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.
Original article

Gastrointestinal manifestations with COVID-19 virus infection: A Moroccan prospective study

Addajou Tarika,⇑, Rokhsi Soukaina,1, Mrabti Samira,1, Sair Asmae,1, Benhamdane Ahlame,1, Berraïda Rida,1, Azali Yasser,1, Elkoti Ilhama,1, Errami Noureddine,1, Seddik Hassan,1, Benkirane Ahmed,1

Article info

Article history:
Received 21 February 2021
Accepted 27 July 2021

Keywords:
SARS-CoV-2
COVID-19
Digestive symptoms
Gastrointestinal manifestations

Abstract

Background and study aims: Gastrointestinal manifestations are common during coronavirus disease (COVID-19) infection. They can occur before respiratory symptoms, resulting in a diagnostic delay and an increased risk of disease transmission. The current study reports major gastrointestinal manifestations as initial symptoms of COVID-19.

Patients and methods: This prospective, descriptive, cross-sectional, and single-center study of 713 cases was conducted in a field hospital in Morocco over a 5-week period from June 21 to July 25, 2020.

Results: The average age of our patients was 31.95 years. Clinically, on admission, anorexia was the main symptom, present in 32.3% of patients. Gastrointestinal manifestations were present in 14.9% of patients, including watery diarrhea in 8.6% of cases, nausea and/or vomiting in 4.6% of cases, and abdominal pain in 1.6% of cases.

Six hundred thirty-two patients were treated in accordance with one of the two therapeutic protocols recommended by the National Ministry of Health. The treatment-related effects that occurred in 61.4% of patients were primarily digestive in 55.3% of cases.

In multivariate analysis, following adjustment of the studied parameters, only the presence of gastrointestinal manifestations (odds ratio [OR]: 1.478 confidence interval [CI]: 1.286–1.698; p < 0.001) and treatment side effects (OR = 1.069, CI: 1.020–1.119, p = 0.005) altered the rate of negative polymerase chain reaction (PCR) tests on day 10.

Conclusion: Gastrointestinal manifestations are common during COVID-19 and seem to be linked to a longer duration of disease. SARS-CoV-2 (the causative virus of COVID-19) can persist in the digestive tract, with the possibility of fecal–oral transmission. Therefore, hygiene is extremely important, especially handwashing and strict precautions when performing gastrointestinal endoscopy and handling stools from infected patients.

© 2021 Pan-Arab Association of Gastroenterology. Published by Elsevier B.V. All rights reserved.

Introduction

Initially reported in China in December 2019, coronavirus disease (COVID-19) was quickly declared a public health emergency on January 30, 2020, and then a pandemic on March 11, 2020, by the World Health Organization. In Morocco, the first case of COVID-19 was announced on March 2, 2020, and as of today, Morocco has reported more than 200,000 infected people, with a death toll exceeding 4000 people and numbers continuing to rise.

Respiratory tract manifestations are the most commonly reported symptoms in COVID-19, which is indicative of droplet transmission and contact transmission. However, emerging data suggest that the gastrointestinal tract might also be affected by SARS-CoV-2, on the basis that gastrointestinal epithelial cells express angiotensin-converting enzyme 2 (ACE2), the major receptor of SARS-CoV-2. The most commonly reported gastrointestinal symptoms associated with COVID-19 are anorexia, diarrhea, nausea or vomiting, and abdominal pain. Gastrointestinal manifestations of SAR-CoV-2 not only pose an important diagnostic challenge to clinicians when dealing with patients with mild
COVID-19 symptoms on initial presentation but also signify potential fecal transmission of this virus. With the increasing number of reported cases of COVID-19, there is an urgent need to systematically summarize the gastrointestinal manifestations of COVID-19 and the temporal profile of fecal shedding of the SARS-CoV-2 virus, particularly for gastroenterologists and endoscopists who may not be familiar with this disease.

In the current study, we aim to report the major gastrointestinal manifestations that occur as initial symptoms of COVID-19, and when to suggest the diagnosis of COVID-19 in patients at risk, who may have been exposed to SARS-CoV-2 and presenting with gastrointestinal manifestations that occur as initial symptoms of COVID-19, and familiar with this disease.

**Patients and methods**

**Study design, setting, and participants**

This prospective descriptive, cross-sectional, and single-center study of 713 cases was conducted in the Sidi Yahya El Gharb Field Hospital in Sidi Slimanine Province, Rabat-Salé-Kénitra Region, Morocco, over a 5-week period from June 21 to July 25, 2020.

The study included all patients with confirmed COVID-19 by a polymerase chain reaction (PCR) on nasopharyngeal swab, irrespective of whether patients were symptomatic, and without any contraindications for the medical treatment provided. Patients who did not meet the above inclusion criteria were excluded from the study.

**Variables**

We extracted the epidemiological history (i.e., contact history), demographic data (such as age, sex, race, smoking status, and body mass index), comorbidities (history of hypertension, diabetes, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, and asthma), clinical characteristics (including digestive symptoms [anorexia, nausea/vomiting, diarrhea, or abdominal pain], and other symptoms [fever, cough, expectoration, and dyspnea]) on admission, treatment programs, and evolutionary data.

**Statistical analysis**

Descriptive data are presented as means (±standard deviation [SD]) for normally distributed continuous variables. Categorical variables were presented as counts and percentages.

No imputation was made for missing data. Because the study cohort was not derived from random selection, all statistics are presumed to be descriptive only.

To investigate the association between the presence of gastrointestinal manifestations and the rate of negative PCR tests on day 10, we performed logistic regression with adjustment for potential confounders to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to identify risk factors for these outcomes.

A two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 program.

**Results**

The average age of our patients was 31.95 ± 12.95 years, with extremes ranging from 11 days to 80 years, and the predominant age range was from 30 to 39 years (Fig. 1).

Our series was characterized by a clear female predominance estimated at 88.9%, compared to 11.1% in men, with a sex ratio of 0.12. This female predominance was linked with our medical facility’s patient population, mostly comprised a COVID-19 cluster which included women working in strawberry packing plants in Lalla Mimouna region.

On admission, the degree of severity of COVID-19 was classified as mild in all patients ( Appendix 1) [1].

The case history revealed pre-existing conditions (diabetes and/or high blood pressure) in 2.1% (n = 15). Clinically, on admission, anorexia was the main symptom and was present in 32.3% of patients (n = 230). Gastrointestinal manifestations were present in 14.9% of patients (n = 106), including watery diarrhea in 8.6% of cases, nausea and/or vomiting in 4.6% of cases, and abdominal pain in 1.6% of cases. A total of 632 patients were treated in accordance with one of the two therapeutic protocols recommended by the National Ministry of Health, which are based on chloroquine (Nivaquine) (500 mg × 2 per day for 10 days) in combination with azithromycin (500 mg on day 1 and then 250 mg per day from days 2 to 7), vitamin C (1 g/12 h), and zinc (100 mg/day) for the first protocol, which was used to treat 51.15% of cases (n = 364), and the second protocol consisted of hydroxychloroquine sulfate (Plaquenil) (200 mg × 3 per day for 10 days) in combination with azithromycin (500 mg on day 1 and then 250 mg per day from days 2 to 7), vitamin C (1 g/12 h), and zinc (100 mg per day). This second protocol was adopted to treat 268 patients (37.6% of cases).

The remainder of the untreated patients included 17 pregnant women (2.4%) and 64 children (9%). All cases were monitored twice daily to detect early signs of worsening; this allowed us to identify adverse treatment-related effects in 61.4% of patients (n = 438), which were primarily digestive in 55.3% of cases (watery diarrhea in 43% of patients, abdominal pain in 16.6% of patients, and nausea and/or vomiting in 13.1% of patients) managed by symptomatic treatment and neurological treatment in 6.1% of patients (insomnia in 9% of cases, dizziness in 9.5% of cases, and hallucinations in only one patient), which were reversible upon discontinuation of treatment. PCR analysis on day 10 of treatment was negative in 75.6% of patients.

In a multivariate analysis following adjustment of the study parameters, namely, age, the presence of associated morbidities, anorexia, and the adopted therapeutic protocol, only the presence of gastrointestinal manifestations (OR: 1.478, CI: 1.286–1.698, p < 0.001) and treatment side effects (OR = 1.069, CI: 1.020–1.119, p = 0.005) altered the rate of negative PCR tests on day 10.

Digestive symptoms appeared to be linked to a longer disease duration; 82.2% of patients without digestive symptoms recovered on the 10th day of treatment, whereas only 37.7% of patients with digestive symptoms recovered on the same day of treatment. Similarly, but to a lesser degree, the presence of therapeutic adverse effects prolongs the duration of the disease; 82.2% of patients without therapeutic adverse effects recovered on the 10th day of treatment, whereas 71.46% of patients with therapeutic adverse effects recovered on the same day of treatment. This could be explained by poor adherence to treatment caused by poor treatment tolerance in the patients. No cases of death were recorded in our series, and the PCR performed on day 14 of admission came back negative for the remaining 24.4% of patients.

**Discussion**

COVID-19 may be responsible for a polymorphic digestive symptomatology, which may precede the onset of respiratory symptoms. The mechanism of action of the virus is similar to that of SARS-CoV, as it uses ACE2 as a functional receptor for cell entry. ACE2 is found on cell membranes primarily belonging to pneumocytes and other body cells including gastrointestinal epithelial cells [2].
The gastrointestinal digestive manifestations of COVID-19 were described in the United States [3], in a 35-year-old man, who had a history of nausea and vomiting 2 days before his admission, followed by diarrhea and abdominal discomfort on the second day of hospitalization. The incidence of gastrointestinal manifestations during COVID-19 infection varies between 12% and 61% [4–6] depending on the study (Table 1). These manifestations may be associated with prolonged disease duration, but they have not been associated with increased mortality [5,7]. In our series, gastrointestinal manifestations were present in 14.9% of patients, which is consistent with data from the literature.

Sometimes, various gastrointestinal symptoms, including epigastric pain, constipation, diarrhea, nausea, vomiting, muscle pain, and melena, which are therapy resistant, may be the only symptoms in patients suspected to have COVID-19. Timely diagnosis and isolation of these patients can guarantee population to avoid the spread of this highly contagious infection [8,9].

In a cohort conducted in 552 Chinese hospitals with 1099 patients published in the New England Journal of Medicine, the authors observed nausea or vomiting in 5% of cases and diarrhea in 3.8% of cases [10]. In a meta-analysis including 35 studies of 6686 patients with COVID-19, of which 29 studies (n = 6064) reported gastrointestinal symptoms at the time of diagnosis, with a prevalence of 15%, the symptoms included anorexia in 21% of cases, diarrhea in 9% of cases, nausea and/or vomiting in 6% of cases, and abdominal pain in 3% of cases [7].

In a Chinese retrospective series of 1141 confirmed cases of COVID-19, 16% of patients had isolated digestive symptoms [11]. These included anorexia in 98% of cases, followed by nausea in 73%, vomiting in 65%, diarrhea in 37%, and abdominal pain in 25% of cases.

A higher prevalence of gastrointestinal symptoms evaluated at 61.3% was reported in a multicentric cohort study conducted in the United States by Walker D. Redd on 318 patients with symptoms, including anorexia in 34.8% of patients, diarrhea in 33.7% of patients, and nausea in 26.4% of cases [6].

In another multicentric study of 204 patients, 51% of patients had digestive involvement, including diarrhea in 34% of cases [5]. Patients with digestive symptoms had a longer period of hospitalization than had patients without digestive symptoms. The authors also observed a correlation between the severity of respiratory involvement and the intensity of digestive symptoms. These elements were confirmed by a study on 651 patients, of whom 11.4% had at least one digestive symptom. Patients with digestive symptoms had more severe disease (p < 0.001) [12].

Anorexia during COVID-19 virus infection appears to be common and is reported to occur in 40% to 50% of cases. Although the onset mechanism of anorexia in patients with COVID-19 remains uncertain, it appears to be associated with dysgeusia in 88% of cases and anosmia in 85.6%, which may be partially explained by its mechanism of onset [13]. In our study, anorexia was the main symptom on admission and was present in 32.3% of patients.

With regard to the characteristics of diarrhea, a single-center study conducted on gastrointestinal manifestations of COVID-19 in Wuhan showed that the onset of diarrhea was 1–8 days after the onset of COVID-19 (with a median duration of 3.3 days). In 34.3% of cases, the stools were liquid, and their analysis showed abnormal results in 6.9% of cases, specifically the presence of white blood cells in 5.2% of cases and a positive Hemoccult test in 1.7% of patients, with the absence of red blood cells [14]. This was consistent with the characteristics of diarrhea, which were non-bloody, usually associated with

### Table 1

| Study          | All patients | Diarrhea (%) | Nausea and/or vomiting (%) | Anorexia (%) | Abdominal pain (%) |
|---------------|--------------|--------------|----------------------------|--------------|--------------------|
| Luo et al. [10]| 1141         | 5.96         | 18.93                      | 15.77        | 3.94               |
| Guan et al. [9]| 1099         | 3.73         | 5                          | —            | —                  |
| Jin et al. [11]| 651          | 8.14         | 2.61                       | —            | —                  |
| Redd WD et al. [7]| 318      | 33.7         | 26.4                       | 34.8         | 78.6               |
| Pan L et al. [6]| 204          | 34           | 3.9                        | 12.23        | 5.75               |
| Zhang et al. [3]| 139          | 12.95        | 17.26                      | 39.85        | 2.17               |
| Wang et al. [17]| 138          | 10.14        | 10.14                      | 32.3         | 1.6                |
| Our study      | 713          | 8.6          | 4.6                        | 10.14        | 32.3               |

Fig. 1. Distribution of patients by age group.
vomiting, and may have been accompanied by nausea, abdominal cramps, and fever [5]. Generally, diarrhea was short term (i.e., not exceeding three to four stools per day) [15,16] and had to be distinguished from diarrhea related to the administered drugs (hydroxychloroquine associated or not with azithromycin) or concomitant infections (especially *Clostridium difficile*). In our study, diarrhea was watery and was present in 8.6% of cases.

SARS-CoV-2 RNA was first detected in a stool sample from the first case of COVID-19 reported in the United States (US) [3]. In another Chinese cohort consisting of 73 hospitalized patients infected with SARS-CoV-2, viral RNA was detected in the stools of 53.42% of patients, and it remained positive for 17 patients (23.29%), even after the virus became undetectable in the airways [17]. Meanwhile, SARS-CoV-2 was also detected in stool samples from patients without gastrointestinal symptoms [18].

A recent study proved the possibility of a prolonged duration of fecal viral shedding up to 5 weeks after patients’ respiratory samples turned negative for detecting SARS-CoV-2 RNA [19].

For these suspected or confirmed COVID-19 patients, the clinical indication for endoscopy should be reassessed, and only urgent when available [20]. Therefore, these findings further validated immunosuppressive drug benefits, especially the IL-6 receptor antagonist for emergency use in critical infected COVID-19 patients [30].

In conclusion, gastrointestinal manifestations are common during COVID-19, and investigating them should be systematically performed during history taking. These manifestations can be the first symptoms that occur before respiratory symptoms and thus result in a potential factor for diagnostic delay with an increased risk of disease transmission. The existence of digestive symptoms may be correlated with more severe respiratory involvement. SARS-CoV-2 can persist longer in the digestive tract than in the respiratory system with the possibility of fecal–oral transmission, thereby underscoring the extreme importance of hygiene, especially handwashing. Strict precautions must be observed when performing gastrointestinal endoscopy and handling stool from patients infected with the COVID-19 virus.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Appendix 1. COVID-19 mild disease severity based on the WHO clinical management of COVID-19 updated on May 27, 2020 (1)

Symptomatic patients presenting with fever, cough, fatigue, anorexia, and myalgias; other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea, and vomiting; loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms without evidence of viral pneumonia or hypoxia.

References

[1] World Health Organization. Clinical management of COVID-19: interim guidance. 2020 May 27. (https://www.who.int/publications/i/item/clinical-management-of-covid-19).
[2] Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. Gut 2020;69(6):1010–8.
[3] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382(10):929–36.
[4] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934–43.
[5] Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115(5):766–73.
[6] Redd WD, Zhou JC, Hathorn KE, et al. Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the United States: a multicenter cohort study. Gastroenterology 2020;159(2).
[7] Mao R, Qu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5(7):667–78.
[8] Hormati A, Shahhamzeh A, Affifan M, et al. Can COVID-19 present unusual GI symptoms? J Microbiol Immunol Infect 2020;53(3):384–5.
[9] Hormati A, Shahhamzeh A, Aminnejad R, et al. Gastrointestinal presentation in patients with COVID-19 without respiratory tract symptoms: A case report from Qom, Iran. Jundishapur J Microbiol 2020;13(5):e102844.
[10] Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20 [PMID: 32109013].
[11] Liao S, Zhang X, Xu H. Do not overlook digestive symptoms with 2019 novel coronavirus disease (COVID-19). Chin Gastroenterol Hepatol 2020;18(7):1636–7 [PMID: 32205220].
[12] 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(6):1002–9 [PMID: 32213556].
[13] Lechien JR, Chiesa-Estomba CM, De Santi DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277(8):2251–61 [PMID: 32253535].
[14] Fang D, Ma JD, Guan J, et al. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study. Chin J Dig 2020;40(03):141–6.
[15] Wong SH, Lui RNS, Sung JY. COVID-19 and the digestive system. J Gastroenterol Hepatol 2020;35(5):744–8.
[16] 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(9):843–51.
[17] Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158(6):1831–1833.e3.
[18] Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323(18):1843–4 [PMID: 32159775].
[19] Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 2020;5(5):434–5.
[20] Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med 2020;26(4):502–5.
[21] Chiu PWY, Ng SC, Inoue H, et al. Practice of endoscopy during COVID-19 pandemic: position statements of the Asian Pacific Society for Digestive Endoscopy (APSDCE-COVID statements). Gut 2020;69(6):991–6.
[22] ASGE Quality Assurance in Endoscopy Committee, Calderwood AH, Day LW, et al. ASGE guideline for infection control during GI endoscopy. Gastrointest Endosc 2018;87(5):1167–70.
[23] Beilenhoff U, Biering H, Blum R, et al. Reprocessing of edible endoscopes and endoscopic accessories used in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology Nurses and Associates (ESGENA) - Update 2018. Endoscopy 2018;50:1205–34.
[24] Kilinc FS. A review of isolation gowns in healthcare: fabric and gown properties. J Eng Fiber Fabr 2015;10(3):180–90 [PMID: 26989351].
[25] Sinonquel P, Roelandt P, Demedts I, et al. COVID-19 and gastrointestinal endoscopy: What should be taken into account? Dig Dis Endosc 2020;32(5):723–31.
[26] Hormati A, Ghadir MR, Zamani F, et al. Preventive strategies used by GI physicians during the COVID-19 pandemic. New Microbe New Infect 2020;35:100676. https://doi.org/10.1016/j.nmni.2020.100676.
[27] Repici A, Maselli R, Colombo M, et al. Coronavirus (COVID-19) outbreak: What the department of endoscopy should know. Gastrointest Endosc 2020;92(1):192–7.
[28] Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020;104(3):246–51.
[29] RutaLA WA, Weber DJ. Best practices for disinfection of noncritical environmental surfaces and equipment in healthcare facilities: A bundle approach. Am J Infect Control 2019;47:9A–A105.
[30] Hormati A, Ghadir MR, Zamani F, et al. Are there any association between COVID-19 severity and immunosuppressive therapy? Immunol Lett 2020;224:12–3.
[31] Liu X, Wang RS, Qu GQ, et al. Gross examination report of a COVID-19 death autopsy. Fa Yi Xue Za Zhi 2020;36(1):21–3 [PMID: 32198987].