Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Indian Journal of Medical Microbiology 40 (2022) 404–408

Contents lists available at ScienceDirect

Indian Journal of Medical Microbiology

journal homepage: www.journals.elsevier.com/indian-journal-of-medical-microbiology

Original Research Article

Presence of diarrhea associated with better outcomes in patients with COVID-19 – A prospective evaluation

Seerat Singh [a,1], Jayanta Samanta [b,*,1], Vikas Suri [a], Ashish Bhalla [a], Goverdhan Dutt Puri [c], Rakesh Sehgal [d], Rakesh Kochhar [b]

[a] Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[b] Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[c] Department of Anesthesia, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[d] Department of Virology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

ARTICLE INFO

Keywords:
Coronavirus
Diarrhea
Gastrointestinal
Fecal
SARS-CoV-2

ABSTRACT

Purpose: Gastrointestinal (GI) manifestations have been well documented in patients with coronavirus disease 2019 (COVID-19), but its clinical impact on the course of the disease is debatable. Majority of the available data is retrospective, and hence this prospective study was planned to study the impact of GI symptoms on COVID-19 outcome.

Methods: All COVID-19 patients admitted in a tertiary care centre from August–October 2020 were screened and patients without pre-existing GI diseases were included. A detailed history of the various symptoms including duration was documented. Various baseline laboratory investigations and inflammatory markers were conducted as per the protocol. Patients with and without diarrhea were compared for the various disease outcome parameters.

Results: Of the 244 patients screened, 203 patients (128 males; 63.1%) were included. Respiratory symptoms alone were present in 49 (24.1%), GI symptoms alone in 20 (9.9%) and 117 (57.6%) had both. Overall GI symptoms was noted in 137 (67.5%) cases with the commonest being diarrhea (61; 30.0%). Patients with both respiratory and any GI symptoms showed a lower trend towards need for mechanical ventilation (12.2% vs 7.7%; $p = 0.35$) and mortality (10.2% vs 4.3%; $p = 0.14$) compared to respiratory symptoms alone, although not statistically significant. Patients with diarrhea ($n = 61$) had no mortality (0% vs 7.7%; $p = 0.036$) or need for mechanical ventilation and shorter hospital stay compared to those who did not have diarrhea.

Conclusion: GI symptoms are frequent in patients with SARS-CoV-2 infection and the commonest is diarrhea. Diarrhea is a harbinger of better outcome with lower mortality among COVID-19 positive patients.

1. Introduction

Since its first report in December 2019, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to become a world-wide pandemic affecting more than 175 million people and claiming more than 3.5 million lives [1]. The virus is primarily a respiratory pathogen, but its extra-pulmonary effects have drawn more and more attention over the ensuing period. The first reported case of coronavirus disease 2019 (COVID-19) from the USA had gastrointestinal (GI) complaints [2]. Since then, multiple studies have reported GI [3], liver [4] and pancreatic manifestations of COVID-19.

The commonly reported GI symptoms in COVID-19 patients are nausea, vomiting and diarrhea. The other symptoms include pain abdomen, loss of taste or smell and loss of appetite [4,5]. Some may even experience severe disease in the form of GI bleed, acute pancreatitis, bowel perforation and liver injury. SARS-CoV-2 enters the human host cells through the angiotensin-converting enzyme 2 (ACE2) [6]. This ACE2 is found to be present in the lining epithelium of most of the small intestine. Thus, the virus infecting the intestinal epithelial cells could explain the GI symptoms [7] and the fecal shedding of the virus [8]. Interestingly, some patients may present with GI manifestations at the outset sans the respiratory complaints or may develop GI symptoms

* Corresponding author. Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Sector-12, Chandigarh, 160012, India.
E-mail address: dj_samanta@yahoo.co.in (J. Samanta).
[1] SS and JS have contributed equally and be considered as co-first authors.

https://doi.org/10.1016/j.ijmmb.2022.04.002
Received 12 December 2021; Received in revised form 2 April 2022; Accepted 8 April 2022
Available online 26 April 2022
0255-0857/© 2022 Indian Association of Medical Microbiologists. Published by Elsevier B.V. All rights reserved.

during the disease [9]. This might lead to a potential risk of prolonged exposure to family members and health care workers, enabling the virus spread by droplet and possible feco-oral transmission.

While GI manifestations of COVID-19 have been well established, its clinical impact on the course of the disease is not clear. While some studies reported no impact of GI symptoms on the severity of the disease [10,11], others have reported GI manifestations to be associated with more severe disease and poor outcomes [4,12,13]. Interestingly, few studies have now shown that GI symptoms, specially diarrhea and/or nausea/vomiting may be associated with less severe disease [7,14,15]. Unfortunately, majority of these are retrospective information collected from electronic database. Hence, this study was planned to prospectively evaluate the impact of GI symptoms on the clinical course and outcome in patients with COVID-19 infection.

2. Materials and methods

This was a prospective, hospital-based study conducted from August 2020 to October 2020, at a tertiary care centre having a special wing for COVID-19 infected patients. All patients, more than 13 years, positive for SARS-CoV-2 by RT PCR of nasopharyngeal swab admitted to the dedicated wards or ICU were included. A detailed history was documented regarding the various symptoms, duration of each symptom, comorbidities, and prior drug intake. For patients who were unable to communicate (due to severe dyspnea, unconsciousness or being on mechanical ventilation), history prior to admission was obtained from the closest kin, medical history and communication with the physician in-charge of the patient whenever necessary. Apart from respiratory symptoms and constitutional symptoms such as fever, cough, sore throat, shortness of breath, chest tightness, chest pain and rhinorrhea, GI symptoms such as nausea, vomiting, loss of taste and smell, diarrhea, pain abdomen/discomfort, heart burn, bloating, dyspepsia, loss of appetite, hematemesis, melena were inquired about, and duration of these symptoms recorded. Diarrhea was defined as altered consistency of stool or evacuation of $\geq$3 stools per day. All patients with pre-existing GI diseases were excluded.

The clinical severity of COVID-19 was defined as per the NIH guidelines into mild, moderate and severe/critical illness [16]. All patients underwent laboratory investigations including complete blood count (CBC), serum electrolytes (SE), renal function test (RFT), lipid profile, amylase, lipase, calcium, phosphorus. Additionally, coagulation markers such as serum D-dimer and fibrinogen and inflammatory markers such as C-reactive protein (CRP) and procalcitonin were measured. Other investigations (ultrasound abdomen, chest X-ray, CT scan) were carried out as per the clinical needs of the patient. Informed consent was obtained from all individual participants included in the study. All patients were managed as per the Institute's protocol based on a multi-disciplinary team decision on a case-to-case basis. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of PGIMER, Chandigarh, India (Date: October 26, 2020./No.: INT/IEC/2020/SPL-1316).

2.1. Outcome measures

The patients were classified by the mode of presentation into those having respiratory symptoms alone, GI symptoms alone or both. The prevalence of the various GI symptoms was documented. Diarrhea being the most common and consistent GI symptom, patients were also classified into those having diarrhea and those without and compared. Various disease outcomes such as severity of the disease, need for ICU admission, need for oxygen/mechanical ventilation, need for other organ support (dialysis/inotropes) and mortality were documented.

2.2. Statistical analysis

All the data was entered into a spreadsheet and analysed using the SPSS (version 21.0, SPSS Inc; Chicago, USA) software. Continuous variables were expressed as mean with standard deviation or median with interquartile range. Dichotomous variables were compared using the Chi-square test or the Fischer's exact test. Other statistical methods were used as appropriate. The p value of less than 0.05 were taken as statistically significant. A multivariate logistic regression analysis was done to study the impact of GI symptoms on the severity of COVID-19.

3. Results

Of the 244 patients screened, 41 were excluded (23 had inadequate data and 18 had pre-existing GI diseases) (Fig. 1). A total of 203 patients (128 males; 63.1%) were included for the final analysis, of which 49 (24.1%) had moderate disease and 32 (15.8%) had severe disease. Respiratory symptoms alone were present in 49 (24.1%), GI symptoms alone in 20 (9.9%) and 117 (57.6%) had both respiratory and any GI symptom (Fig. 2). Remaining 17 patients (8.4%) had presented with fever and non-specific symptoms such as malaise, body ache etc. Overall, 27 patients (13.3%) required ICU stay, 39 (19.2%) needed some form of organ support, 15 (7.4%) required mechanical ventilation and 11 (5.4%) succumbed. Of the 117 patients having both respiratory and GI symptoms, 33 (28.2%) had GI symptoms followed by respiratory, 75 (64.1%) had respiratory symptoms followed by GI symptoms, while 9 (7.7%) had both respiratory and GI symptoms at presentation. Of the 75 patients who had respiratory symptoms followed by GI symptoms, the median interval between development of first symptom and GI symptom development was 3.0 (1–11) days.

Overall GI symptoms was noted in 137 (67.5%) cases of which 47 (23.2%) had GI symptoms at presentation, while the remaining developed during the course of illness. While 56 (40.9%) had single GI symptom, 81 (59.1%) had more than one GI symptoms. The commonest GI symptom reported was diarrhea (61; 30.0%) followed by loss of taste (28.6%), smell (27.6%) and appetite (27.6%). Nausea was seen in 29 (14.3%) while vomiting in 17 (8.4%) cases (Table 1). The median duration of diarrhea was 4.0 (range 1–15) days with a stool frequency of 3–8 bowel movements per day. The median duration of vomiting was 2.0 (IQR 1.0) days.

The GI symptoms such as nausea and vomiting were treated symptomatically. Diarrhea was mostly self-limiting and did not require any specific therapy.

The baseline characteristics of the patients with/without diarrhea were similar (Table 2), and so were the co-existing co-morbidities (45.9% vs 44.4%; p = 0.84). The various drugs received during hospitalisation were similar between those with/without diarrhea.

3.1. Comparison based on overall symptomatology

Patients with respiratory symptoms alone (n = 49) were compared with those with both respiratory and any GI symptoms (n = 117) (Supplementary Table 1). Patients with both respiratory and any GI symptoms showed a lower trend towards need for mechanical ventilation (12.2% vs 7.7%; p = 0.35) and mortality (10.2% vs 4.3%; p = 0.14) compared to respiratory symptoms alone, although not statistically significant.

3.2. Comparison of patients with/without diarrhea

Patients with diarrhea (n = 61) had no mortality (0% vs 7.7%; p = 0.036) or need for mechanical ventilation (0% vs 10.6%; p = 0.006) compared to those who did not have diarrhea. (Table 3). Patients without diarrhea also had higher requirements of ICU stay, dialysis and inotropic support compared to those with diarrhea, although not statistically significant.

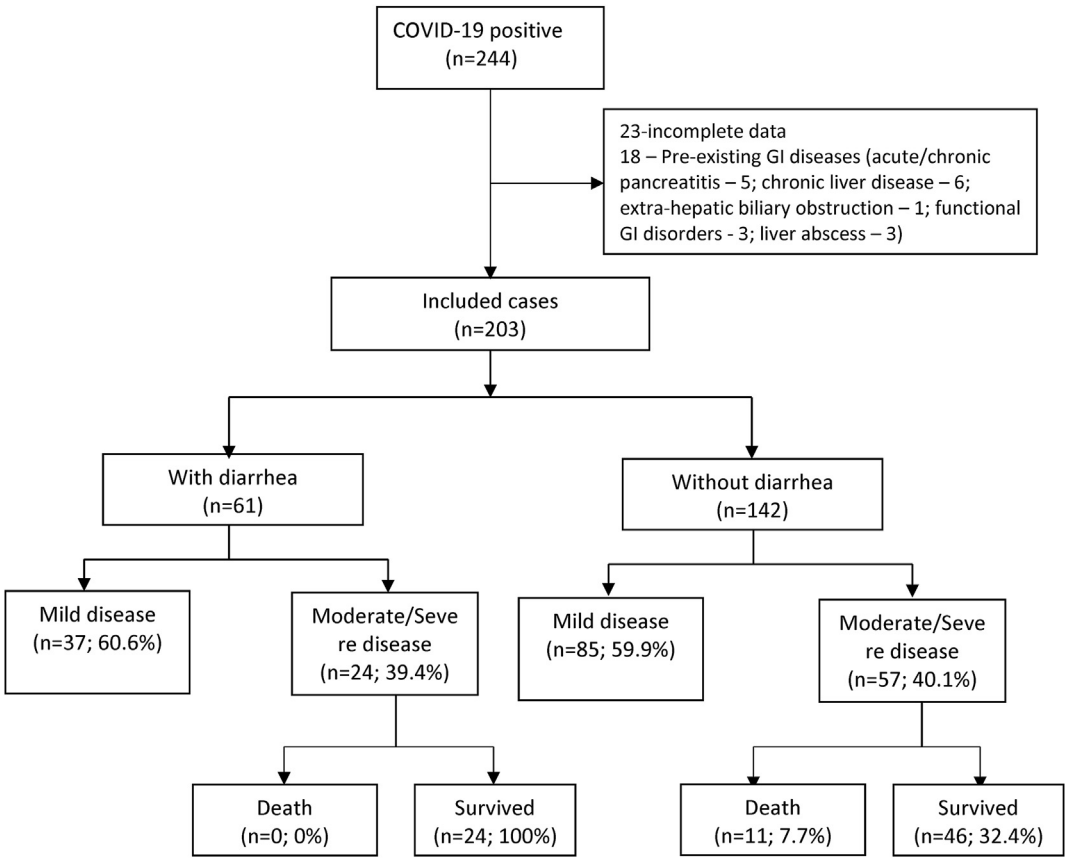

Fig. 1. Flowchart of the study.

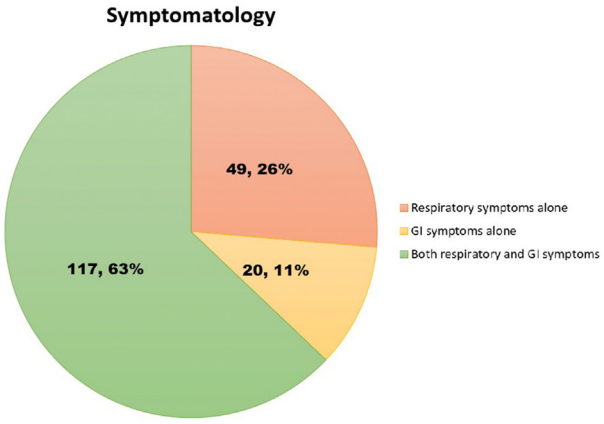

Fig. 2. Pie-chart showing the distribution of COVID-19 patients' symptomatology.

Table 1
Symptomatology of patients.

Symptom	Frequency (n = 203)	Percentage
Nausea	29	14.3%
Vomiting	17	8.4%
Diarrhea	61	30.0%
Loss of Taste	58	28.6%
Loss of Smell	56	27.6%
Loss of Appetite	56	27.6%
Abdominal discomfort/Pain Abdomen	19	9.4%
Gastrointestinal Bleed	1	0.5%

Table 2
Baseline characteristics of the patients with/without diarrhea.

Parameters	Patients with diarrhea (n = 61)	Patients without diarrhea (n = 142)	P value
Age (years) (Mean ± SD)	41.75 ± 17.5	41.34 ± 15.6	0.87
Sex Male (N, Percentage)	42 (68.9%)	86 (60.6%)	0.26
Female (N, Percentage)	19 (31.1%)	56 (39.4%)	
Co-morbidities (N, Percentage)	28 (45.9%)	63 (44.4%)	0.84
Diabetes (N, Percentage)	17 (27.9%)	38 (26.8%)	0.87
Chronic kidney disease (N, Percentage)	7 (11.5%)	15 (10.6%)	0.85
Drugs received (N, Percentage)	25 (41.0%)	55 (38.7%)	0.76
Steroids	26 (42.6%)	58 (40.8%)	0.81
LMWH	14 (23.0%)	31 (21.8%)	0.86
Remdesivir	55 (90.2%)	112 (78.9%)	0.053
Antibiotics			

Abbreviations: SD: Standard deviation; LMWH: Low molecular weight heparin.

Various laboratory parameters assessed did not show any significant differences between patients with/without diarrhea (Supplementary Table 2).

3.3. *Multivariate analysis for predictors of moderate/severe disease*

On multivariate analysis, presence of GI symptoms was found to be significant negative predictor of moderate/severe disease (p = 0.004), even after adjusting for age, sex and comorbidities (Supplementary Table 3).

Table 3
Outcome parameters among patients with/without diarrhea.

Parameters	Patients with diarrhea (n = 61)	Patients without diarrhea (n = 142)	P value
Severity of COVID-19 (N, Percentage)	37 (60.7%)	85 (59.9%)	0.47
Mild	17 (27.9%)	32 (22.5%)	
Moderate	7 (11.5%)	25 (17.6%)	
Severe			
Need for oxygen supplementation (N, Percentage)	23 (37.7%)	57 (40.1%)	0.75
Need for mechanical Ventilation (N, Percentage)	0 (0%)	15 (10.6%)	**0.006**
Need for dialysis (N, Percentage)	3 (4.9%)	12 (8.5%)	0.56
Need for inotropic support (N, Percentage)	0 (0%)	5 (3.5%)	0.33
ICU stay (N, Percentage)	5 (8.2%)	22 (15.5%)	0.18
Hospital stay (days) (Mean ± SD)	12.46 ± 4.2	14.94 ± 5.8	**0.001**
Mortality (N, Percentage)	0 (0.0%)	11 (7.7%)	**0.036**

Abbreviations: COVID-19: Coronavirus disease 2019; SD: Standard deviation; ICU: Intensive care unit.

4. Discussion

In this prospective study we found that GI symptoms in COVID-19 patients were not uncommon with 1/4th having GI symptoms at presentation while overall, 2/3rd developed GI symptoms. The commonest GI symptom reported was diarrhea (n = 61; 30.0%) followed by loss of taste, smell and appetite. Patients having diarrhea had lower need for mechanical ventilation, shorter hospital stay and lower mortality compared to those without diarrhea.

The interest in the extra-pulmonary manifestations of COVID-19 has been steadily growing and the commonest of them is the GI manifestations. In the initial phase of the pandemic, a mere 3%–3.8% cases of diarrhea and 5% cases of nausea and/or vomiting were reported [11,17]. But as awareness grew, more studies reported GI manifestations and overall reported GI symptoms ranged from 2% to 57% [3]. Unfortunately, most of the studies are based on retrospective, electronic database driven information and thus, suffer from information bias. Active, prospective questioning from patients, as has been carried out in the current study, will lead to a better assessment of the actual prevalence of the GI symptoms. We found that as high as 68.0% of the patients had at least one GI symptom with 23.2% of them having it as one of the presenting symptoms, similar to other recent prospective data [18]. Very few earlier studies have systematically reported the occurrence of isolated GI symptoms in the absence of respiratory symptoms. While Jin et al. [19] had reported 3.2% cases of isolated GI symptom presentation, Luo et al. [20], in a larger study, reported it to be 16%. Interestingly, we found that 20 patients (9.9%) had only GI symptoms without any respiratory symptoms. This sub cohort of cases have evidently mild disease. This underlines the significance of keeping a high index of suspicion for diagnosing these cases, which might go unnoticed and might lead to inadvertent spread of the virus.

The commonest GI symptom reported has been diarrhea with a pooled prevalence of 16.5% [21] followed by nausea, loss of appetite and vomiting. We, too, found diarrhea to be the commonest symptom but with a higher prevalence compared to the previous reports. Of them, 8.4% had diarrhea at presentation, akin to previous studies [19,22], while the remaining developed during the course of illness. The diarrhea lasted for a median of 4 days (range 1–15 days). This has been recorded in limited earlier studies. While Jin et al. reported a median diarrhea duration of 4 days [19], Han et al. had [23] patients with a mean diarrhea duration of 5.4 days. The stool frequency ranged from 2 to 8 bowel movements per day, similar to previous studies [22,23].

SARS-CoV-2 virus enters the host cell via the interaction of the viral spike protein with the host cell angiotensin-converting enzyme 2 (ACE2) receptor and cellular *trans*-membrane serine protease 2 (TMPRSS2) [24]. These host receptors are present not only in the respiratory epithelium but along the whole of the GI tract [7]. The fact that SARS-CoV-2 infects the gut enterocytes has been established in human small intestinal organoids [25] and nonhuman primate model [26]. The viral nucleocapsid protein (NP) has been demonstrated in the infected intestinal epithelial cells [7] and viral particles on electron microscopy. Interestingly, both intranasal and *trans*-gastric inoculation led to respiratory and GI system dysfunction highlighting the role of inflammatory cytokines in the viral pathogenesis [26]. The viral NP has been found more in the ileum than the duodenum [7]. Fecal shedding of the virus even in cases without diarrhea [27] reiterates the fact that GI involvement is an integral part of the pathogenesis of COVID-19 infection. The pathophysiology of diarrhea in SARS-CoV-2 infection has been postulated to be multifactorial [3]. Viral infection related cytopathic effects, alteration in the intestinal permeability leading to malabsorption, cytokine driven inflammation and altered gut flora are some of the key mechanistic pathways [28]. Diarrhea is more objective clinical evidence for gut inflammation, compared to other symptoms like nausea or vomiting. Thus, akin to recent studies, we have evaluated COVID-19 patients with and without diarrhea to understand the effect of GI involvement on the disease dynamics. Although drug induced diarrhea has been postulated as an additional mechanism, the current study showed that patients with/without diarrhea had similar drug treatment profile during hospitalisation. This underlines the fact that diarrhea is a key manifestation in the patho-mechanistic pathway of SARS-CoV-2 infection rather than a silent bystander.

Whether GI involvement has any impact on the overall outcome in COVID-19 patients has been the subject of contention since the initial reports of GI involvement by SARS-CoV-2 infection. Initial reports and collated data had suggested adverse outcomes in patients with GI involvement [4,19]. However, these initial data were retrospective, database based and with the lack of adequate awareness could have led to documentation bias. With increased cognizance and better understanding, recent data has shown that diarrhea or GI involvement is associated with better outcomes [7,14,18,23]. We established similar findings in a prospective cohort and found that patients with diarrhea, in spite of similar baseline characteristics, had better outcomes with lower need for mechanical ventilation, shorter hospital stay and lower mortality. Livanos et al. [7] had demonstrated that cytokines associated with poor outcomes such as IL-6 and IL-8 were lower in patients with GI symptoms. It has been argued that GI involvement might lead to a plausible attenuated immune response, a lower systemic inflammation and cytokine storm and thus better outcome in patients with SARS-CoV-2 infection [7,29]. The current study, too, demonstrated that GI symptoms alone was a significant negative predictor for moderate/severe disease.

The strengths of the study include a) prospective design of the study; b) active probing for the specific symptoms from patients, relatives and treating physicians to minimise documentation bias; c) excluding patients with prior GI symptoms/disease to remove confounders; d) using the objective parameter of diarrhea to assess the effect of GI involvement on the outcome. However, this study do have few limitations. Measurement of cytokine levels would have enabled an objective comparison of the disease dynamics between those with or without diarrhea. Assessment of fecal calprotectin and intestinal biopsies additionally could have led to better understanding of the enterocyte-virus interaction. The patients developing diarrhea later during the hospital course might have additional confounding contributing factors and this cannot be completely ruled out. Additionally, the included cohort had lower proportion of severe disease. Larger prospective studies would be needed to confirm the findings of the current study.

5. Conclusion

GI symptoms are frequent in patients with SARS-CoV-2 infection and the commonest is diarrhea. Diarrhea is a harbinger of better outcome with lower mortality among COVID-19 positive patients.

Author contributions

SS: data acquisition, data interpretation, patient care, intellectual review of the work, final approval.

JS: conception and design, data interpretation, data analysis, drafting the work, and final approval.

AB, VS, GDP, RS, RK: data interpretation, patient care, intellectual review of the work, final approval.

Grant support

Nil.

Writing assistance

Nil.

Declaration of competing interest

All the authors declare no potential conflicts of interest.

Acknowledgements

The graphical abstract was made using BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijmmb.2022.04.002.

References

[1] WHO. Weekly epidemiological update on COVID-19 - 20 April 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—20-april-2021.
[2] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.
[3] Dhar J, Samanta J, Kochhar R. Corona Virus Disease-19 pandemic: the gastroenterologists' perspective. Indian J Gastroenterol 2020;39:220–31.
[4] Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. The lancet Gastroenterology & hepatology 2020;5:667–78.
[5] Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther 2020;51:843–51.
[6] Satija N, Lal SK. The molecular biology of SARS coronavirus. Ann N Y Acad Sci 2007;1102:26–38.
[7] Livanos AE, Jha D, Cossarini F, et al. Intestinal host response to SARS-CoV-2 infection and COVID-19 outcomes in patients with gastrointestinal symptoms. Gastroenterology 2021. https://doi.org/10.1053/j.gastro.2021.02.056.
[8] Halaji M, Farahani A, Ranjbar R, et al. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Inf Med 2020;28:6–17.
[9] Samanta J, Dhar J, Khaliq A, et al. Novel coronavirus infection: gastrointestinal manifestations. J Dig Endosc 2019;11:13.
[10] Dan F, Jingdong M, Jialun G, et al. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study. Chinese Journal of Digestion 2020:E005.
[11] Guan WJ, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[12] Henry BM, de Oliveira MHS, Benoit J, et al. Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis. Internal and Emergency Medicine 2020;15:857–9.
[13] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in wuhan, China. JAMA 2020;323:1061–9.
[14] Aghemo A, Piovani D, Parigi TL, et al. COVID-19 digestive system involvement and clinical outcomes in a large academic hospital in milan, Italy. Clin Gastroenterol Hepatol 2020;18:2366–2368 e3.
[15] Nobel YR, Phipps M, Zucker J, et al. Gastrointestinal symptoms and coronavirus disease 2019: a case-control study from the United States. Gastroenterology 2020;159:373–375 e2.
[16] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. [Accessed 10 December 2021].
[17] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[18] Schettino M, Pellegrini L, Picascia D, et al. Clinical characteristics of COVID-19 patients with gastrointestinal symptoms in northern Italy: a single-center cohort study. Am J Gastroenterol 2021;116:306–10.
[19] Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020;69:1002–9.
[20] Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol 2020;18:1636–7.
[21] Shehab M, Alrashed F, Shuaibi S, et al. Gastroenterological and hepatic manifestations of patients with COVID-19, prevalence, mortality by country, and intensive care admission rate: systematic review and meta-analysis. BMJ Open Gastroenterol 2021;8.
[22] Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020;69:997–1001.
[23] Han C, Duan C, Zhang S, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol 2020;115:916–23.
[24] Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444–8.
[25] Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369:50–4.
[26] Jiao L, Li H, Xu J, et al. The gastrointestinal tract is an alternative route for SARS-CoV-2 infection in a nonhuman primate model. Gastroenterology 2021;160:1647–61.
[27] Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology 2020;159:81–95.
[28] D'Amico F, Baumgart DC, Danese S, et al. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol 2020;18:1663–72.
[29] Miller J, Yan KS. COVID-19 gastrointestinal symptoms and attenuation of the immune response to SARS-CoV-2. Gastroenterology 2021;160:2251–4.