea/vomiting, abdominal pain) could be very common.

Area covered: In this article, we reviewed current published data of the gastrointestinal aspects involved in SARS-CoV-2 infection, including prevalence and incidence of specific symptoms, presumptive biological mechanism of GI infection, prognosis, clinical management and public health related concerns on the possible risk of oral-fecal transmission.

Expert opinion: Different clues point to a direct virus infection and replication in mucosal cells of the gastrointestinal tract. In vitro studies showed that SARS-CoV-2 could enters into the gastrointestinal epithelial cells by the Angiotensin-Converting enzyme 2 membrane receptor. These findings, coupled with identification of viral RNA found in stools of patients, clearly suggest that a direct involvement of gastrointestinal tract is very likely. This can justify most of the gastrointestinal symptoms but also suggest a risk for an oral fecal route for transmission, additionally or alternatively to the main respiratory route.

Key words: Coronavirus; COVID-19; gastrointestinal involvement; fecal-oral transmission; management

Article highlights

- A significant portion of patients with SARS-CoV-2 infection develop gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain.
- SARS-Cov-2 enters into the gastrointestinal cells by binding of the envelope's spike protein (S) with the angiotensin-converting enzyme 2 (ACE2) membrane receptor of the host cell.

- A high level of ACE2 receptor found in the gastrointestinal epithelium and virus nucleocapsid protein detected in cell cytoplasm, suggest a direct involvement of gastrointestinal tract.
- The virus replication in the gastrointestinal tract may occur even after clearance of the virus in the respiratory tract.
- The available evidence suggests the possibility of a fecal-oral transmission. If confirmed, this can have enormous implications for public and global health.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified in early December in Wuhan (Hubei, China), is a newly described betacoronavirus, now identified as the etiologic agent of coronavirus disease 2019 (Covid-19), that the World Health Organization (WHO) has declared a public health emergency of international concern[1]. Globally, until June 12th 2020, 7.598.201 cases were confirmed, and a total of 423.866 patients have died from this viral infection[2].

SARS-CoV-2 infection can occur with a completely asymptomatic[3] and pauci-symptomatic course, extra-respiratory illness (cardiac, gastrointestinal, hepatic, renal, neurological, olfactory, gustatory, ocular, cutaneous and haematological symptoms)[4], a moderate and mild upper

respiratory tract illness, or a severe viral pneumonia with possible respiratory failure and death[5,6]. It has been established that airway exposure to respiratory droplets from a COVID-19 infected patient is the main mechanism for transmission[7–11]. Also, SARS-CoV-2 has the potential to be transmitted through fomites or surfaces, when aerosolized, remaining viable for up to 3 hours in average, and for up to 4 hours on copper, 24 hours on cardboard, and 72 hours on plastic and stainless steel[12].

However, different authors have reported that a portion of patients with SARS-CoV-2 infection also develop gastrointestinal (GI) symptoms, such as nausea, vomiting, abdominal pain and diarrhea[5,13]. The prevalence of GI symptoms is not well defined, being reported variably from 4.6% to 78.5% of all COVID-19 patients[14,15].

Few studies recently reported evidences of a direct infection of the GI tract. In particular, SARS-CoV-2 RNA has been consistently found in stools of affected patients and also in wastewaters of a metropolitan area, strongly suggesting that GI tract maybe a direct target of the virus and that faecal–oral transmission could be possible[7,16].

Overall, an indirect clue of the involvement of the GI tract and COVID-19 is pointed from previous studies on other coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which RNAs were also found in stool samples of patients with confirmed infection[17,18].

The aim of this review is to provide an overview on the current published data of the GI aspects involved in SARS-CoV-2 infection, including prevalence and incidence of specific symptoms, presumptive biological mechanism of GI infection, prognosis, clinical management and public health related concerns on the possible risk of oral-fecal transmission.

2. Methods

2.1 Data source and search strategy

A review of the literature was performed based on Pubmed database to detect studies that providing information on biologic characteristics, clinical and therapeutic features and management of patients with COVID-19 GI manifestations (abdominal pain, nausea/vomiting, diarrhea), published until April 2020. The following MeSH search headings were used: “COVID-19”, “SARS COV2”, “clinical features”, “gastrointestinal symptoms”, “faecal”, “stool”.

2.2 Inclusion and exclusion criteria

We included in the review prospective and retrospective studies. Every study reporting data on adult patients with COVID-19 infection and GI manifestation was considered. Therefore, we excluded studies on solid organs, such as pancreas or liver, and any other organs rather than luminal GI tract. Case report, case series of less than 10 patients, review articles, meta-analysis and other forms (e.g. letters to the Editor, commentary) were excluded. This has been chosen to select clinical manifestations with a solid link with COVID-19. Nevertheless, some infrequent GI tract signs or symptoms, not described in the current manuscript, could thus still have clinical significance in single cases.

Also, we excluded studies published in languages rather than English.

2.3 Data extraction

We extracted data on institution, study time period, type of study, number of participants, number of patients with GI symptoms, number of patients for each type of symptoms (abdominal pain, nausea/vomiting, diarrhea), need of intensive care unit (ICU) admission, death and severity of infection. We also extracted data on available test methods for the detection of virus RNA on each study.

2.4 Statistical analysis

A meta-analysis was performed to better define if there was a relationship between disease severity and GI symptoms. The statistical analysis was performed using Review Manager software 5.3

(RevMan 5.3). Variables were pooled using the odds ratio (OR) with 95% confidence intervals (CI). We used the Mantel-Haenszel method to estimate the OR. Heterogeneity was investigated by the use of I^2 statistic.

3. Results

3.1 Clinical features of GI involvement

In symptomatic cases the mean clinical onset is estimated between day 4 and 7 (min 2–max 14) from the initial exposure. In accordance to the main site of infection, the most common reported symptoms are fever (77%-98% of patients), dry cough (46%-82% of patients), shortness of breath (3-31%) and myalgia/fatigue (11%-52%). Nevertheless, GI presentation seems also very common, possibly involving up to half of patients. Zhang et al[19] reported that 39.6% (55/139) of infected patients experienced GI symptoms. In some cases, they may also arise before the respiratory symptoms, and on rare occasions, GI manifestations may be the only sign of COVID-19. In this regard, Pan et al[20] identified that 103 out of 204 patients (50.9%), presented digestive symptoms such as lack of appetite (78.6%), diarrhea (34%), vomiting (3.9%) and abdominal pain (1.9%). Among these patients, 97 (47%) developed respiratory symptoms along with digestive symptoms and 6 (3%) presented with only GI symptoms in the absence of respiratory tract involvement. Interestingly, they also reported that patients with digestive symptoms had a significantly longer time (9.0 days vs 7.3 days) from onset to admission than those without digestive symptoms. A possible explanation is that patients who might not exhibit typical clinical signs on the onset, eventually do not receive a timely diagnosis.

In order to better characterize this and other aspects, we explored the overall reported rates of GI symptoms (abdominal pain, nausea/vomiting, diarrhea), linked disease severity, death rates, and intensive care unit (ICU) hospitalizations from 15 studies (out of 86), including a total of 3185 COVID-19 patients (Table 1). Twelve studies (80%) were from China, 2 (13.3%) from United

States (USA), and one from Singapore (6.6%). Of these, two were multicenter studies, including 1303 COVID-19 patients[7,20].

Among all selected studies, ten[5,8,19–26] reported a global rate of patients with GI symptoms [33.9% (534/1577)]. Considering individual GI symptoms, almost all studies reported diarrhea[5,8,9,13,19–22,25–28], there were five studies reporting on general complaints as abdominal pain[9,19–21,25] and ten reported nausea and vomiting[5,9,13,19,20,22,25–28]. Overall, diarrhea and nausea/vomiting were reported in 12.5% (191/1525) and 11.5% (139/1210) of COVID-19 patients, respectively. Few patients manifested abdominal pain, 2.7% (27/1010). Diarrhea appears the most constant GI clinical sign and usually consist in a non-severe non dehydrating form, consisting in up to thrice daily episodes of low volume loose stools evacuation[20].

Different studies report a slightly direct correlation between ICU admission and presence of GI symptoms, suggesting that GI involvement may be associated with severe disease[9,22,29,30]. Wang et al[9] showed that ICU patients had a higher probability to have diarrhea [16.7% (6/36) vs 7.8% (8/102); $p=0.20$], nausea [11.1% (4/36) vs 9.8% (10/102); $p>0.99$] and vomiting [8.3% (3/36) vs 2% (2/102); $p=0.13$] but just abdominal pain [8.3% (3/36) vs 0 (0/102); $p=0.02$] emerged as a statistically significant factor. Nevertheless, data on the possible correlation between GI symptoms and ICU admission are contrasting. In this regard, another observational study from China including more than 200 patients showed that those with GI symptoms had a slightly lower probability to receive ICU care [5.94% (6/103) vs 9.9% (10/101); $p=0.28$][20].

Additionally, studies which explored the correlation between death and presence of GI symptoms showed that mortality may be increased in patients with GI involvement[5,12,20,25]. Interestingly, Nobel et al[22] suggest that GI involvement might, conversely, be a marker of better prognosis. In this last study, the presence of GI symptoms was, in fact, associated with a statistically significant lower rate of death [0% (0/97) vs 9% (9/181); $p=0.03$].

Considering these controversial results, we reviewed and analyzed data obtained by studies reporting disease severity, ICU admissions, or mortality. To explore if the presence of GI symptoms (diarrhea, nausea/vomiting and abdominal pain) is associated with a more severe behavior and a worst prognosis, we divided patients into two groups. The “Severe disease” group included patients who had either one of the following three different outcomes: severe disease (defined according to every single study), admission to intensive care unit (ICU) or death. The “Non- Severe disease” group included all other patients (Figure 1).

We did not find a statistically significant difference for the presence of any gastrointestinal symptoms between “Severe” and “Non-Severe” groups of patients (OR 1.16, 95% CI 0.89 – 1.52). Considering each specific symptom, only abdominal pain resulted consistently associated with a more severe behavior (OR 2.83, 95% CI 1.34 - 6.01; $p=0.007$). Indeed, the presence of the most common GI manifestations does not seem to correlate with outcomes, either in direction for better or worsening conditions. This might signify that viral replication in the gastrointestinal tract is not a worrying event from a strict clinical point of view. Direct virus GI involvement per se, might not be capable of determining or changing the overall course of the disease. Accordingly, vomiting and diarrhea in most of cases consist of light or mild manifestations that do not lead into more serious consequences such as dehydration or severe electrolyte imbalance. On the other hand, abdominal pain can be considered as a marker of disease severity. However, there are clues that this might be more likely associated with an indirect involvement of the gastrointestinal tract, secondary to the systemic inflammation syndrome that has been described in severe cases. In this regard, a recent study described some abdominal imaging, surgical, and pathological findings in context of COVID disease, which included small vessel intestinal thrombosis and mesenteric ischemia. In detail, among 412 COVID-19 patients, an abdominal CT scan was performed in 42 patients, showing abnormal bowel wall signs in 31% (13/42), fluid-filled colon in 43% (18/42), solid organ involvement such as pancreatitis and hepatitis in 5% (2/42). Interestingly, some of these signs correlated with a higher rate of admission in ICU where patients were more likely to have abnormal

bowel wall signs [50% (10/20) vs 14% (3/22); $p=0.02$] and fluid-filled colon [65% (13/20) vs 23% (5/22); $p=0.01$][24]. In conclusion, abdominal radiological findings could be useful to identify more severe forms of the disease and in differential diagnosis of acute abdomen syndromes, some of which might be virus related.

3.2 Biological mechanism of GI infection

One of the open questions is whether and how the SARS-CoV-2 virus might actually infect and replicate in mucosae cells of the gastrointestinal tract. Next point would be to understand the physiopathology of GI tract damage. In particular, whether the GI clinical consequences are related to virus direct damage by replication and cell lysis or to an indirect effect caused by the immunological answer. Genomic characterization of SARS-CoV-2 showed a high homologous degree between SARS-CoV-2 and SARS-CoV in the receptor-binding domain structure[31–35]. SARS-Cov enters into the target cells by binding of the envelope's spike protein (S) with the angiotensin-converting enzyme 2 (ACE2) membrane receptor of the host cell. The next step consists in the fusion of virus with cell membrane and enter the cytoplasm. This passage is mediated by a cellular proteases that splits the Spike protein allowing fusion of its S2 subunit with cellular membrane[35–37]. SARS-COV-2 seems to share the same mechanism. This has been showed in vitro, where SARS and SARS2 virus have shown to infect a similar spectrum of susceptible cell lines. Moreover, the entry can be enhanced or blocked by changing the expression of ACE 2 receptor in cell lines or by using an inhibitor of the cellular serine protease TMPRSS2 which is responsible of the Spike protein splicing[35]. Also, ACE2 is a chaperone to B0AT1 an amino-acid transporter, that inserts tryptophan, used to create antimicrobial peptides. Therefore, when SARS-CoV-2 blocks ACE2 and B0AT1, a lack of antimicrobial peptides leads to an abnormal composition of the microbiome. An alteration of the microbiome may cause more systemic inflammation and an imbalance of the innate immune system of the gut[38].

Some studies indicate that ACE2 expression in human body is not limited to the alveolar type II cells in the lung, where this receptor has the lowest concentration in the human body. Other extrapulmonary tissues, such as the cholangiocytes, cells of renal and cardiovascular system, as well as gastrointestinal epithelium, have the highest number and density of ACE2[34,39–43].

In this regard, Liang et al[45] analyzed 7216 individual cells derived from the small intestine of mice. ACE2 receptor was highly expressed in the small intestine, especially in proximal and distal enterocytes. In mice, the interaction between SARS-Cov-2 and ACE2 led to malabsorption, unbalanced intestinal secretion and stimulation of the enteric nervous system, resulting in diarrhea.

Another study[37][46], using human small intestine organoids for detection of virus particles and viral RNA, showed that SARS-Cov-2 could have a similar tropism for ciliated airway and enterocytes cells. In humans, infection of the gastrointestinal tract has been demonstrated by endoscopic biopsies on individuals who tested positive to virus RNA in stools. Immunofluorescence showed that ACE2 is expressed in gastrointestinal epithelial cells. These were also found positive for the presence of virus nucleocapsid protein in the cytoplasm of the stomach, duodenum, and rectum epithelium[35].

Also the expression of these receptors in the GI tract seems to depend on patients age[44]. ACE2 gene expression was determined by duodenal biopsy in 43 healthy human adults. Results of this study showed that there is a higher intestinal ACE2 mRNA expression in older patients than in younger. This may impact on their susceptibility to develop intestinal symptoms.

Uzzan et al[47] showed that enterocytes may be infected by SARS-CoV-2, leading to GI symptoms and worsening of inflammation. They measured citrulline, a very specific biomarker of small bowel enterocytes mass and function, to assess enterocytes function in patients with SARS-CoV-2 infection. They found that digestive symptoms were more frequent in patients who had low citrulline plasma level, as compared with patients who had normal citrulline.

These findings, coupled with continuous identification of viral RNA found in stools of patients, clearly suggest that a direct involvement of GI tract is very likely. This can justify most of the GI

symptoms but also suggest a risk for an oral fecal route for transmission, additionally or alternatively to the main respiratory route.

As noted above, however, direct damage may not explain all the disease related GI consequences. An inflammatory response could have a significant role in the pathogenesis of COVID-19. As showed by previous studies, SARS-CoV-2 infects enterocytes causing cytokine and chemokine release, leading to an acute intestinal inflammation. In this regard, Effenberger et al[48] showed that SARS-CoV-2 infection in patients with symptomatic disease, leads to an intestinal inflammatory response, as evidenced by elevated fecal calprotectin and a systemic IL-6 response.

Moreover, it is now well known that a number of patients, especially those experiencing severe forms, may present with vascular thromboembolic complications[40]. These might be secondary to the so called cytokine storm syndrome[41] which has been described in many cases. We speculate that this might be the case also in severe gastrointestinal forms, where the major clinical consequences might rather be secondary to the systemic inflammation state[49]. As cited above, and similarly to what happens with lung disease, occasionally also gastrointestinal tract may be involved with more severity. These severe forms may include acute abdomen syndromes which might be secondary to thromboembolic complications, consisting in small mesenteric vessel thrombosis leading to bowel ischemia.

3.3 Fecal test and diagnostic implications

Diagnostic strategy for COVID-19 patients is based on nucleic acid detection, mostly in the oropharyngeal swabs or other respiratory tract samples[42]. Nevertheless, some studies showed that fecal samples could be useful to detect SARS-CoV-2 infection. Real-time reverse transcriptase-PCR (RT-PCR) is currently used to analyzed oropharyngeal and anal samples, while reports based on other methods such as viral isolation in cell cultures are scarce[42,45]. In order to better define the role of fecal testing in diagnosis, we explored four[26,35,50,51] studies including a total of 443 patients all with positive oropharyngeal samples (Table 2). Overall, positive fecal RNA test was

reported in 52.9% (64/121) patients. Lin et al[26] explored the associations between GI symptoms and the presence of SARS-CoV-2 in feces of 65 hospitalized patients, 42 with and 23 without GI symptoms. Overall, 47.7% (31/65) had positive fecal test, and patients with GI symptoms had a slightly higher probability to have positive fecal test [52.4% (22/42)] but a proportion of those without any symptoms was also positive [39.1% (9/23)]. In this regard, Zhang et al[51] also reported on 14 hospitalized patients with positive oropharyngeal swabs and without gastrointestinal symptoms. Stool samples were collected for each patient, and five out of 14 patients (35.7%) resulted positive. Moreover, some showed that stool samples can be detected positive for SARS-CoV-2 RNA even after negative RT-PCR test results for viral RNA in respiratory swabs. The clearance of viral RNA in stools may be delayed comparing to oropharyngeal swabs; Ling et al[52] showed that stool specimens turned negative for SARS-Cov-2 RNA with a median of 11.0 (9.0-16.0) days. The median time from negative throat swabs to stool specimens negativity was 2.0 (1.0-4.0) days. In another series of 98 patients, both respiratory and fecal samples were collected from 74. Fecal samples from 55% (41/74) were positive for SARS CoV-2 RNA. After the first symptom, fecal samples remained positive for a mean of 27.9 days (10-7) with one patient being still positive after 47 days and another patient had positive fecal samples for 33 days after the respiratory samples became negative. These evidences, although not conclusive, strongly suggest that the virus replication in the gastrointestinal tract may occur for a long period, even after clearance of the virus in the respiratory tract[53]. Current guidelines suggest discharge from hospital if patient has no symptoms and at least two negative RT-PCR test results for SARS-CoV-2 RNA from two sequential respiratory tract specimens collected more than 24 hours apart. However, following these evidences, detection of fecal RNA should in our opinion also be considered for diagnostic confirmation and as a proof of recovery.

3.4 Possibility of fecal-oral transmission

Studies on other coronaviruses, such as SARS-CoV and MERS-CoV, showed a relationship between environmental condition (temperature, humidity and type of surface) and the possibility of fecal-oral transmission[54–56]. SARS-CoV and MERS-CoV are both viable in conditions with low temperatures and humidity. SARS-Cov can survive for up to 2 weeks after drying, remaining viable for up to 5 days at temperatures of 22–25°C and 40–50% relative humidity, with a gradual decline in virus infectivity thereafter[54]. Also, MERS-Cov is viable in low temperature, low humidity conditions[55]. The virus is viable on different surfaces for 48 h at 20°C and 40% relative humidity, although viability decreased to 8 h at 30°C and 80% relative humidity conditions[55]. SARS-CoV has also been detected in sewages. The virus can survive for 14 days in sewage at 4 °C, 2 days at 20 °C, and its RNA can be detected for 8 days after the virus has been inactivated[56]. In 2003, Leug et al [53] reported that patients could discharge SARS-CoV in their stool up to 73 days after symptom onset and the stools with the virus became the resource of contamination of airdrops and a variety of environmental surfaces, which may contributed to the clusters of infection. Based on the available data of SARS-CoV and MERS-CoV, taking into consideration both environmental dynamics and the persistence of viral infectivity, Heller et al[57] propose a similar framework for the fecal-oral hypothesis of SARS-CoV-2 transmission. They describe three possible primary routes: water, surfaces and places where insect vectors are present. Also, they suggest a new route defined as “water-cleaning”, in which contaminated water used to clean surfaces may, via hand contact, bring the virus to the mouth.

Viral RNA has been detected in 29–55% of stool samples from COVID-19 patients[35,58,59], as well as for positive samples obtained from toilet sites[60]. Other reports of virus viability in stools have also been isolated from specimens[59,61]. Other studies reported that viral RNA can be detected in stools or rectal swabs even after oro/naso-pharyngeal swabs turn negative[58,62].

These data raise the concern for elucidating a possible fecal–oral transmission route of SARS-CoV-2[63,64], as was suspected with the SARS outbreak of 2002–2003 on aerosolization of fecal waste[65].

3.5 Impact on public health

A recent study, researched the presence of SARS-CoV-2 in the wastewater to investigate the possible hidden virus circulation in human population[66]. Authors performed a time-course quantitative analysis of SARS-CoV-2 by RT-qPCR in 23 raw and 8 treated wastewater samples collected from 3 major wastewater treatment plant of the Parisian. All raw wastewater samples scored positive for SARS-CoV-2, and 6 out of 8 samples from treated wastewater scored positive. Furthermore, they correlated the genome units in raw wastewater with the increase in the number of deaths observed. They found that an increase of genome units was followed by an increase in the number of fatal cases. Unfortunately, to our knowledge, this is the only report of this kind. Similar quantitative monitoring of SARS-CoV-2 genomes in wastewaters in other contexts may be of important interest from a scientific perspective as well as from a public health government point of view. This could bring important and additional information for better survey of SARS-CoV-2 circulation at the local or regional scale, as well as for advice on specific hygiene policies.

4. Conclusion

In summary, although COVID-19 clearly express its worst nature in the respiratory tract, available data point to the importance of not underestimating the presence of gastrointestinal symptoms. As already noted above, if patients are screened just for respiratory involvement, we may completely miss those who initially present with extrapulmonary symptoms and/or resulting on a late diagnosis, increasing the risks of disease progression and the risk for a fecal-oral route for transmission, additionally or alternatively to the main respiratory route.

5. Expert opinion

Clinical knowledge about COVID 19 is developing and growing as disease spread. During the past 3 months we have learned from sparse reports and few case series that gastrointestinal involvement may play an important part during the infection. This might have, in fact, important consequences not just from a clinical point of view but also from a public health and prevention prospective. However, giving also the constant state of emergency, a clear summary of what is known and yet to understand in this field still lacks. By exploring the current published data concerning gastrointestinal aspects of SARS-CoV-2 infection, we here propose an overview of the argument that includes a critical analysis of the published data as well as personal thoughts and considerations on clinical relevance of specific symptoms, presumptive biological mechanism of gastrointestinal infection and public health related concerns on the possible risk of oral-fecal transmission.

Different clues point to a direct virus infection and replication in mucosal cells of the gastrointestinal tract. In vitro studies showed that SARS-CoV-2 could enter into the gastrointestinal epithelial cells by the Angiotensin-Converting enzyme 2 membrane receptor. These findings, coupled with identification of viral RNA found in stools of patients, clearly suggest that a direct involvement of gastrointestinal tract is very likely. This can justify most of the gastrointestinal symptoms but also suggest a risk for an oral fecal route for transmission, additionally or alternatively to the main respiratory route.

In our opinion, although it is still unclear if possible, and if so, under in which amount the oral-fecal route may participate in the spreading of the disease, the available biological and environmental evidences strongly suggest that this possibility must not be overlooked.

According to this, and to the previous evidence shown in relation to the virus viability timeline on different surfaces, in addition to the already known aerosolization risk as the main route for transmission, we accentuate the need for further environmental studies to be followed. If confirmed, this hypothesis of transmission route can have enormous implications to public and global health.

Based on the information that has been exposed and while more environmental studies are elucidated, we suggest a strong preventive and education communication campaigns for hand washing, with great emphasis when using the toilet, and if possible, adhering to disinfection protocols, as well as continue to pay special attention to healthcare professionals performing gastrointestinal procedures.

Among all the diagnostic and therapeutic procedures, upper endoscopy has been noted as one of the major risk procedures for infection due to inhalation of droplets, conjunctival contact, and contact contamination. Supporting this consideration, the risk of performing upper, and also of lower one, gastrointestinal tract diagnostic and surgical procedures should be considered as high risk of infection[66]. Considering the previous descriptions in relation to the findings of viral particles in feces, it is in our straightforward opinion that all procedures where fecal contamination is possible, strict protocols must be followed and should be considered as high risk. This may also apply to other frequent acts as rectal digital examination, anoscopy or endorectal ultrasound. The first strategy for risk reduction is decontamination of the room and all equipment before and after every procedure using an alcohol-based solutions[67]. In addition, all health workers involved during these procedures should use personal protective equipment (PPE), including gloves, hairnet, protective eyewear (goggles or face shield), waterproof gowns, and respiratory protective equipment as when dealing with invasive procedures over the respiratory tract[68].

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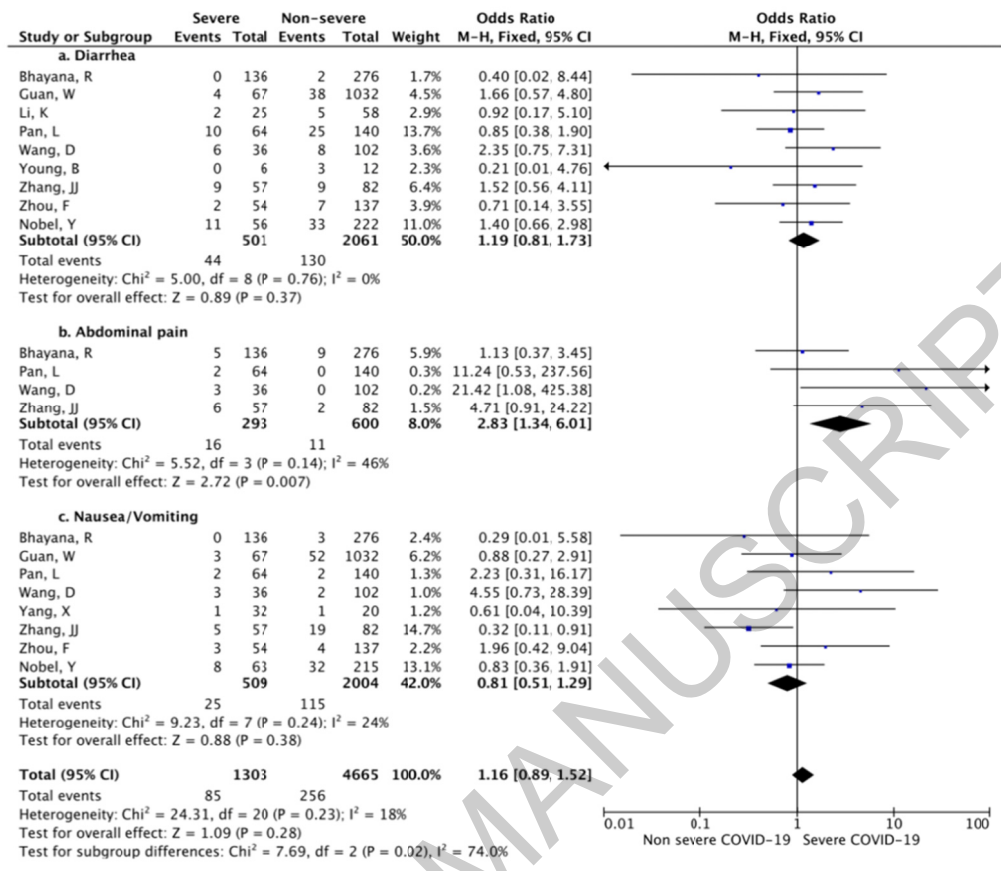
Figure and table legends

Figure 1: Comparison of prevalence of diarrhea (a), abdominal pain (b), nausea/vomiting (c) in severe disease compared with non-severe disease

Table 1: Gastrointestinal symptoms and severity of new COVID-19 in patients with SARS-Cov-2 infection

Table 2: Fecal test in patients with SARS-CoV-2 infection

Figure 1



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Tables

Table 1. Gastrointestinal symptoms and severity of new COVID-19 in patients with SARS-Cov-2 infection

Authors	References	Institutions	Recruitment	Patients included n	Patients with GI symptoms n(%)[§]	Abdominal pain/discomfort n(%)	Nausea/vomiting n(%)	Diarrhea n(%)	ICU n(%)	Death n(%)	Disease severity n(%)
Chen, N	[27]	Wuhan, China	Jan 1 – Jan 20, 2020	99	≥2 (3%)	NA	1 (1%)	2 (2%)	NA	NA	NA
Guan, W	[7]	552 hospitals in 30 provinces, China	Dec 11, 2019 – Jan 31, 2020	1099	≥55 (5%)	NA	55 (5%)	42 (3.8%)	NA	NA	22 (2%)
Huang, C	[8]	Wuhan, China	Dec 1, 2019 – Jan 2, 2020	41	1 (2.4%)	NA	NA	1 (2.4%)	NA	NA	NA

Li, K	[21]	Chongqing, China	Jan – Feb 2020	83	7 (8.4%)	7 (8.4%)*	NA	7 (8.4%)*	NA	NA	2 (2.4%)
Nobel, Y	[22]	New York, USA	Mar 10 – Mar 21, 2020	Case 278 Control 238	97 (61%)	NA	63 (58%)	56 (61%)	14 (14%)	0	NA
Shi, H	[30]	Wuhan, China	Dec 20, 2019 – Jan 23, 2020	81	≥4(5%)	NA	4 (5%)	3 (4%)	NA	NA	NA
Yang, X	[5]	Wuhan, China	Dec 24, 2019 – Jan 26, 2020	52	2 (4%)	NA	2 (4%)	NA	NA	1 (5%)	NA
Young, B	[23]	Singapore	Jan 23 – 3 Feb 2020	18	3 (17%)	NA	NA	3 (17%)	NA	NA	0
Zhang, JJ	[19]	Wuhan, China	Jan 13 – Feb 3, 2020	140	55 (39.6%)	8 (5.8%)	24/139 (17.3%)	18/139 (12.9%)	NA	NA	24/57 (42.1%)
Zhou, F	[13]	Wuhan, China	Dec 29, 2019 – Jan 31, 2020	191	≥9 (5%)	NA	7 (4%)	9 (5%)	NA	4 (2%)	NA

Zhou, Z	[25]	Wuhan, China	Dec 20, 2019 – Feb 9, 2020	254	66 (26%)	3 (1.2%)	36 (14.2%)	46 (18.1%)	NA	4 (1.6%)	NA
Pan, L	[20]	3 Wuhan Hospitals, China	Jan 18 - Feb 28, 2020	204	103 (50.5%)	2 (1.9%)	4 (3.9%)	35 (34%)	6 (5.9%)	19 (18.4%)	12 (11.6%)
Bhayana, R	[24]	Boston, USA	Mar 27 - Apr 10, 2020	412	142 (34%)	14 (33%)	3 (7.1%)	2 (4.8%)	40 (29%)	NA	NA
Wang, D	[9]	Wuhan, China	Jan 1 – Jan 28, 2020	138	≥19 (13.8%)	3 (2.2%)	19 (13.8%)	14 (10.1%)	16 (11.6%)	NA	NA

*Two symptoms merged together

§ If the global number of gastrointestinal symptoms were not reported by authors, the global number of gastrointestinal symptoms was defined with the number of the most frequent symptom

GI= gastrointestinal; ICU= intensive care unit; NA= not available

Table 2. Fecal test in patients with SARS-CoV-2 infection

Authors	References	Institutions	Recruitment	Patients included n	Patients with GI symptoms n(%)	Positive fecal test n(%)	Time difference between negative oropharyngeal test and negative fecal test
Lin, L	[26]	Guangdong, China	Jan 15 – Feb 15 2020	95	58	31/65 (47.7%)	NA
Zhang, J	[51]	Jinhua, China	Jan 27 – Feb 10 2020	14	0	5/14 (37.5%)	NA
Chen, Y	[50]	Wuhan, China	Jan 20 - Feb 9, 2020	42	8 (19.05%)	28/42 (66.67%)	7 (6-10)*
Ling, Y	[52]	Shanghai, China	Jan 20 - Feb 10, 2020	292	NA	NA	11 (9-16)*

*Median (Interquartile range)

GI= gastrointestinal; NA= not available

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