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Gastrointestinal symptoms and digestive comorbidities in an Italian cohort of patients with COVID-19

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Abstract. – OBJECTIVE: The Coronavirus Disease 2019 (COVID-19) pandemic mainly involves respiratory symptoms, though gastrointestinal (GI) symptoms are increasingly being recognized. In this context, the presence of comorbidities appears to be associated with adverse outcomes. However, the role of digestive manifestations is not yet well defined. The primary aim of this study was to assess the prevalence of GI symptoms and digestive comorbidities in a cohort of patients with COVID-19 compared to controls. The secondary aim was to determine the association of GI-symptoms and digestive comorbidities with clinical outcomes.

PATIENTS AND METHODS: Inpatients with COVID-19 and controls with similar symptoms and/or radiological findings were enrolled. Symptoms at admission and throughout hospitalization were collected as they were comorbidities. The measured clinical outcomes were mortality, intensive care unit admission and cumulative endpoint.

RESULTS: A total of 105 patients were included: 34 with COVID-19 and 71 controls. At admission, the prevalence of GI symptoms among COVID-19 patients was 8.8%. During hospitalization, the frequency of GI symptoms was higher in patients with COVID-19 than in controls (p=0.004). Among patients with COVID-19, the mortality and a cumulative endpoint rates of those with GI symptoms were both lower than for those without GI symptoms (p=0.016 and p=0.000, respectively). Finally, we found digestive comorbidities to be associated with a milder course of COVID-19 (p=0.039 for cumulative endpoint).

CONCLUSIONS: Our results highlighted the non-negligible frequency of GI symptoms in patients with COVID-19, partly attributable to the therapies implemented. In addition, the presence of GI symptoms and digestive comorbidities is associated with better outcomes. Most likely, digestive comorbidities do not hinder the host's immune response against SARS-COV-2, and the occurrence of GI symptoms might be linked to a faster reduction of the viral load via the faecal route.

Key Words:
SARS-Cov-2, COVID-19, Gastrointestinal symptoms, Diarrhoea, Digestive comorbidities.

Introduction

Since December 2019, when Coronavirus 2019 disease (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, as named by the World Health Organization, WHO) was described in Wuhan, China, the situation has dramatically evolved[1]. Europe and the United States are the center of the pandemic that, as declared by the WHO, has led to 3,090,445 cases and 217,769 dead

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worldwide, as of 30th April 2020[2]. Fever, cough and dyspnoea are the most common presenting symptoms, though gastrointestinal (GI) manifestations are increasingly being recognized among patients with COVID-19[3]. Such manifestations may be explained by the finding that SARS-CoV-2 enters cells after binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This protein is expressed not only in lung alveolar T2 cells, but also in oesophageal epithelial cells and absorptive enterocytes of the terminal ileum and colon with one of highest levels in the body[4]. The presence of the ACE2 receptor in the intestine allows the spread of SARS-CoV-2 through the orofaecal route[5,6]. However, the frequency of GI symptoms among COVID-19 patients differs significantly depending on the features of the studied populations, the geographical area, and the timing of symptom assessment[5-8]. Indeed, the prevalence reported in the available studies is extremely variable, from 3 to 79%[9]. Furthermore, it is not clear whether the presence of GI symptoms affects the course of COVID-19[10,11]. In addition, the clinical outcomes of patients with COVID-19, such as mortality, have been associated with the age of the patients and the presence of cardiovascular, respiratory and metabolic comorbidities, whereas the role of digestive comorbidities is not yet well defined[12]. Thus, the primary aim of this prospective case-control study was to evaluate the prevalence of GI symptoms and digestive comorbidities in a cohort of COVID-19 patients compared to patients with suspected COVID-19 who had tested negative for SARS-CoV-2. The secondary aim of the study was to assess the association of GI symptoms and digestive comorbidities with the clinical outcomes of COVID-19 patients.

Patients and Methods

All consecutive adult patients (aged ≥18 years) hospitalized from March 15 to April 14 of 2020 in the Gastro-COVID Unit (GCU), so called because it was previously the Gastroenterology Department, were included in this study. Admission criteria from the Emergency Department (ED) included at least one of the following: 1. positive Polymerase Chain Reaction (PCR) detection of SARS-CoV-2 using a nasopharyngeal swab; 2. symptoms compatible with COVID-19 (cough, fever, dyspnoea); and 3. radiological findings (chest-X-ray or at high-resolution computed tomography [(HRCT) scan] compatible with COVID-19 pneumonia. All patients with a negative nasopharyngeal swab for SARS-CoV-2 at admission were subjected to a second swab test at 24-48 hours after the first. Patients with a diagnosis of SARS-CoV-2 infection based on a positive PCR result were considered to have COVID-19; all other patients were included in the control group. Symptoms at admission, including GI symptoms, were reported in a specially designed database. In detail, the GI symptoms recorded were diarrhoea, nausea, vomiting, abdominal pain and digestive bleeding. The definition of diarrhoea was the passing of loose stools >3 times per day. GI symptoms that occurred during hospitalization were also recorded. A stool culture was performed for all patients with diarrhoea at admission or during hospitalization. In cases of previous or concomitant antibiotic therapy or according to clinical suspicion, *Clostridioides difficile* toxin was assessed. For all patients, digestive comorbidities, including digestive cancers, liver and pancreatic pathologies (cirrhosis, acute and chronic pancreatitis), inflammatory bowel disease (Crohn's disease and ulcerative colitis), diverticular disease, peptic ulcer and its complications, and gastrointestinal bleeding were prospectively noted. In addition, cardiovascular, respiratory, neurologic and metabolic comorbidities were recorded. COVID-19 patients were treated according to local guidelines, as follows. Hydroxychloroquine was prescribed for mild infections starting at 400 mg bid the first day, followed by 200 mg bid until day 10. Lopinavir/ritonavir 200/50 mg bid until day ten was initially indicated in patients with moderate to severe infection and relevant comorbidities. However successive evidence led to its withdrawal from the guidelines when associated with hydroxychloroquine (this occurred in the last days of the study). Treatment with anti-interleukin-6 agents (tocilizumab or sarilumab) started in cases of worsening respiratory symptoms or acute respiratory distress syndrome (ARDS). Any other therapies, including antibiotics, low-molecular-weight heparin and steroids, were administered on a case-by-case basis. The measured clinically relevant outcomes were the following: in-hospital mortality, intensive care unit (ICU) admission, and cumulative endpoint (mortality plus ICU admission). Patients gave their verbal informed consent to participate in the study in the presence of a witness because of the contamination risk of the material necessary for written consent. All the collected data were

anonymously recorded. The Ethics Committee of the Fondazione Policlinico Gemelli, IRCCS approved the study.

Statistical Analysis

Continuous variables were compared by univariate analysis with the Mann-Whitney U test, and the results are reported as the median [interquartile range]. Categorical variables were compared using the Chi-square test (with Fisher's test if appropriate), and the results were reported as absolute numbers (percentages). A two-sided α of <0.05 was considered statistically significant. Data were analyzed with SPSS v25® (IBM Corp., Armonk, NY, USA).

Results

Demographic Features and Symptoms

During the study period, 105 patients were admitted to the GCU of the Fondazione Policlinico Gemelli, IRCCS Rome, Italy. Of these 34 (32.4%) had confirmed SARS-CoV-2 infection. The median age of the COVID-19 patients was 71 years (IQR, 59-81), and 22 were males (64.7%). Sex, age, prevalence of fever and respiratory symptoms, and smoking did not differ statistically between the case and controls (Table I). Furthermore, the prevalence of GI symptoms on admission was comparable between the patients with COVID-19 and controls (8.8% *vs.* 7.0%, p=0.748). In detail, among COVID-19 patients, one had diarrhoea, one had abdominal pain and one had nausea. However, when considering the prevalence of GI symptoms throughout the hospitalization period, we observed a statistically significant difference between the patients with COVID-19 and controls (32.3% *vs.* 9.8%, p=0.004). Indeed, diarrhoea appeared in 8 additional patients during hospitalization.

Comorbidities and Pharmacological Treatments

The prevalence of hypertension, coronary heart disease (CHD), diabetes mellitus, obesity [body mass index (BMI) ≥30 kg/m^2], chronic obstructive pulmonary disease (COPD), neurological diseases (including Alzheimer's disease and Parkinson's disease or ischaemic/haemorrhagic cerebral disease) and digestive diseases for the cases and controls is reported in Table II. We did not observe any statistically significant difference in the prevalence of any of the comorbidities considered. Only for CHD there was a borderline statistical significance found (p=0.05). Additionally, the median number of comorbidities did not differ between the COVID-19 patients and controls (p=0.193). In detail, 8 patients with COVID-19 had the following digestive comorbidities: one case of acute necrotic-haemorrhagic pancreatitis, one case of HCV-cirrhosis, one case of colon cancer, one case of non-alcoholic fatty liver disease (NAFLD), one case of lower gastrointestinal bleeding, two cases of peptic ulcer disease and one case of oesophageal cancer. The pharmacological treatment used for the COVID-19 patients is reported in Table III.

Outcomes

The mortality and ICU admission rates were significantly higher in the patients with COVID-19 than in the controls (p=0.001 and p=0.002, respectively). Notably, only 1 of the 8

Table I. Demographic and clinical features of COVID-19 patients and controls.

	COVID-19 patients (No. = 34)	Controls (No. = 71)	p
Median Age (IQR)	71 (64-82)	74 (59.5-81)	0.409
Sex (male)	22	43	0.683
Smoking (No.)	8	13	0.531
Symptoms (No.)			
Fever	29	52	0.169
Dyspnoea	19	26	0.062
Cough	11	16	0.281
GI-symptoms (No.)			
At admission	3	5	0.748
Throughout hospitalization	11	7	0.004
Clinical Outcomes (No.)			
Mortality	9	3	0.001
Admission to the ICU	6	1	0.002

Abbreviations: No., number; IQR, interquartile range; GI-symptoms, gastro-intestinal symptoms; ICU, intensive care unit.

Table II. Demographic and clinical features of COVID-19 patients and controls.

Comorbidities (No.)	COVID-19 patients (No. = 34)	Controls (No. = 71)	*p*
Hypertension	8	13	0.532
Coronary heart disease	5	23	0.05
Diabetes mellitus	3	8	0.702
Obesity (BMI ≥ 30)	4	7	0.765
Chronic obstructive pulmonary disease	3	9	0.562
Neurological disease	4	5	0.419
Digestive comorbidities	8	25	0.228
Median number of comorbidities (IQR)	1 (0-2)	1 (0-2)	0.193

Abbreviations: No., number; IQR, interquartile range; BMI, body mass index.

COVID-19 patients with digestive comorbidities died, and no one was admitted to the ICU, with a statistically significant difference compared to the controls for the cumulative endpoint (mortality plus ICU admission) (p=0.039). Regarding the association between GI symptoms and outcomes, the mortality rate and cumulative endpoint rate of the COVID-19 patients were both significantly lower than those in the patients without GI symptoms (p=0.016 and p=0.000, respectively).

Discussion

Fever and respiratory symptoms represent the most frequent and serious manifestations of SARS-CoV-2 infection. However, some studies[5,6,9] from China have reported a frequency of GI symptoms of 79% among COVID-19 patients and, these data were recently partially confirmed by other studies[7,8] from the United States that highlighted the involvement of the gastrointestinal tract in COVID-19. The prevalence of GI symptoms in our cohort of patients at admission was comparable to that reported in other studies[13]. However, the frequency of symptoms, particularly for diarrhea, increased significantly during the hospital stay, affecting approximately one-third of patients. This may be essentially due to the side effects of therapies, especially to antiviral agents, such as ritonavir and lopinavir[14], as well as to hydroxychloroquine[15]. Nonetheless, a causal role for SARS-CoV-2 in causing GI symptoms not evidenced at the beginning of hospitalization, cannot be excluded. In addition, none of the patients showed GI symptoms as the only initial manifestation of COVID-19. Interestingly, we observed better disease outcomes (a lower mortality rate and a lower combined rate of ICU admission and mortality) in patients with GI symptoms than in those without GI symptoms. These data resemble those reported by Nobel et al[7] in a case-control study conducted in the United States that found a significantly lower mortality rate among patients with GI symptoms (0.0% with GI symptoms *vs.* 5.0% without, p=0.03). To explain these data, we can assume that patients with GI symptoms, particularly diarrhea, might significantly eliminate the virus through the faecal route and quickly reduce the SARS-CoV-2 viral load. Unfortunately, we have not been able to confirm this hypothesis because we have not checked for SARS-CoV-2-RNA in our patients' faeces. Thus, to confirm this hypothesis further data are needed. It is now known that several comorbidities, including cardiovascular (hypertension, coronary heart disease), neurological, metabolic (diabetes, obesity) and COPD, are associated with worse outcomes in patients with COVID-19[12,16]. Conversely, data on the impact of digestive comorbidities on the clinical course of COVID-19 are limited[17]. In our cohort of COVID-19 patients, the presence of digestive comorbidities was not associated with a worse prognosis but rather with a better cumulative outcome. Most likely, digestive comorbidities do not hinder the host's immune response against SARS-COV-2 infection as the above-mentioned comorbidities do. Our study has

Table III. Treatment of COVID-19.

Treatment (No. of patients)	COVID-19 patients (N = 34)
Hydroxychloroquine	33
Lopinavir/ritonavir	33
Anti-IL-6 inhibitor	
Tocilizumab	7
Sarilumab	3

Abbreviations: No., number; IL-6, interleukin-6.

several limitations. First, a possible underestimation of GI-symptoms and digestive comorbidities could not be excluded since many of the patients were in serious clinical condition and unable to report symptoms or previous/coexisting diseases. Second, the study did not include patients with milder symptoms who did not require hospitalization. Third, a relatively limited number of patients was included because of the urgent need for information that may guide future clinical decisions. Thus, further studies should incorporate larger patient populations to confirm these results.

Conclusions

We found that GI symptoms affected more than one-third of patients with COVID-19, representing a frequent clinical issue that physicians treating COVID-19 patients should be aware of and manage. Furthermore, the presence of digestive comorbidities was associated with a better prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-269.
2) Coronavirus disease 2019 (COVID-19) – Situation Report. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200430-sitrep-101-covid-19.pdf?sfvrsn=2ba4e093_2.
3) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.
4) Aroniadis OC, DiMaio CJ, Dixon RE, Elmunzer BJ, Kolb JM, Mendelsohn R, Singal AG, Ordiah CO, Rockey DC, Spitzer RL, Tierney WM, Wani S, Yadav D. Current knowledge and research priorities in the digestive manifestations of COVID-19. Clin Gastroenterol Hepatol 2020; pii: S1542-3565(20)30536-X. doi: 10.1016/j.cgh.2020.04.039. [Epub ahead of print].
5) Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther 2020; 51: 843-851.
6) Gu J, Han B, Wang J. COVID19: gastrointestinal manifestations and potential fecaloral transmission. Gastroenterology 2020; 158: 1518-1519.
7) Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, Freedberg DE. Gastrointestinal symptoms and COVID-19: case-control study from the United States. Gastroenterology 2020; pii: S0016-5085(20)30490-X. doi: 10.1053/j.gastro.2020.04.017. [Epub ahead of print].
8) Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and characteristics of gastrointestinal symptoms in patients with sars-cov-2 infection in the united states: a multicenter cohort study. Gastroenterology 2020; pii: S0016-5085(20)30564-3. doi: 10.1053/j.gastro.2020.04.045. [Epub ahead of print].
9) Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, Hao SR, Jia HY, Cai H, Zhang XL, Yu GD, Xu KJ, Wang XY, Gu JQ, Zhang SY, Ye CY, Jin CL, Lu YF, Yu X, Yu XP, Huang JR, Xu KL, Ni Q, Yu CB, Zhu B, Li YT, Liu J, Zhao H, Zhang X, Yu L, Guo YZ, Su JW, Tao JJ, Lang GJ, Wu XX, Wu WR, Qv TT, Xiang DR, Yi P, Shi D, Chen Y, Ren Y, Qiu YQ, Li LJ, Sheng J, Yang Y. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; pii: gutjnl-2020-320926. doi: 10.1136/gutjnl-2020-320926.
10) Wei XS, Wang X, Niu YR, Ye LL, Peng WB, Wang ZH, Yang WB, Yang BH, Zhang JC, Ma W, Wang XR, Zhou Q. Diarrhea is associated with prolonged symptoms and viral carriage in COVID-19. Clin Gastroenterol Hepatol 2020; pii: S1542-3565(20)30526-7. doi: 10.1016/j.cgh.2020.04.030.
11) Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 Novel Coronavirus Disease (COVID-19). Clin Gastroenterol Hepatol 2020; pii: S1542-3565(20)30401-8. doi: 10.1016/j.cgh.2020.03.043.
12) Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-95.
13) Guan WJ, ZY N, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; doi: 10.1056/NEJMoa2002032.
14) Ford N, Vitoria M, Rangaraj A, Norris SL, Calmy A, Doherty M. Systematic review of the efficacy

and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. J Int AIDS Soc 2020; 23: e25489.

15) Sinha N, Balayla G. Hydroxychloroquine and covid-19. Postgrad Med J 2020; pii: postgradmedj-2020-137785. doi: 10.1136/postgradmedj-2020-137785.

16) Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; and the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020; doi: 10.1001/jama.2020.6775. [Epub ahead of print].

17) Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer S, Kim D, Hsing A, Ahmed A. High prevalence of concurrent gastrointestinal manifestations in patients with SARS-CoV-2: early experience from California. Gastroenterology 2020; doi: https://doi.org/10.1053/j.gastro.2020.04.008. [Epub ahead of print].