DAFTAR PUSTAKA

(OMS), W. H. O. (2020). *COVID-19 Weekly Epidemiological Update*. *November*, 1;4. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201012-weekly-epi-update-9.pdf

Aghemo, A., Piovani, D., Parigi, T. L., Brunetta, E., Pugliese, N., Vespa, E., Omodei, P. D., Preatoni, P., Lleo, A., Repici, A., Voza, A., Cecconi, M., Malesci, A., Bonovas, S., & Danese, S. (2020). COVID-19 Digestive System Involvement and Clinical Outcomes in a Large Academic Hospital in Milan, Italy. *Clinical Gastroenterology and Hepatology*, *18*(10), 2366-2368.e3. https://doi.org/10.1016/j.cgh.2020.05.011

Amaral, L. T. W., Brito, V. M., Beraldo, G. L., Fonseca, E. K. U. N., Yokoo, P., Talans, A., Oranges Filho, M., Chate, R. C., Baroni, R. H., & Szarf, G. (2020). Abdominal symptoms as initial manifestation of COVID-19: a case series. *Einstein (Sao Paulo, Brazil)*, *18*, eRC5831. https://doi.org/10.31744/einstein_journal/2020RC5831

Ceraolo, C., & Giorgi, F. M. (2020). Genomic variance of the 2019-nCoV coronavirus. *Journal of Medical Virology*, *92*(5), 522–528. https://doi.org/10.1002/jmv.25700

Cholankeril, G., Podboy, A., Aivaliotis, V. I., Pham, E. A., Spencer, S. P., Kim, D., & Ahmed, A. (2020). Association of Digestive Symptoms and Hospitalization in Patients with SARS-CoV-2 Infection. *American Journal of Gastroenterology*, *115*(7), 1129–1132. https://doi.org/10.14309/ajg.0000000000000712

Crespo, J., Iglesias-García, J., Del Val, J. H., García, F. G., De Miguel, Á. G., Carrillo, C. F., Ampuero, J., & Martínez, E. P. C. (2020). COVID-19 and the digestive system: Protection and management during the SARS-CoV-2 pandemic. *Revista Espanola de Enfermedades Digestivas*, *112*(5), 389–396. https://doi.org/10.17235/reed.2020.7128/2020

Ferm, S., Fisher, C., Pakala, T., Tong, M., Shah, D., Schwarzbaum, D., Cooley, V., Hussain, S., & Kim, S. H. (2020). Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. *Clinical Gastroenterology and Hepatology*, *18*(10), 2378-2379.e1. https://doi.org/10.1016/j.cgh.2020.05.049

Han, E. S., & goleman, daniel; boyatzis, Richard; Mckee, A. (2019). 済無No Title No Title. *Journal of Chemical Information and Modeling*, *53*(9), 1689–1699. https://covid19.kemkes.go.id/downloads/#.Xtva%0AkWgzbIU

Hoffmann, M., Kleine-Weber, H., Krüger, N., Müller, M., Drosten, C., & Pöhlmann, S. (2020). The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for

entry into target cells. *BioRxiv*. https://doi.org/10.1101/2020.01.31.929042

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, *181*(2), 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Jin, X., Lian, J. S., Hu, J. H., Gao, J., Zheng, L., Zhang, Y. M., Hao, S. R., Jia, H. Y., Cai, H., Zhang, X. L., Yu, G. D., Xu, K. J., Wang, X. Y., Gu, J. Q., Zhang, S. Y., Ye, C. Y., Jin, C. L., Lu, Y. F., Yu, X., … Yang, Y. (2020). Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*, *69*(6), 1002–1009. https://doi.org/10.1136/gutjnl-2020-320926

Khairuzzaman, M. Q. (2016). *No Title**血清及尿液特定蛋白**检测在糖尿病肾病早期诊断中的意义*. *4*(1), 64–75.

Lapostolle, F., Schneider, E., Vianu, I., Dollet, G., Roche, B., Berdah, J., Michel, J., Goix, L., Chanzy, E., Petrovic, T., & Adnet, F. (2020). Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. *Internal and Emergency Medicine*, *15*(5), 813–817. https://doi.org/10.1007/s11739-020-02379-z

Lee, J. J., Kopetz, S., Vilar, E., Shen, J. P., Chen, K., & Maitra, A. (2020). Relative abundance of sars-cov-2 entry genes in the enterocytes of the lower gastrointestinal tract. *Genes*, *11*(6), 1–9. https://doi.org/10.3390/genes11060645

Lin, L., Jiang, X., Zhang, Z., Huang, S., Zhang, Z., Fang, Z., Gu, Z., Gao, L., Shi, H., Mai, L., Liu, Y., Lin, X., Lai, R., Yan, Z., Li, X., & Shan, H. (2020). Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*, *69*(6), 997–1001. https://doi.org/10.1136/gutjnl-2020-321013

Lingeswaran, M., Goyal, T., Ghosh, R., Suri, S., Mitra, P., Misra, S., & Sharma, P. (2020). Inflammation, Immunity and Immunogenetics in COVID-19: A Narrative Review. *Indian Journal of Clinical Biochemistry*, *35*(3), 260–273. https://doi.org/10.1007/s12291-020-00897-3

Liu, T., Hu, J., Xiao, J., He, G., Kang, M., Rong, Z., Lin, L., Zhong, H., Huang, Q., Deng, A., Zeng, W., Tan, X., Zeng, S., Zhu, Z., Li, J., Gong, D., Wan, D., Chen, S., Guo, L., … Ma, W. (2020). *Time-varying transmission dynamics of Novel Coronavirus Pneumonia in China*.

https://doi.org/10.1101/2020.01.25.919787

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., … Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, *395*(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Moura, D. T. H. de, Proença, I. M., McCarty, T. R., Sagae, V. M. T., Ribeiro, I. B., Oliveira, G. H. P. de, Souza, G. M. V. de, Hirsch, B. S., Scatimburgo, M. V. C. V., Thompson, C. C., Carrilho, F. J., Cecconello, I., & Moura, E. G. H. de. (2020). Gastrointestinal Manifestations and Associated Health Outcomes of COVID-19: A Brazilian Experience From the Largest South American Public Hospital. *Clinics (Sao Paulo, Brazil)*, *75*, e2271. https://doi.org/10.6061/clinics/2020/e2271

Nassar, M. S., Bakhrebah, M. A., Meo, S. A., Alsuabeyl, M. S., & Zaher, W. A. (2018). Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics. *European Review for Medical and Pharmacological Sciences*, *22*(15), 4956–4961. https://doi.org/10.26355/eurrev_201808_15635

Nguyen, T. M., Zhang, Y. Y. G. W. Y. Y. Z. L., Pandolfi, P. P., Chen, P. Y. P.-Y., Mao, L., Nassis, G. P., Harmer, P., Ainsworth, B. E., Li, F. B. F., Liu, Y. Y. Y. Y. Y. L., Gayle, A. A., Wilder-Smith, A., Rocklov, J., Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., Hsueh, P. R., Allam, Z., … Leung, G. M. (2020). 済無No Title No Title. *The Lancet*, *9*(20), 2019–2020. https://ophrp.org/upload/pdf/ophrp-11-60.pdf%0Ahttp://dx.doi.org/10.1016/S0140-6736(20)30260-9%0Ahttp://dx.doi.org/10.1016/S2468-1253(20)30057-1%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/32091533%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/32109011%0Ahttps://doi.org/

Organization, W. H. (2020a). No Title. *Global Surveillance for Human Infection with Novel Coronavirus (2019-NCoV)*. https://www.who.int/publications/i/item/globalsurveillance-%0Afor-human-infection-with-novelcoronavirus-(%0ACOVID-19)

Organization, W. H. (2020b). No Title. *Coronavirus Disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update*, *68*. https://www.who.int/emergencies/diseases/nov%0Ael-coronavirus-2019/situation-reports

Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., Yan, J., Li, P., Hu, B., Wang, J., Hu, C., Jin, Y., Niu, X., Ping, R., Du, Y., Li, T., Xu, G., Hu, Q., & Tu, L. (2020). Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. *American Journal of Gastroenterology*, *115*(5), 766–773.

https://doi.org/10.14309/ajg.0000000000000620

Papa, A., Covino, M., Pizzolante, F., Miele, L., Lopetuso, L. R., Bove, V., Iorio, R., Simeoni, B., Vetrone, L. M., Tricoli, L., Mignini, I., Schepis, T., D'Alessandro, A., Coppola, G., Nicoletti, T., Visconti, E., & Rapaccini, G. (2020). Gastrointestinal symptoms and digestive comorbidities in an Italian cohort of patients with COVID-19. *European Review for Medical and Pharmacological Sciences*, *24*(13), 7506–7511. https://doi.org/10.26355/eurrev_202007_21923

Ramachandran, P., Onukogu, I., Ghanta, S., Gajendran, M., Perisetti, A., Goyal, H., & Aggarwal, A. (2020). Gastrointestinal Symptoms and Outcomes in Hospitalized Coronavirus Disease 2019 Patients. *Digestive Diseases*, *38*(5), 373–379. https://doi.org/10.1159/000509774

Ramanathan, K., Antognini, D., Combes, A., Paden, M., Zakhary, B., Ogino, M., Maclaren, G., & Brodie, D. (2020a). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, *2020*(January), 19–21.

Ramanathan, K., Antognini, D., Combes, A., Paden, M., Zakhary, B., Ogino, M., Maclaren, G., & Brodie, D. (2020b). *Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- research that is available on the COVID-19 resource centre - including this for unrestricted research re-use a*. *January*, 19–21.

RI, K. (2020). No Title. *Situasi Terkini Perkembangan Coronavirus Disease (COVID-19) 22 November 2020*. https://covid19.kemkes.go.id/situasi-infeksi-emerging/info-corona-virus/situasi-terkini-perkembangan-coronavirus-disease-covid-19-22-november-2020/#X75BTWj7TIV.

Siegel, J. D., Rhinehart, E., Jackson, M., & Chiarello, L. (2007). 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *American Journal of Infection Control*, *35*(10 SUPPL. 2). https://doi.org/10.1016/j.ajic.2007.10.007

Sierpiński, R., Pinkas, J., Jankowski, M., Zgliczyński, W. S., Wierzba, W., Gujski, M., & Szumowski, Ł. (2020). Sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders in 1942 nonhospitalized patients with coronavirus disease 2019 (COVID-19). *Polish Archives of Internal Medicine*, *130*(6), 501–505. https://doi.org/10.20452/pamw.15414

Song, M., Li, Z. lin, Zhou, Y. jiang, Tian, G., Ye, T., Zeng, Z. rui, Deng, J., Wan, H., Li, Q., & Liu, J. bo. (2020). Gastrointestinal involvement of COVID-19 and potential faecal transmission of SARS-CoV-2. *Journal of Zhejiang University: Science B*, *21*(9), 749–751. https://doi.org/10.1631/jzus.B2000253

Suresh Kumar, V. C., Mukherjee, S., Harne, P. S., Subedi, A., Ganapathy, M. K., Patthipati, V. S., & Sapkota, B. (2020). Novelty in the gut: A systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. *BMJ Open Gastroenterology*, *7*(1). https://doi.org/10.1136/bmjgast-2020-000417

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. (2020). Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - Journal of the American Medical Association*, *323*(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

World Health Organization. (2020). Laboratory biosafety guidance related to coronavirus disease (COVID-19). *Interim Guidance*, *19 March*, 1–5.

Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

Zhao, W., Zhang, J., Meadows, M. E., Liu, Y., Hua, T., & Fu, B. (2020). A systematic approach is needed to contain COVID-19 globally. *Science Bulletin*, *65*(11), 876–878. https://doi.org/10.1016/j.scib.2020.03.024

Zhou, J., Li, C., Zhao, G., Chu, H., Wang, D., Yan, H. H. N., Poon, V. K. M., Wen, L., Wong, B. H. Y., Zhao, X., Chiu, M. C., Yang, D., Wang, Y., Au-Yeung, R. K. H., Chan, I. H. Y., Sun, S., Chan, J. F. W., To, K. K. W., Memish, Z. A., … Yuen, K. Y. (2017). Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Science Advances*, *3*(11). https://doi.org/10.1126/sciadv.aao4966

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/nejmoa2001017

LAMPIRAN

CLINICS

ORIGINAL ARTICLE

Gastrointestinal Manifestations and Associated Health Outcomes of COVID-19: A Brazilian Experience From the Largest South American Public Hospital

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OBJECTIVES: Brazil has rapidly developed the second-highest number of COVID-19 cases in the world. As such, proper symptom identification, including gastrointestinal manifestations, and relationship to health outcomes remains key. We aimed to assess the prevalence and impact of gastrointestinal symptoms associated with COVID-19 in a large quaternary referral center in South America.

METHODS: This was a single-center cohort study in a COVID-19 specific hospital in São Paulo, Brazil. Consecutive adult patients with laboratory confirmed SARS-CoV-2 were included. Baseline patient history, presenting symptoms, laboratory results, and clinically relevant outcomes were recorded. Regression analyses were performed to determine significant predictors of the gastrointestinal manifestations of COVID-19 and hospitalization outcomes.

RESULTS: Four-hundred patients with COVID-19 were included. Of these, 33.25% of patients reported $\geqslant 1$ gastrointestinal symptom. Diarrhea was the most common gastrointestinal symptom (17.25%). Patients with gastrointestinal symptoms had higher rates of concomitant constitutional symptoms, notably fatigue and myalgia ($p<0.05$). Gastrointestinal symptoms were also more prevalent among patients on chronic immunosuppressants, ACE/ARB medications, and patient with chronic kidney disease ($p<0.05$). Laboratory results, length of hospitalization, ICU admission, ICU length of stay, need for mechanical ventilation, vasopressor support, and in-hospital mortality did not differ based upon gastrointestinal symptoms ($p>0.05$). Regression analyses showed older age [OR 1.04 (95% CI, 1.02-1.06)], male gender [OR 1.94 (95% CI, 1.12-3.36)], and immunosuppression [OR 2.60 (95% CI, 1.20-5.63)], were associated with increased mortality.

CONCLUSION: Based upon this Brazilian study, gastrointestinal manifestations of COVID-19 are common but do not appear to impact clinically relevant hospitalization outcomes including the need for ICU admission, mechanical ventilation, or mortality.

KEYWORDS: COVID-19; SARS-CoV-2; Gastrointestinal Symptoms; Prevalence; Pandemic.

INTRODUCTION

The new coronavirus infection, as known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China in late 2019 (1). The virus has quickly spread across the world, becoming a pandemic as declared by the World Health Organization in March 2020 (2). As of July 2020, more than 10 million confirmed cases of Coronavirus Disease (COVID-19) across five continents and over 500 thousand deaths have been reported (3). While respiratory symptoms are the main presentation of COVID-19, such as dry cough and dyspnea gastrointestinal manifestations have also been reported (4,5). As the number of cases has increased, so too has our knowledge grown about various symptoms associated with the SARS-CoV-2 infection.

SARS-CoV-2 is known to affect host cells via the angiotensin-converting enzyme receptor (ACE2), which in addition to being highly expressed in pulmonary AT2 cells, are also found in the gastrointestinal system such as cells in the esophagus, pancreas, hepatobiliary tract, small bowel, and colon – indicating that in addition to the respiratory system, the gastrointestinal system is a possible means of

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infection by COVID-19 (6). Several studies report patients with COVID-19 presenting with concomitant or isolated gastrointestinal symptoms; however, there remains a paucity of data from the continent of South America (7–9). Although the United States has become the new epicenter of COVID-19 with 2.84 million confirmed cases, Brazil has become an emerging hot bed of SARS-CoV-2 infection with 1.54 million cases reported to date – approximately 13.5% of all confirmed cases (10). As disease prevalence, presenting symptoms, and outcomes have varied from reports in China to those in the United States and Europe, examination of COVID-19 specific characteristics is highly relevant for the population of Brazil and South America. Therefore, the primary aim of this study was to assess the prevalence of gastrointestinal symptoms associated with SARS-CoV-2 infection and examine gastrointestinal-specific health outcomes in a quaternary referral hospital exclusively treating COVID-19 patients in São Paulo, Brazil (11).

MATERIAL AND METHODS

Study Design and Patient Selection

This is a single-center cohort study in a quaternary hospital specifically treating patients with COVID-19 in São Paulo, Brazil. Out the outset of the pandemic, this quaternary university referral center instituted a protocol to exclusively care for COVID-19 patients. This hospital and institution is comprised of the largest public hospital in South America (11). The hospital is designed to care for patients presenting with moderate and severe disease and receives patient referrals following local government protocol. A total of 400 consecutive, adult patients underwent complete hospitalization from May 1 to June 20, 2020, and were included in this analysis. All patients were followed to hospital discharge or death. Inclusion criteria for hospitalization and study enrollment comprised of only patients with laboratory confirmed SARS-CoV-2 via polymerase-chain reaction (PCR). Patients with suspicion for COVID-19 based upon symptoms alone or imaging with computed tomography (CT) without PCR confirmation were excluded from this analysis.

Data Items

Demographic patient data (age and gender), and symptoms at the time of presentation were recorded. Symptoms were stratified initially as general symptoms (fever, fatigue, myalgia, chills, arthralgia, or diaphoresis), respiratory symptoms (cough, productive cough, dyspnea, pharyngitis, or rhinorrhea), gastrointestinal symptoms (diarrhea, nausea, anorexia, vomiting, abdominal pain, dysphagia, weight loss, gastrointestinal bleeding, or constipation), as well as other non-specific symptoms including anosmia/ageusia. Additional data abstracted through manual chart review included past medical history including pre-existing comorbid medical conditions, chronic use of angiotensin converting enzyme-inhibitor (ACE-I) or angiotension receptor blocker (ARB), chronic use of immunosuppressant medications, clinically relevant laboratory data at time of presentation, and relevant hospitalization characteristics (hospitalization days, intensive care unit [ICU], admission, need for mechanical ventilation, need for vasopressors support, and mortality). All data was abstracted manually from electronic medical records using a structured abstraction tool.

Outcomes

The primary outcome was the to evaluate the impact of gastrointestinal symptoms among COVID-19 patients and clinically relevant health outcomes including need for ICU stay, mechanical ventilation, and in-hospital mortality. Secondary analyzes included assessment of prevalence of any gastrointestinal symptoms among patients hospitalized with COVID-19 at initial presentation, associations between gastrointestinal symptoms and other clinical manifestations, comorbidities, and laboratory results.

Ethical Concerns

This study was approved by the Research Ethics Committee of Hospital das Clínicas - University of São Paulo Medical School (HC-FMUSP).

Statistical Analyses

Baseline patient characteristics, COVID-19 manifestations, laboratory data, as well as hospitalization outcomes were summarized as means ± standard deviation for continuous data and frequencies and proportions for categorical data. Continuous data were compared using the two-sample t-test or Wilcoxon rank-sum test and categorical data were compared using the Chi-square or Fisher's exact test, as appropriate (12). Multivariable analyses were performed using logistic regression. Logistic regression analyses were conducted to determine significant predictors of the gastrointestinal manifestations of COVID-19 and hospitalization outcomes and were reported as standardized β coefficients as well as odds ratio (OR) with corresponding 95% confidence intervals (CIs). With regard to gastrointestinal symptoms, a regression analysis was performed based upon the 3 most common manifestations while key hospitalization outcomes included need for ICU admission, need for mechanical ventilation, or in-hospital mortality. Variables for regression analyses included age, gender, obesity, chronic use of ACE-I or ARB and use of immunosuppressant medications, with additional variables determined based upon significant findings on univariable analyses. Statistical significance was defined as a two-tailed p value <0.05. Statistical analyses were performed using the Stata 15.0 software package (Stata Corp LP, College Station, TX).

RESULTS

Patients Characteristics

This study included 400 patients with COVID-19 with laboratory confirmed SARS-CoV-2 (COVID-19). Of these patients included in this analysis, 56.25% (n=225) were male, with an average age of 56.4 ± 16.07 years. The most frequent comorbid medical conditions among this population included hypertension (54.64%; n=218), diabetes mellitus (35.93%; n=143), and obesity (21.55%; n=86). A complete breakdown of demographic information and comorbidities is summarized in Table 1.

Gastrointestinal symptoms at presentation

A total of 133 (33.25%) patients reported at least one gastrointestinal symptom at the time of presentation, with diarrhea (17.25%) being the most prevalent. Other common gastrointestinal manifestations included nausea (13.75%) and anorexia (11.5%), followed by vomiting and abdominal pain observed 7.50% and 6.0% of individuals, respectively.

Table 1 - Baseline Clinical Characteristics, Comorbidities, Social Factors, Medications, and Laboratory Data on Admission, and Outcomes of COVID-19 Hospitalizations.

	All Patients (n=400)	GI Symptoms (n=133)	No GI Symptoms (n=267)	*P* Value
Baseline Characteristics				
Age	56.40 (16.07)	57.52 (15.95)	55.83 (16.12)	0.3208
Male Gender	225 (56.25)	79 (59.40)	146 (54.68)	0.3716
Comorbid Conditions				
Obesity	86 (21.55)	24 (18.05)	62 (23.31)	0.2291
Coronary Artery Disease	43 (10.78)	12 (9.02)	31 (11.65)	0.4255
Heart Failure	39 (9.77)	8 (6.02)	31 (11.65)	0.0741
Cardiac Arrythmia	29 (9.77)	10 (7.52)	19 (7.14)	0.8919
Hypertension	218 (54.64)	76 (57.14)	143 (53.38)	0.4783
Dyslipidemia	36 (9.05)	12 (9.02)	24 (9.06)	0.9911
Diabetes	143 (35.93)	45 (34.09)	98 (36.84)	0.5913
Cerebrovascular Accident	14 (3.51)	1 (0.75)	13 (4.89)	0.0344
Pulmonary Disease	32 (8.02)	10 (7.52)	22 (8.27)	0.795
Chronic Kidney Disease	62 (15.79)	30 (22.56)	32 (12.41)	0.0087
Thyroid Disease	36 (9.02)	17 (12.78)	19 (7.14)	0.0641
Malignancy	49 (12.31)	15 (11.45)	34 (12.73)	0.759
Social Factors				
Active Tobacco Use	16 (4.01)	5 (3.76)	11 (4.14)	0.8573
Former Tobacco Use	71 (17.88)	30 (22.56)	41 (15.53)	0.0851
Alcohol Use Disorder	19 (4.76)	6 (4.51)	13 (4.89)	0.8684
Medications				
Immunosuppressants	45 (11.28)	21 (15.79)	24 (9.02)	0.0441
ACE-I or ARB	117 (29.62)	50 (38.46)	67 (25.28)	0.0069
Laboratory Data				
Hemoglobin in g/dL	11.87 (2.20)	11.96 (2.12)	11.83 (2.24)	0.5792
Leukocytes in in /microL	9288.38 (13721.94)	8748.03 (8330.11)	9556.51 (15634.12)	0.5821
Lymphocytes in in /microL	1620.31 (9702.31)	1073.87 (546.75)	1893.52 (11874.71)	0.4305
Platelets x1000/microL	228 (122)	223 (106)	230 (129)	0.5816
ALT in U/L	46.94 (49.89)	49.06 (51.16)	45.79 (49.26)	0.5525
AST in U/L	50.92 (48.91)	56.01 (64.77)	48.18 (37.55)	0.1463
Total Bilirubin in mg/dL	0.56 (1.00)	0.48 (0.46)	0.61 (1.19)	0.2858
Direct Bilirubin in mg/dL	0.44 (0.98)	0.35 (0.44)	0.48 (1.17)	0.294
Alkaline Phosphatase in U/L	120.55 (130.45)	106.21 (78.15)	128.38 (151.27)	0.247
GGT in U/L	195.91 (251.16)	175.73 (207.03)	206.68 (271.93)	0.4032
Amylase in U/L	76.77 (51.92)	77.71 (45.71)	75.94 (57.53)	0.8961
INR	1.17 (0.79)	1.09 (0.24)	1.20 (0.94)	0.2579
D-Dimer in ng/mL	4648.45 (12025.48)	3954.72 (10423.51)	5027.44 (12823.68)	0.4367
NT-pro-BNP in pg/mL	4145.42 (11212.44)	3425.63 (8471.85)	4552.58 (12522.54)	0.5495
Lactic acid in mg/dL	15.35 (18.75)	13.56 (6.38)	16.28 (22.58)	0.2614
LDH in U/L	416.28 (238.18)	397.13 (232.45)	426.83 (241.17)	0.2753
CRP in mg/dL	141.87 (110.53)	130.60 (98.64)	147.60 (115.88)	0.1601
Hospitalization Characteristics				
Length of Hospital Stay in days	14.15 (10.71)	13.77 (9.66)	14.34 (11.21)	0.6153
ICU Admission	201 (50.25)	62 (46.62)	139 (52.06)	0.3062
Length of ICU Stay in days	12.16 (8.52)	12.02 (9.13)	12.22 (8.28)	0.8732
Endotracheal Intubation	161 (40.25)	48 (36.09)	113 (42.32)	0.2322
Vasopressor Support	142 (35.50)	42 (31.58)	100 (37.45)	0.2485
Mortality	89 (22.25)	28 (21.05)	61 (22.85)	0.6896

A complete list of gastrointestinal symptoms at the time of presentation among patients is summarized in Table 2.

Correlation between gastrointestinal symptoms and other manifestations

Patients with *gastrointestinal* symptoms had higher rates of constitutional symptoms, including fatigue (59.40% vs 44.57%; p=0.0051) and myalgia (42.11% vs 29.96%; p=0.0157). In addition, ageusia was a more common among these patients (22.56% vs 11.24%; p=0.0027). The occurrence of respiratory symptoms did not predominate in a group with or without gastrointestinal symptoms (90.98% vs 93.26%; p=0.4158). Further breakdown of constitutional, respiratory,

Table 2 - Prevalence of Gastrointestinal Symptoms at Time of Presentation Among Hospitalized Patients with COVID-19.

Prevalence of Gastroenterology (GI) Symptoms	
⩾1 Symptom	133 (33.25)
Diarrhea	69 (17.25)
Nausea	55 (13.75)
Anorexia	46 (11.5)
Vomiting	30 (7.50)
Abdominal Pain	24 (6.00)
Dysphagia	3 (0.75)
Weight Loss	2 (0.50)
GI Bleeding	4 (1.00)
Constipation	2 (0.50)

and other symptoms as stratified by the presence of absence of gastrointestinal manifestations is described in Table 3.

Correlation between gastrointestinal symptoms and medical history

Among included patients, 117 (29.62%) were chronic users of an ACE-I or ARB medication. Forty-five (11.28%) patients were prescribed and taking immunosuppressive medication. Regarding the use of specific medications, there was an association between gastrointestinal symptoms and the use of ACE-I or ARBs (38.46% vs 25.28%; p=0.0069). Patients using immunosuppressants also had a higher rate of gastrointestinal symptoms (15.79% vs 9.02%; p=0.0441). Patients with chronic kidney disease had a higher prevalence of gastrointestinal symptoms (22.56% vs 12.41%; p=0.0087), while patient with previous cerebrovascular accident had lower prevalence (0.75% vs 4.89%; p=0.034). Other comorbidities were not significantly different between groups (Table 1).

Correlation between gastrointestinal symptoms and laboratory data

Although some laboratory tests were altered such as lymphocytes, C-reactive protein, and lactate dehydrogenase, there was no statistically significant difference between patients with and without gastrointestinal symptoms at time of presentation. Hematological parameters as well as other inflammatory markers were also similar between groups (Table 1).

Correlation between gastrointestinal symptoms and clinical outcomes

Main outcomes related to COVID-19 such as length of hospitalization, need for ICU admission, ICU length of stay, need of mechanical ventilation, and need for vasopressor support did not differ between patients with or without gastrointestinal symptoms (Table 1). There was also no significant difference for in-hospital mortality rates between the two groups (21.05% vs 22.85%, p=0.6896).

Regression analyses for gastrointestinal symptoms and clinical outcomes

A multivariable logistic regression analysis was then performed for the 3 most common gastrointestinal manifestations to determine their impact on clinically relevant health outcomes (Table 4). After controlling for confounders, diarrhea was more common among patients with a history of ACE-I or ARB use [OR 1.87 (95% CI 1.04 to 3.36); p=0.036], those on immunosuppressant medications [OR 2.54 (95% CI 1.19 to 5.41); p=0.016], and presenting symptoms of fever [OR 3.47 (95% CI 1.66 to 7.27); p=0.001]. With regard to anorexia, older age [OR 0.21 (95% CI 1.04 to 1.05); p=0.021] and loss of taste or smell were predictors [OR 2.83 (95% CI 1.32 to 6.05); p=0.007] while ACE-I or ARB use [OR 2.05 (95% CI 1.07 to 3.95); p=0.031] or ageusia or anosmia were predictors for nausea [OR 2.12 (95% CI 1.04 to 4.32); p=0.039].

Among included patients, gastrointestinal symptoms did not appear to be influence hospitalization outcomes after controlling for other variables (Table 4). Significant predictors of admission to the ICU included male gender [OR 1.60 (95% CI 1.04 to 2.46); p=0.032], obesity [OR 2.18 (95% CI 1.30 to 3.67); p=0.003] and presence of fatigue [OR 1.64 (95% CI 1.03 to 2.60); p=0.036]. Myalgia and ageusia or anosmia appeared to be protective factors in relation to admission to ICU [OR 0.52 (95% CI 0.32 to 0.85); p=0.009] and [OR 0.38 (95% CI 0.20 to 0.71); p=0.003, respectively].

The need for mechanical ventilation in patients with gastrointestinal symptoms was related to male gender [OR 1.63 (95% CI 1.05 to 2.55); p=0.030] and obesity [OR 2.33 (95% CI 1.39 to 3.95); p=0.001]. There was also a negative correlation between mechanical ventilation and use of ACE-I or ARB medications [OR 0.58 (95% CI 0.36 to 0.96); p=0.033], the presence of myalgia [OR 0.56 (95% CI 0.33 to 0.94); p=0.027] and ageusia or anosmia [OR 0.27 (95% CI 0.13 to 0.57); p=0.001].

Mortality was associated with older age [OR 1.04 (95% CI 1.02 to 1.06); $p<0.001$], male gender [OR 1.94 (95% CI 1.12 to 3.36); p=0.018] and use of immunosuppressants [OR 2.60 (95% CI 1.20 to 5.63); p=0.016]. There was a negative relationship between mortality in patients with gastrointestinal symptoms and use of ACE-I or ARB [OR 0.54 (95% CI 0.30 to 0.97); p=0.041].

DISCUSSION

In this single-center study of quaternary referral care center in São Paulo, Brazil, we found approximately one-third of the patients (33.25%) presented with at least one

Table 3 - Constitutional, Respiratory, and Other Symptoms at Time of Presentation Among Hospitalized Patients with COVID-19.

	All Patients	GI Symptoms (n=133)	No GI Symptoms (n=267)	*P* Value
General Symptoms				
⩾1 Symptom	275 (82.25)	117 (87.97)	212 (79.40)	0.0347
Fever	69.5	99 (74.43)	179 (67.04)	0.1308
Fatigue	49.5	79 (59.40)	119 (44.57)	0.0051
Myalgia	34	56 (42.11)	80 (29.96)	0.0157
Chills	4.25	7 (5.26)	10 (3.75)	0.4796
Arthralgias	5.25	9 (6.77)	12 (4.49)	0.3383
Diaphoresis	1.25	3 (2.26)	2 (0.75)	0.204
Respiratory Symptoms				
⩾1 Symptom	370 (92.50)	121 (90.98)	349 (93.26)	0.4158
Cough	291 (72.75)	103 (77.44)	188 (70.41)	0.1374
Productive Cough	22 (8.25)	10 (7.52)	23 (8.61)	0.7084
Dyspnea	332 (82.96)	107 (81.61)	224 (83.90)	0.4799
Pharyngitis	17 (4.25)	4 (3.01)	13 (4.87)	0.3859
Rhinorrhea	40 (10.00)	9 (6.77)	31 (11.61)	0.1288
Other Symptoms				
Ageusia/Anosmia	68 (17.00)	33 (24.81)	35 (13.11)	0.0033
Ageusia	60 (15.00)	30 (22.56)	30 (11.24)	0.0027
Anosmia	46 (11.50)	20 (15.04)	26 (9.74)	0.1181

Table 4 - Multivariable Logistic Regression Model for Gastrointestinal Symptoms.

Multivariable Regression Model for Diarrhea	Odds Ratio (95% CI)	*P* Value	Multivariable Regression Model for ICU Admission	Odds Ratio (95% CI)	*P* Value
Age	1.00 (0.98 to 1.02)	0.856	Age	1.00 (0.98 to 1.01)	0.684
Gender	1.21 (0.68 to 2.13)	0.519	Gender	1.60 (1.04 to 2.46)	0.032
Obesity	0.71 (0.35 to 1.44)	0.345	Obesity	2.18 (1.30 to 3.67)	0.003
ACE-I or ARB	1.87 (1.04 to 3.36)	0.036	ACE-I or ARB	0.78 (0.49 to 1.25)	0.305
Immunosuppressants	2.54 (1.19 to 5.41)	0.016	Immunosuppressants	1.19 (0.61 to 2.31)	0.605
Tobacco Use	1.90 (0.48 to 7.42)	0.358	⩾1 GI Symptom	0.90 (0.57 to 1.41)	0.631
Alcohol Use	0.42 (0.09 to 2.01)	0.28	Myalgia	0.52 (0.32 to 0.85)	0.009
Fever	3.47 (1.66 to 7.27)	0.001	Fatigue	1.64 (1.03 to 2.60)	0.036
Ageusia or Anosmia	1.45 (0.74 to 2.85)	0.28	Ageusia or Anosmia	0.38 (0.20 to 0.71)	0.003
Multivariable Regression Model for Diarrhea	**Odds Ratio (95% CI)**	***P* Value**	**Multivariable Regression Model for ICU Admission**	**Odds Ratio (95% CI)**	***P* Value**
Age	1.03 (1.01 to 1.05)	0.021	Age	1.01 (0.99 to 1.02)	0.28
Gender	1.08 (0.54 to 2.17)	0.82	Gender	1.63 (1.05 to 2.55)	0.03
Obesity	1.06 (0.47 to 2.39)	0.879	Obesity	2.33 (1.39 to 3.95)	0.001
ACE-I or ARB	1.45 (0.72 to 2.91)	0.294	ACE-I or ARB	0.58 (0.36 to 0.96)	0.033
Immunosuppressants	1.11 (0.39 to 3.13)	0.844	Immunosuppressants	1.48 (0.74 to 2.92)	0.261
Tobacco Use	0.65 (0.08 to 5.39)	0.69	⩾1 GI Symptom	0.87 (0.55 to 1.39)	0.567
Alcohol Use	1.97 (0.50 to 7.82)	0.336	Myalgia	0.56 (0.33 to 0.94)	0.027
Fever	1.78 (0.80 to 3.98)	0.16	Fatigue	1.30 (0.81 to 2.07)	0.275
Ageusia or Anosmia	2.83 (1.32 to 6.05)	0.007	Ageusia or Anosmia	0.27 (0.13 to 0.57)	0.001
Multivariable Regression Model for Diarrhea	**Odds Ratio (95% CI)**	***P* Value**	**Multivariable Regression Model for ICU Admission**	**Odds Ratio (95% CI)**	***P* Value**
Age	0.99 (0.97 to 1.00)	0.22	Age	1.04 (1.02 to 1.06)	<0.001
Gender	0.67 (0.36 to 1.27)	0.217	Gender	1.94 (1.12 to 3.36)	0.018
Obesity	0.47 (0.20 to 1.23)	0.088	Obesity	1.67 (0.90 to 3.13)	0.104
ACE-I or ARB	2.05 (1.07 to 3.95)	0.031	ACE-I or ARB	0.54 (0.30 to 0.97)	0.041
Immunosuppressants	1.94 (0.86 to 4.36)	0.109	Immunosuppressants	2.60 (1.20 to 5.63)	0.016
Tobacco Use	3.47 (0.99 to 12.08)	0.051	⩾1 GI Symptom	0.99 (0.56 to 1.74)	0.974
Alcohol Use	1.40 (0.36 to 5.52)	0.627	Myalgia	0.46 (0.24 to 0.89)	0.021
Fever	1.53 (1.04 to 4.32)	0.241	Fatigue	0.90 (0.52 to 0.16)	0.715
Ageusia or Anosmia	2.12 (1.04 to 4.32)	0.039	Ageusia or Anosmia	0.48 (0.19 to 1.23)	0.125

gastrointestinal symptom. Diarrhea (17.25%), nausea (13.75%), and anorexia (11.5%) were the most prevalent symptoms. However, the presence of gastrointestinal symptoms did not impact need for ICU admission, mechanical ventilation, or all-cause inpatient mortality. To date, this is the largest Brazilian study to report the prevalence of gastrointestinal symptoms in a cohort of COVID-19 hospitalized patients and evaluate the impact of gastrointestinal manifestations among key health outcomes.

Interestingly, the prevalence of gastrointestinal symptoms (33.25%), most notably diarrhea, has been highly variable worldwide – with our results approximately 3-times higher

than previous meta-analyses have demonstrated (10% to 13%)(5,13,14). However, a recent multi-center study in the United States, not included in those meta-analyses, has reported a prevalence as high as 61.3%(7). A plausible explanation may be that hospitalized patients have a more systemic disease and thus, would have a higher prevalence of gastrointestinal symptoms. Additionally, the 10% to 13% prevalence reported in these meta-analyses is based upon inpatient and outpatient populations. While this may vary on a global scale, the referral natural of this hospital caring for moderate-to-severe disease may result in a greater prevalence of gastrointestinal manifestations. This is supported in this study by the observation that patients with gastrointestinal symptoms had more general symptoms than patients without gastrointestinal. Anosmia and/or ageusia also had a higher prevalence among patients with gastrointestinal symptoms, similar to an association previously highlighted in a United States study (7).

While baseline demographic and laboratory data were not different between patients with or without gastrointestinal symptoms, history of a cerebrovascular accident was less prevalent among patients presented with gastrointestinal symptoms (p=0.0344). This is a new negative association found in this study though difficult to truly explain – and may be difficult to determine given the few patients with gastrointestinal manifestations. On the other hand, chronic kidney disease was more prevalent among patients with GI symptoms (p=0.0087), which could potentially be explained by chronic use of ACE-I/ARB among those patients – also more common among patients with gastrointestinal manifestations. It is known that SARS-CoV-2 enters host cells via cell receptor ACE2 (6). ACE2 is highly expressed in the respiratory tract cells but also in the gastrointestinal tract cells (6). That may explain the high prevalence of gastrointestinal symptoms among patients with COVID-19 and the association with ACE-I/ARB chronic use – usually taken by patients with chronic kidney disease , which could upregulate natural receptors for the virus on those cells (15,16).

In this study, after a multivariable logistic regression, diarrhea was associated with use of ACE-I/ARB [OR 1.87 (95% CI 1.04 to 3.36); p=0.036]. However, the role of ACE-I/ARB and COVID-19 symptoms remains controversial. Initial concerns were raised about ACE2 upregulation in patients in chronic use of ACE-I/ARB and its impact on severity and mortality of COVID-19 (17). At least one study supposed a higher mortality among these patients (18). Two meta-analyses have reached different results: one demonstrating no association between ACE-I/ARB chronic use with disease severity (19) while the other one showed a possible protective effect with lower mortality among ACE-I/ARB users (20). Our study reported that chronic use of ACE-I/ARB is a protective factor for mechanical ventilation and associated with a lower mortality. A Randomized Clinical Trial comparing suspending or continuing use of ACE-I/ARB in chronic users is currently under way and should aid in understanding the role of those drugs among COVID-19 patients (21).

The main outcomes related to COVID-19 infection such as hospitalization days, ICU admission, ICU days, endotracheal intubation, and need of vasopressor support did not differ between patients with or without gastrointestinal symptoms. Although gastrointestinal symptoms are frequent and may be associated with specific constitutional symptoms, this finding suggests that gastrointestinal symptoms are not associated to severity of disease nor worse outcomes – a finding consistent with other literature (7,22). Two meta-analyses found relation between abdominal pain and severe disease, but this did not significantly impact mortality. Severe disease was reported with high heterogeneity between those studies, including oxygen saturation parameters, pulmonary involvement on image exams, and ICU admission, which may lead to imprecision on analyses (13,14).

On multivariable logistic regression, myalgia and anosmia/ageusia were associated with a decrease in need for ICU admission and mechanical ventilation. Myalgia was even associated with lower mortality among hospitalized patients. Classically, myalgia and anosmia/ageusia are reported as early symptoms in COVID-19 (23,24) which may translate in our study to mean earlier diagnosis and possibly result in an improved prognosis. Although myalgia is commonly associated with generalized inflammation and cytokine response, a meta-analysis showed that myalgia is not relate with severity or mortality (24). With regards of anosmia/ageusia, a systematic review that included 42 studies showed an inverse relation with severity and hospitalization, suggesting that anosmia/ageusia are more frequently associated with mild-to-moderate COVID-19 (25).

Among patients with gastrointestinal symptoms, obesity and male gender were associated with a higher rate of ICU admission and need for mechanical ventilation. Studies, including one meta-analysis, have shown obesity and male gender are associated with more severe disease and poorer outcomes in general population (25,26). Fatigue was also an independent factor associated with more ICU admission among patients (25). Our study demonstrated that fatigue was also associated with more severe disease (i.e., ICU admission). This is an important finding that should prompt attention to the possibility for more severe disease or a prolonged hospital course should patients report fatigue on presentation. With regards to increased mortality, older age, male gender, and immunosuppressed patients were predictors – similar to what is known in the general population and for a variety of other illnesses (25,26).

Despite this is the largest single-center Western study related to patients with COVID-19 and gastrointestinal symptoms, our study is not without limitations. First, the retrospective study design and manual chart review may introduce the possibility of bias – including possible missed or incomplete data, poor medical documentation, and potential for under or over appreciating symptoms at time of hospital presentation. Furthermore, the referral based nature of the hospital may introduce selection bias and inclusion of only hospitalized patients. Yet despite these limitations, our study possesses several strengths. Notably, this study provides important insights regarding COVID-19 from the largest hospital in Brazil, a nation with the second most confirmed cases in the world. As the rate continues to skyrocket, increasing faster than that of the United States, examination of this unique population may prove exceedingly important to determine next steps in identification and understanding of the disease in a South American population.

CONCLUSION

Gastrointestinal symptoms are prevalent among patients with COVID-19, with diarrhea being the most common manifestation. Patients in chronic use of ACE-I/ARB are

more likely to present with gastrointestinal symptoms, as well as the concomitant presentation of myalgia or anosmia/ageusia with gastrointestinal symptoms. Based upon this analysis, gastrointestinal symptoms do not appear to impact key COVID-19 associated hospitalization outcomes including the need for ICU admission, mechanical ventilation, or all-cause inpatient mortality. Older age, male gender, and immunosuppressed patients were the only conditions associated with higher mortality.

CONFLICT OF INTEREST

Dr. Christopher C. Thompson reports fee as a consultant for Boston Scientific and Medtronic; fees as consultant and institutional grants from USGE Medical, Olympus, and Apollo Endosurgery. Dr. Eduardo Guimarães Hourneaux de Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work.
The others authors reported no potential conflict of interest.

AUTHOR CONTRIBUTIONS

de Moura DTH participate in the study concept and design, manuscript preparation, critical revisions. Proença IM participate in the acquisition of data, manuscript and data preparation, critical revisions. Sagae VMT participate in the study concept and design, data acquisition and interpretation, critical revisions. McCarty TR participate in the statistical analyses, data interpretation, critical revisions. Ribeiro IB participate in the acquisition of data, manuscript preparation, data interpretation, critical revisions. Hirsch BS, De Oliveira GHP, De Souza GMV and Scatimburgo MVCV participated in the acquisition of data, statistical analyses, data interpretation. Thompson CC participate in the study concept and design, critical revisions. Carrilho FJ and Cecconell I participated in the critical revisions. de Moura, EGH participate in the study concept and design, data interpretation, critical revisions.

All authors approve of the final version of the manuscript.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med [Internet]. 2020;382(8):727-3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31978945
2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. 2020 [cited 2020 Sep 7]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
3. World Health Organization. COVID-19 Dashboard [Internet]. 2020 [cited 2020 Sep 7]. Available from: https://who.sprinklr.com/
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA [Internet]. 2020;323(11):1061. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32031570
5. Parasa S, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019. A Systematic Review and Meta-analysis. JAMA Netw Open [Internet]. 2020;11;3(6):e2011335. Available from:http://www.ncbi.nlm.nih.gov/pubmed/32525549
6. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, 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 [Internet]. 2020;69(6):1010-8. Available from: http://gut.bmj.com/lookup/doi/10.1136/gutjnl-2020-320953
7. Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC,, et al. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. Gastroenterology [Internet]. 2020 Apr 22; 2020;159(2):765-67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32333911
8. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut [Internet]. 2020;69(6):1002-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32213556
9. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol [Internet]. 2020;115(5):766-73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32287140
10. Johns Hopkins Universty and Medicine. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE). 2020.
11. Franzini TAP, Kotinda APST, Moura DTH, Badana MLV, Medeiros MS, Lima PGR, et al. Approach to Endoscopic Procedures: A Routine Protocol from a Quaternary University Referral Center Exclusively for Coronavirus Disease 2019 Patients. Clinics [Internet]. 2020;75:e1989. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32555947
12. Campbell I. Chi-squared and Fisher–Irwin tests of two-by-two tables with small sample recommendations. Stat Med [Internet]. 2007;26(19):3661-75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17315184
13. Suresh Kumar VC, Mukherjee S, Harne PS, Subedi A, Ganapathy MK, Patthipati VS, et al. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. BMJ Open Gastroenterol [Internet]. 2020;7(1):e000417. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32457035
14. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol [Internet]. 2020;5(7):667-78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32405603
15. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. JAMA [Internet]. 2020;324(2):168-177. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32558877
16. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature [Internet]. 2003;426(6965):450-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14647384
17. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med [Internet]. 2020;8(4):e21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32171062
18. Selçuk M, Çınar T, Keskin M, Çiçek V, Kılıç Ş, Kenan B, et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens [Internet]. 2020;42(8):738-742. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32569491
19. Grover A, Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Eur Hear J - Cardiovasc Pharmacother [Internet]. 2020 Jun 15; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32542337
20. Zhang X, Yu J, Pan L-Y, Jiang H-Y. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. Pharmacol Res [Internet].2020;158:104927. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32422341
21. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda G, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. Am Heart J [Internet]. 2020;226:49-59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32502882
22. Cao C, Chen M, He L, Xie J, Chen X. Clinical features and outcomes of COVID-19 patients with gastrointestinal symptoms. Crit Care [Internet]. 2020;24(1):340. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32539863
23. Lippi G. Myalgia may not be associated with severity of coronavirus disease 2019 (COVID-19). World J Emerg Med [Internet]. 2020;11(3):193-194. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32351656
24. von Bartheld CS, Hagen MM, Butowt R. Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences. medRxivi [Preprint]. 2020 Jun 17; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32587993
25. Yu C, Lei Q, Li W, Wang X, Liu W, Fan X, et al. Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China. Am J Prev Med [Internet]. 2020;59(2):168-175. 2020 May 27; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32564974
26. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male [Internet]. 2020;1-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32508193

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CASE REPORT

Abdominal symptoms as initial manifestation of COVID-19: a case series

Sintomas abdominais como manifestação inicial da COVID-19: uma série de casos

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ABSTRACT

The COVID-19 became a pandemic in early 2020. It was found, at first, that the main manifestations of this new virus occur through respiratory and constitutional symptoms. Therefore, chest tomography was elected as the best imaging test to assess the extent of pulmonary involvement and as a good prognostic predictor for the disease. However, as new studies were produced, the gastrointestinal involvement of COVID-19 becomes more evident, with reports from patients who manifested mainly or only gastrointestinal symptoms in the course of the disease. Thus, in some cases, the initial investigation is carried out at the emergency department with an abdominal computed tomography. We report a case series of ten patients who came to the emergency department of our institution with a chief gastrointestinal complaint, and were initially submitted to an abdominal computed tomography as the first investigation. Although most of the patients did not have significant changes in the abdominal images, most reported patients had pulmonary findings visualized at the lung bases, which were later designated as typical COVID-19 pulmonary findings on chest computed tomography. Only one patient had atypical COVID-19 lung changes on chest computed tomography. All patients had a positive real-time polymerase chain reaction for COVID-19. It is imperative to alert radiologists, especially abdominal radiologists, with the possibility of COVID-19 isolated gastrointestinal symptoms. Besides, it must become a habit to radiologists to assess the pulmonary basis on abdominal scans, a site commonly affected by the new coronavirus.

Keywords: COVID-19; Coronavirus infections; Computed tomography, X-ray computed; Thorax/diagnostic imaging; Gastrointestinal diseases/diagnostic imaging; Abdomen/diagnostic imaging

RESUMO

A COVID-19 foi declarada uma pandemia no início de 2020. Constatou-se, inicialmente, que as principais manifestações desse novo vírus ocorrem por meio de sintomas respiratórios e constitucionais. A tomografia do tórax foi eleita o exame de imagem para avaliar a extensão do comprometimento pulmonar e como um fator preditivo do prognóstico para a doença. No entanto, à medida que novos estudos são produzidos, o envolvimento gastrointestinal da COVID-19 torna-se mais evidente, com relatos de pacientes que manifestaram principalmente ou apenas sintomas gastrointestinais no decorrer da doença. Em alguns casos, a investigação inicial é realizada no pronto-socorro, com tomografia computadorizada do abdome. Relatamos uma série de casos de dez pacientes que compareceram ao serviço de emergência da instituição com uma queixa principal gastrointestinal e foram submetidos inicialmente a uma tomografia computadorizada de abdome como primeira investigação. Embora a maioria dos pacientes não tenha apresentado alterações significativas nas imagens abdominais, eles apresentaram achados pulmonares visualizados nas bases pulmonares, que depois foram caracterizadas como achados pulmonares típicos de COVID-19

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nas tomografias de tórax subsequentes. Apenas um paciente apresentou achados atípicos para COVID-19 na tomografia. Todos os pacientes tiveram reação em cadeia da polimerase em tempo real positiva para o novo coronavírus. É muito importante alertar os radiologistas, principalmente os radiologistas abdominais, da possibilidade de sintomas gastrointestinais isolados no contexto da COVID-19. Além disso, deve ser um hábito para todos os radiologistas avaliar as bases pulmonares nas tomografias de abdome, local comumente afetado pela COVID-19.

Descritores: COVID-19; Infecções por coronavírus; Tomografia computadorizada por raios X; Tórax/diagnóstico por imagem; Gastroenteropatias/diagnóstico por imagem; Abdome/diagnóstico por imagem

INTRODUCTION

The new coronavirus disease (COVID-19) was initially described in December 2019 in Wuhan (Hubei, China), rapidly spread worldwide and was classified as pandemic by the World Health Organization (WHO), on March 11, 2020.[1]

So far, the primordial measures against this new agent are early detection and isolation of suspected patients. The most common initial symptoms described for the COVID-19 infection include constitutional and respiratory symptoms, such as fever, malaise, cough, coryza, and dyspnea.[2]

Recent studies showed that the new coronavirus, an RNA virus, uses the angiotensin-converting enzyme 2 (ACE2) to enter the cells, yielding potential to infect different organs and systems of the human body.[3,4] This mechanism may explain the occurrence of gastrointestinal symptoms in patients with COVID-19, such as diarrhea, nausea, vomits, and lack of appetite, who may or may not be present with respiratory symptoms. However, it was observed that some patients are asymptomatic from the respiratory point of view, and have only abdominal complaints as their initial clinical findings. This phenomenon can be a diagnostic challenge and a potential risk of COVID-19 transmission, not only to other patients but also to the health professionals involved in healthcare.

Therefore, it is important for the abdominal radiologists, radiologists on-call, and other physicians that are on the frontline against the COVID-19, to be aware of the importance of evaluating the lung bases on abdominal computed tomography (CT) in this present pandemic, even in the absence of respiratory complaints.

CLINICAL PRESENTATION

We retrospectively analyzed all emergency abdominal CT of our institution performed between March 15, 2020 and April 21, 2020, looking for changes caused by COVID-19 on the pulmonary basis included on abdominal images, which could lead to further investigation for this viral pneumonia.

Ten patients met these inclusion criteria, and we further reviewed their past medical history.

Of the patients assessed, five were male (50%). The mean age was 62 years, ranging from 41 to 84 years. All ten patients tested positive for COVID-19 in real-time polymerase chain reaction (RT-PCR), obtained from an nasopharyngeal swab sample.

The most frequent gastrointestinal symptoms were abdominal pain, diarrhea, nausea, vomiting, and lack of appetite (Table 1), in agreement with other studies in the literature.[5,6] All patients analyzed had gastrointestinal symptoms that preceded the respiratory symptoms.

Table 1. Gastrointestinal symptoms

Pacient	Sex	Age	Abdominal pain	Diarrhea	Nausea/ vomiting	Lack of appetite
1	M	84	+	+	-	+
2	F	52	+	-	-	-
3	M	72	+	-	-	+
4	F	73	+	+	-	-
5	F	75	-	+	-	-
6	M	76	+	+	+	+
7	M	41	+	+	-	-
8	M	77	+	+	+	+
9	F	56	-	+	+	-
10	F	22	+	+	+	+

M: male; F: female.

Abdominal pain was the most prevalent complaint in the patients assessed; - two presented with diffuse abdominal pain and four with epigastric pain. One patient had pain in the left flank, and another had pain in the right iliac fossa.

Eight patients presented with diarrhea, with a mean duration of 7 days, range of 3 to 20 days. The patient with history of diarrhea for 20 days stayed longer at the hospital, took several antibiotics, which may have contributed to longer duration of this symptom.

Since the chief complaint of the analyzed patients was related to gastrointestinal symptoms, the investigation initiated with an abdominal CT exam, and 80% (8/10) of the exams had no significant abdominal changes. Two CT had positive findings. Nine out of ten of the subsequent chest CT, all of which were motivated by the initial abdominal CT findings had typical COVID-19 alterations,[7] such as peripheral and basal predominant

ground-glass opacities, with septal thickening and thin reticulation, sparse consolidations and subpleural curvilinear lines (Figure 1). One chest CT demonstrated atypical COVID-19 findings, characterized by a unique alveolar consolidation in the right lower lobe (Figure 2).

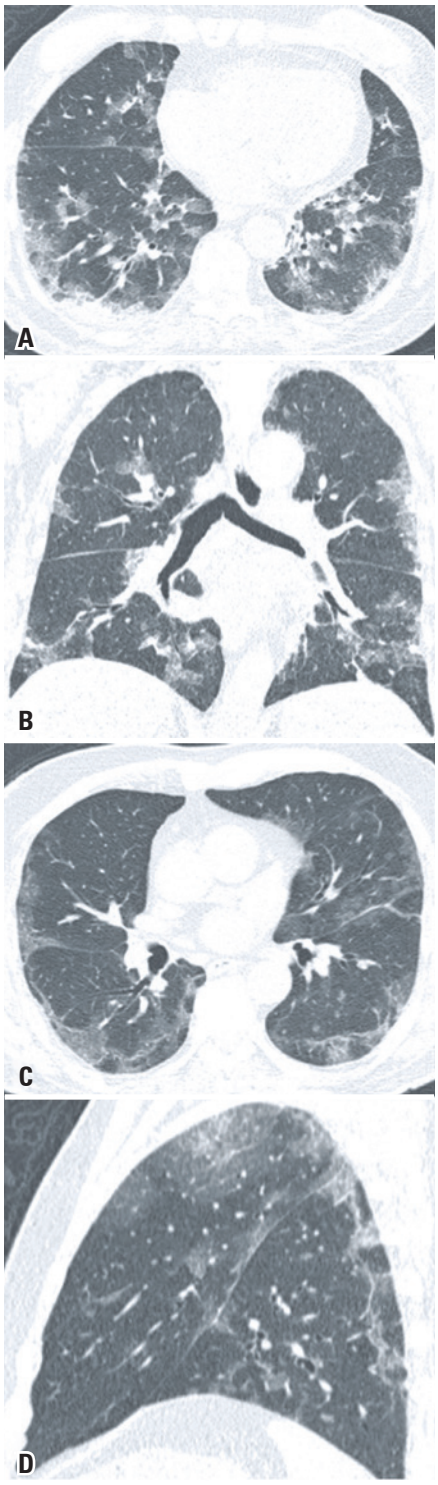

Figure 1. Axial (A, C), coronal (B) and sagital (D) images of chest computed tomography showing typical COVID-19 pulmonary findings

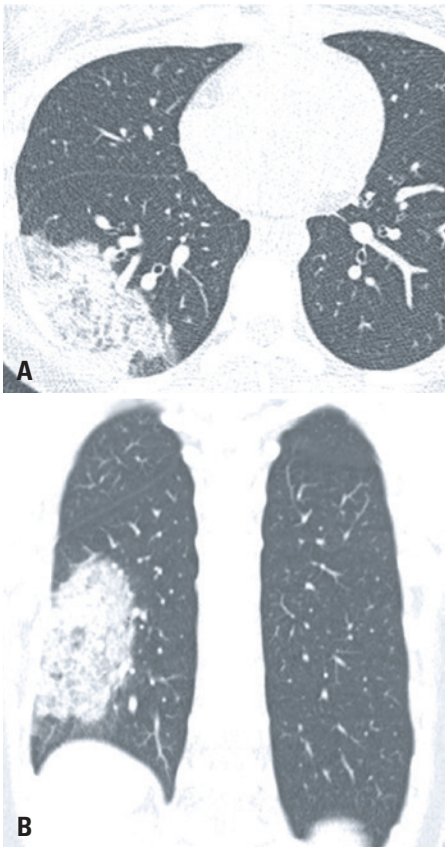

Figure 2. Axial (A) and coronal (B) chest computed tomography images show an unique pulmonary consolidation in the right lower lobe, an atypical finding in COVID-19

CASE REPORTS

First case

A 74-year-old female patient, presented to the emergency department on March 18, 2020, with a history of abdominal pain, on the right iliac fossa, for 15 days. She referred fever for 4 days, and denied having diarrhea, nausea, vomiting, or respiratory symptoms. She presented diffuse abdominal pain upon palpation, more intense on the right iliac fossa. Her chest auscultation was unremarkable. The patient was submitted to a contrast-enhanced CT of the abdomen, with findings consistent with non-complicated acute diverticulitis in the sigmoid colon (Figure 3). She received analgesics and antibiotics and was discharged.

After 4 days of antibiotics, the patient returned to the emergency department complaining of weakness, abdominal cramps, and lack of appetite, still with no respiratory symptoms. She was admitted to the hospital, and presented diarrhea, cough, and desaturation. A RT-PCR was requested from the oropharyngeal swab, and it was positive for COVID-19. A chest CT was performed on March 23, 2020, and showed typical findings for COVID-19 (Figure 4). A retrospective analysis

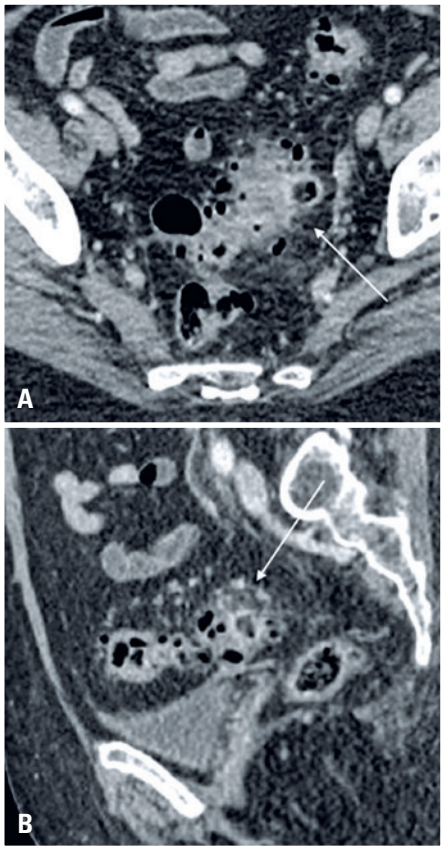

Figure 3. Axial (A) and sagital (B) images of an abdomen computed tomography illustrates multiple diverticula in the sigmoid colon. One showed thickened walls (arrows) with adjacent fat stranding, findings consistent with acute diverticulitis

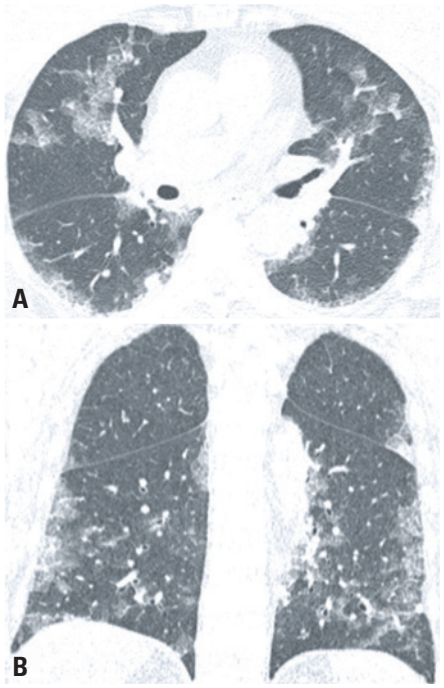

Figure 4. Axial (A) and coronal (B) images of a chest computed tomography illustrate multiple and bilateral ground glass opacities, septal thickening and reticulation, findings consistent with COVID-19

of the lung basis on the abdomen CT on March 18, 2020 revealed discrete ground-glass opacities with areas of thin reticulation and septal thickening on the periphery of the medium lobe and on the posterior basal segments of both lungs, findings that possibly were related to incipient COVID-19 changes (Figure 5). The patient had a good progression, being discharged home on March 31, 2020, in a good general status.

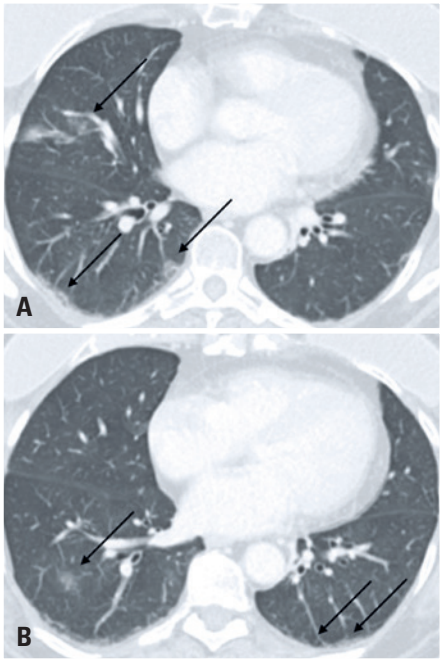

Figure 5. Axial images (A and B) of the lung basis in an abdomen computed tomography show subtle ground glass opacities with some septal thickening, which possibly represented incipient COVID-19 changes (arrows)

Second case

A 75-year-old female patient came to the emergency department on March 18, 2020, presenting with malaise, fever, diarrhea, and dyspnea. The hypothesis of an abdominal sepsis was raised, and the patient was admitted to an intensive care unit. An abdominal CT with no contrast enhancement was requested, which revealed a thickened ascending colon and distal ileum, associated with adjacent fat stranding, findings that suggested enterocolitis (Figure 6). In the same exam, on the pulmonary basis, areas of peripheral ground-glass opacities were observed on both lungs, especially on the left, and pleural effusion on the right lung (Figure 7). These changes led to the request of a chest CT, which had findings consistent with viral pneumonia (typical of COVID-19). With this suspect, RT-PCR was done and it returned positive. The patient progressed with severe respiratory failure and was intubated. She had a slow but steady recovery, being discharged from the hospital after one month.

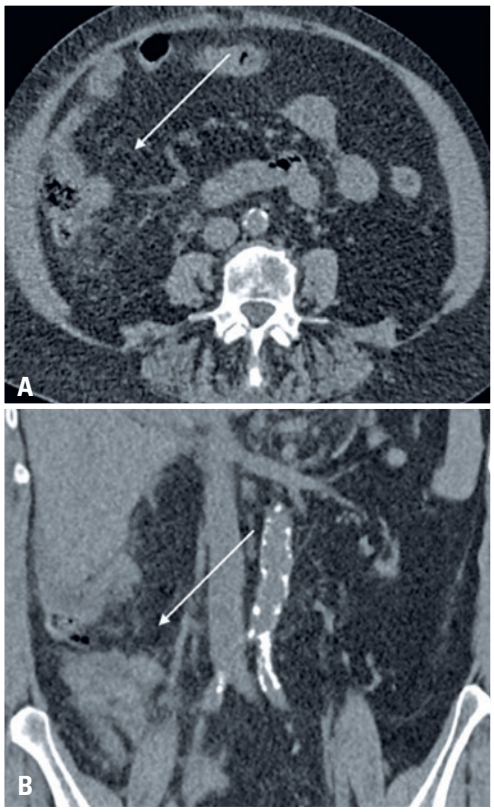

Figure 6. Axial (A) and coronal (B) images of a non-enhanced abdomen computed tomography show thickened walls in the cecum and terminal ileum, with fat stranding (arrows), consistent with enterocolitis

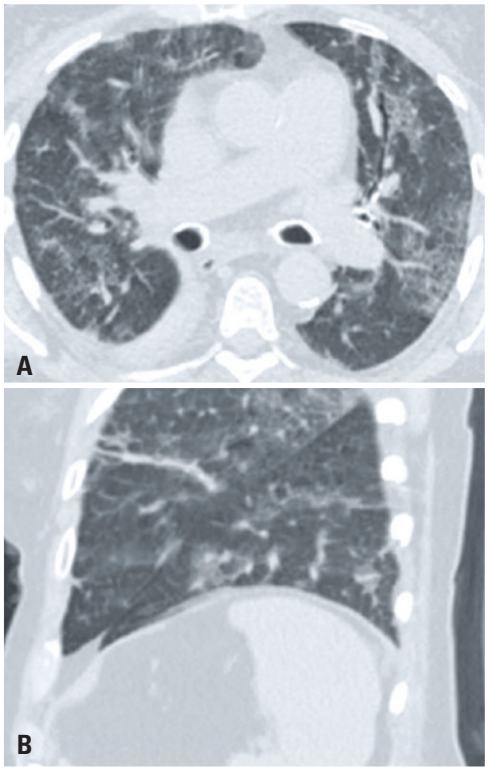

Figure 7. Axial (A) and sagital (B) images of the lung basis in an abdomen computed tomography show ground-glass opacities with septal thickening and fine reticulation, typical COVID-19 pulmonary findings

DISCUSSION

As the COVID-19 spreads and new studies are finalized, its gastrointestinal effects become more evident: some symptoms, such as abdominal pain, diarrhea, nausea, and vomiting are not rare, as deemed in the beginning of the pandemic. A study by Lin et al.,[6] reported a 61% prevalence of gastrointestinal symptoms upon admission or in the course of the disease.

We illustrated one case of acute diverticulitis that preceded a new coronavirus infection, and another presenting with diarrhea and signs of enterocolitis during de course of the disease. We questioned if the findings of enterocolitis could be a manifestation of COVID-19 infecting enterocytes, or if there was an intestinal coinfection.

New evidence in the literature suggests that there is ACE2 expression in the enterocytes,[4,8] acting as an inflammatory mediator. Besides, new studies found the virus in feces of infected patients, supporting not only the possibility of direct intestinal infection but also the possibility of a fecal-oral transmission route.[8,9]

Abdominal complaints are frequently assessed with imaging studies, and some protocols include images of the pulmonary bases, which are frequent sites of involvement by COVID-19. We believe that some COVID-19 patients will not show respiratory symptoms, leading to a challenging diagnosis, delaying adequate isolation measurements. In addition, some studies have demonstrated that abdominal symptoms are not rare in this group of patients and can appear earlier in the course of the disease.[10,11] Therefore, in the actual pandemic, it is of paramount importance that radiologists keep a high grade of suspicion even when analyzing an exam not directed to the chest, and even when there is no suspicion by the clinical staff, assuring a prompt COVID-19 diagnosis. Since there is no specific treatment for COVID-19, the early diagnosis has an impact on the medical care concerning isolation, reducing transmissibility of the disease not only at home but also at hospitals.

CONCLUSION

COVID-19 has a broad spectrum of gastrointestinal symptoms, which are much common than we originally considered. In this pandemic context, we believe radiologists, especially abdominal radiologists, should be aware of the typical and atypical pulmonary changes of coronavirus disease when assessing the lung bases.

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REFERENCES

1. World Health Organization (WHO). WHO announces COVID-19 outbreak a pandemic [Internet]. Geneva: WHO; 2020 [cited 12 May 2020]. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic
2. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, et al. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology. 2020;296(2):E15-E25. Review.
3. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J Virol. 2020;94(5). pii:e02015-19.
4. Liang W, Feng Z, Rao S, Xiao C, Xue X, Lin Z, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020; 69(6):1141-3.
5. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, 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.
6. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997-1001.
7. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020;30(8):4381-9. Review.
8. Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut. 2020;69(6):973-4.
9. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin Gastroenterol Hepatol. 2020;18(8):1663-72.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. Erratum in: Lancet. 2020 Jan 30.
11. Gao QY, Chen YX, Fang JY. 2019 Novel coronavirus infection and gastrointestinal tract. J Dig Dis. 2020;21(3):125-6.

ORIGINAL ARTICLE

Sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders in 1942 nonhospitalized patients with coronavirus disease 2019 (COVID-19)

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KEY WORDS

coronavirus disease 2019, gastrointestinal symptoms, severe acute respiratory syndrome coronavirus 2, smell, taste

EDITORIAL

by Lippi and Mattiuzzi, see p. 478

ABSTRACT

INTRODUCTION The coronavirus disease 2019 (COVID-19) is a communicable disease caused by a novel coronavirus.

OBJECTIVES This study aimed to assess self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in nonhospitalized patients with COVID-19 in Poland.

PATIENTS AND METHODS This cross-sectional survey was conducted between April 17 and 18, 2020, in 4516 nonhospitalized patients with COVID-19 in Poland. The questionnaire included 8 questions related to the health status, symptoms of COVID-19, comorbidities, and smoking status.

RESULTS Completed questionnaires were obtained from 1942 patients with COVID-19 with a response rate of 43%. The median age of the respondents was 50 years; 60.2% were women. Among nonhospitalized patients with COVID-19, 21.3% had hypertension, 4.5% had diabetes, and 3.1% had a chronic respiratory disease. Regular tobacco use was declared by 11.2% of patients with COVID-19. At least one gastrointestinal symptom was reported by 53.6% of patients. Almost half of patients (47%) with COVID-19 reported lack of appetite and 24.2% reported diarrhea. Among 1942 interviewed patients, 54.2% reported at least 1 olfactory or taste disorder and 42.5% reported both alterations. Self-reported olfactory and taste disorders were 49.2% and 47.5%, respectively. Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 was significantly higher ($P < 0.001$) in women than men.

CONCLUSIONS This study demonstrated that olfactory and taste disorders are frequent symptoms in patients with mild-to-moderate COVID-19. Moreover, our study indicated sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among nonhospitalized patients with COVID-19.

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INTRODUCTION Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] To confirm the diagnosis of COVID-19, it is required to detect SARS-CoV-2 RNA by reverse transcription–polymerase chain reaction (RT-PCR).[3] Most COVID-19 cases (approximately 80%) manifest only mild to moderate symptoms while in 14% of cases, symptoms are severe (dyspnea, hypoxia, or >50% lung involvement on imaging) and only 5% of COVID-19 cases are critical (respiratory failure, shock, or multiorgan system dysfunction).[2,4,5] Older age and comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer are risk factors for a severe

WHAT'S NEW?

This study used data from a cross-sectional survey to assess the self-reported prevalence of gastrointestinal symptoms and olfactory or taste disorders in 1942 nonhospitalized patients with coronavirus disease 2019 (COVID-19) in Poland. The sample size was relatively large, compared with other available studies. Our findings indicate that more than half of patients with mild COVID-19 reported gastrointestinal (53.6%) or neurological (olfactory or taste disorders; 54.2%) symptoms. The present findings also indicate that self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during the COVID-19 course was significantly higher in women than in men. This finding suggests that gastrointestinal symptoms and olfactory or taste disorders should be considered as potential clinical manifestations of COVID-19 in patients with mild to moderate symptoms.

course of illness, complications, and death from COVID-19.[6,7]

The most common COVID-19 symptoms are fever (83%–99%), cough (59%–82%), and fatigue (44%–70%). Less common reported symptoms include shortness of breath (31%–40%), expectoration of sputum (28%–33%), muscle and joint pain (11%–35%), headaches (10%–15%), rhinitis and sore throat (14%–15%), hemoptysis (<10%), nausea or vomiting (5.8%), and diarrhea (3.8%–4.2%).[2,5,8-10] Moreover, it is suggested that the clinical presentation of COVID-19 may include gastrointestinal symptoms and olfactory or gustatory dysfunctions.[11-15] However, data on the frequency of gastrointestinal and neurological manifestation of nonhospitalized patients with mild or asymptomatic COVID-19 have not been sufficiently documented.

This study aimed to assess self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in nonhospitalized patients with COVID-19 in Poland.

PATIENTS AND METHODS

Study design and population This cross-sectional survey was carried out between April 17 and 18, 2020, among 4516 nonhospitalized patients with COVID-19 in Poland. In Poland, all mild and moderate cases of COVID-19 may be referred to as institution-based isolation or home-based isolation, depending on the physician's decision. All COVID-19 cases in home-based isolation were eligible to be included in the research. As of April 17, 2020, a total of 8379 laboratory-confirmed COVID-19 cases were reported in Poland (including severe and fatal cases). The laboratory diagnosis of COVID-19 was based on the detection of SARS-CoV-2 RNA in throat or nasal swabs samples by RT-PCR. Laboratory testing for COVID-19 followed the European Centre for Disease Prevention and Control guidelines.[3]

Detailed contact information for adults of Polish nationality was available for 4516 cases. All patients with COVID-19 in home-based isolation were called by phone as part of sanitary and epidemiological supervision. Participation in the study was voluntary. Participants had the right to refuse to participate without giving a reason. The data was encoded anonymously, making it impossible to identify individuals. All procedures followed the ethical standards of the national research committee and the 1964 Helsinki Declaration (and its later amendments).

Study questionnaire The questionnaire included 8 questions related to the health status, symptoms of COVID-19, comorbidities, and smoking status. Questions also addressed attitudes toward the potential SARS-CoV-2 vaccine.

Self-reported presence of symptoms of COVID-19 was based on a positive response to the following: "During your illness, did you have any of the following symptoms: (1) lack of appetite, (2) diarrhea, (3) olfactory disorder, (4) taste disorder?" The presence of comorbidities was based on a positive response to the following: "Do you have any of the following: (1) hypertension, (2) cardiovascular disease, (3) diabetes, (4) chronic respiratory disease, (5) chronic kidney disease?"

Smoking status was based on a positive response to the following: "Do you currently smoke?" Attitude toward potential SARS-CoV-2 vaccine was based on the question: "If a SARS-CoV-2 coronavirus vaccine becomes available, will you choose to get vaccinated?" (Yes / No).

One of the main goals of the study was to obtain a high response rate. Therefore, the number of questions was limited to those having practical implications for mitigating the early spread of the SARS-CoV-2 epidemic in Poland.

Statistical analysis Data analysis was performed using the procedures available in the Statistica 13 package (TIBCO Software Inc., Palo Alto, California, United States). The distribution of categorical variables was shown by frequencies and proportions along with 95% CI. Categorical variables were compared with the independent samples χ^2 test. Statistical significance was based on a P value of less than 0.05.

RESULTS

Completed questionnaires were obtained from 1942 patients with COVID-19 with a response rate of 43% (41.8% among men and 43.8% among women). The median age of the respondents was 50 years. The group included more women (60.2%) than men (39.8%). Among nonhospitalized patients with COVID-19, 21.3% had hypertension, 4.5% had diabetes, and 3.1% had a chronic respiratory disease (TABLE 1). Regular tobacco use was declared by 11.2% of patients with COVID-19.

If a coronavirus vaccine becomes available, 72.7% of nonhospitalized patients with COVID-19 declared willingness to get vaccinated against SARS-CoV-2 coronavirus (70.5% among women and 76.6% among men; $P = 0.03$).

At least one gastrointestinal symptom was reported by 53.6% of patients (FIGURE 1). Both

TABLE 1 Baseline characteristics of 1942 nonhospitalized patients with coronavirus disease 2019

Parameter		Overall (n = 1942)
Age, y, median		50
Sex	Female	1169 (60.2)
	Male	773 (39.8)
Comorbidities		
Hypertension		413 (21.3)
Cardiovascular disease		116 (6)
Diabetes		88 (4.5)
Chronic respiratory disease		60 (3.1)
Chronic kidney disease		29 (1.5)
Current smokers (n = 1087)	Yes	122 (11.2)
	No	965 (88.8)

Data are presented as number (percentage) unless otherwise indicated.

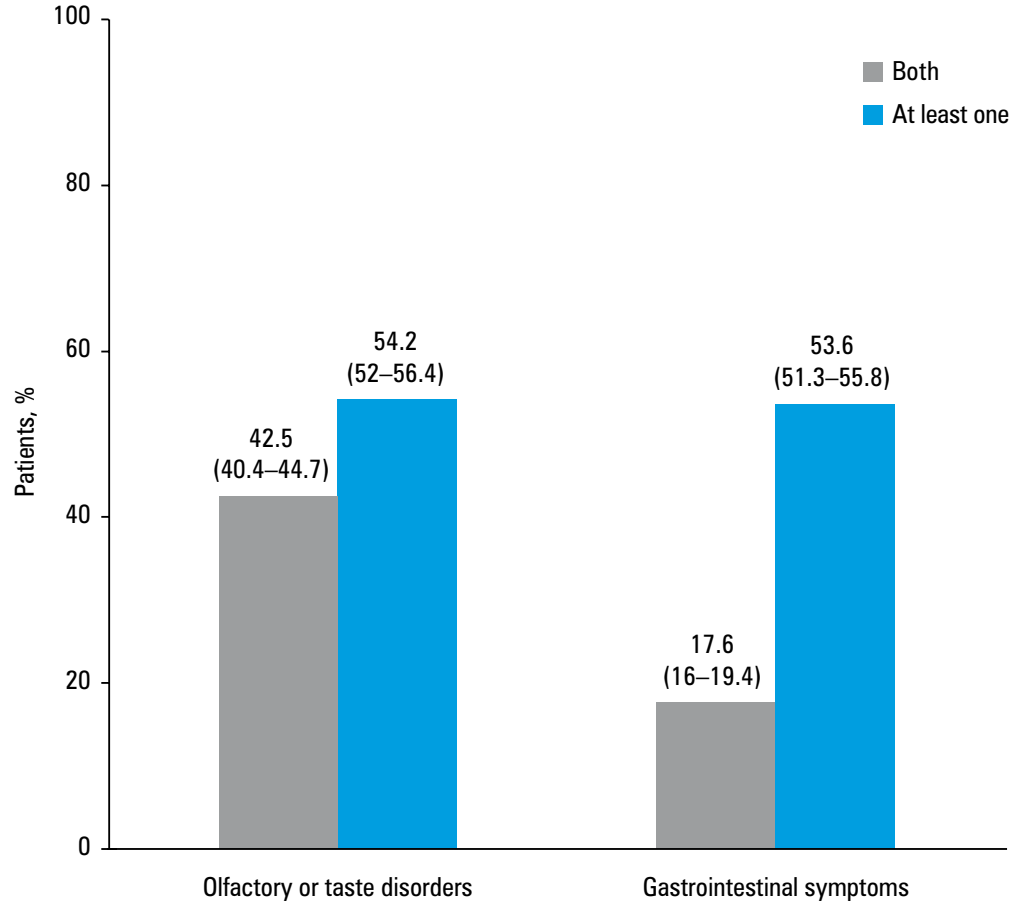

FIGURE 1 Self-reported symptoms of coronavirus disease 2019 in 1942 nonhospitalized patients. Gastrointestinal symptoms include lack of appetite and diarrhea. Data are presented as percentage (95% CI).

gastrointestinal symptoms (lack of appetite and diarrhea) were reported by 17.6% of patients with COVID-19. Almost half of patients (47%) with mild symptoms of COVID-19 reported lack of appetite and 24.2% reported diarrhea during COVID-19 course. Among 1942 interviewed patients, 54.2% reported at least 1 olfactory or taste disorder and 42.5% reported both alterations. Self-reported olfactory and taste disorders were 49.2% and 47.5%, respectively. No gastrointestinal symptoms and olfactory or taste disorders were reported by 31.6% of patients.

There were sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among nonhospitalized patients with COVID-19 (TABLE 2). Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 course was significantly higher among women than men ($P < 0.001$). Details are presented in TABLE 2.

DISCUSSION This study used data from a cross-sectional survey to assess the self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in 1942 nonhospitalized patients with COVID-19 in Poland. Our findings indicate that more than half of patients with mild COVID-19 course reported gastrointestinal

TABLE 2 Sex differences in the prevalence of gastrointestinal symptoms and olfactory or taste disorders in 1942 nonhospitalized patients with coronavirus disease 2019

Symptom	Overall (n = 1942)		Women (n = 1169)		Men (n = 773)		*P* value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Lack of appetite	912 (47)	44.8–49.2	637 (54.5)	51.6–57.3	275 (35.6)	32.3–39	<0.001
Diarrhea	470 (24.2)	22.4–26.2	311 (26.6)	24.2–29.2	159 (20.6)	17.9–23.6	0.002
Olfactory disorder	956 (49.2)	47–51.5	636 (54.4)	51.5–57.2	320 (41.4)	38–44.9	<0.001
Taste disorder	923 (47.5)	45.3–49.8	617 (52.8)	49.9–55.6	306 (39.6)	36.2–43.1	<0.001

symptoms (53.6%) or neurological manifestations (olfactory or taste disorders) (54.2%) of COVID-19. The present findings also point to sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among nonhospitalized patients with COVID-19. Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during the course of COVID-19 was significantly higher among women than men. This finding suggests that gastrointestinal symptoms and olfactory or taste disorders should be considered as potential clinical manifestations of COVID-19 among patients with mild to moderate symptoms.

We observed a higher proportion of COVID-19 among women than men. The frequency of smoking (11.2%) among nonhospitalized patients with COVID-19 was lower compared with the general population (21%).[16] However, this study includes only nonhospitalized patients with a mild course of COVID-19.

The majority of currently available data on gastrointestinal symptoms in COVID-19 was derived from hospitalized patients. Among 138 hospitalized patients with COVID-19 in Wuhan, China, 39.9% reported anorexia / lack of appetite and 10.1% had diarrhea.[9] Another study carried out among 651 patients in China, showed that 11.4% of hospitalized patients presented with at least 1 gastrointestinal symptom.[12] A multicenter cohort study across 9 hospitals in the United States showed that 61.3% patients reported at least 1 gastrointestinal symptom, wherein 34.8% of patients reported anorexia and 33.7% reported diarrhea.[11] To the best of our knowledge, this study is one of the few studies conducted in nonhospitalized patients with COVID-19. Our findings indicate that more than half of nonhospitalized patients with COVID-19 (53.6%) reported at least 1 gastrointestinal symptom, wherein 47% reported lack of appetite and 24.2%, diarrhea. The frequency of gastrointestinal symptoms in our study is higher than in studies from China but comparable to those observed in the United States.

Moreover, it is suggested that a significant proportion of patients with COVID-19 may report olfactory or gustatory dysfunctions.[13-15] In a multicenter PCR-based case-control study in Spain, out of 79 patients enrolled, 35.4% reported a smell disorder and 31.6% reported a taste disorder.[17] A study carried out in Wuhan, China in 214 patients with COVID-19 showed that 5.6% of those reported taste impairment and 5.1%, smell impairment.[15] A higher frequency of olfactory and gustatory dysfunctions was observed in a multicenter European study by Lechien et al.[13] Among 417 patients with mild-to-moderate COVID-19, olfactory dysfunction was reported by 85.6% of patients and gustatory dysfunctions by 88%.[13] In our study, 49.2% of patients reported an olfactory disorder and 47.5% reported a taste disorder. Our findings are in line with the study by Lechien et al[13] and indicate that olfactory and taste disorders are frequent symptoms in European patients with COVID-19.

Our findings indicate that the frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 is higher among women than men. This phenomenon may be explained by the sex differences in human olfaction.[18] Oliveira-Pinto et al[18] showed that women have more neurons and gial cells in the olfactory bulbs than males. Moreover, the impact of hormonal modulation on the gustatory system should be considered.[19] Further studies may be required to address nonrespiratory symptoms among patients with COVID-19 and sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders in COVID-19.

This study has several limitations. The presence of symptoms of COVID-19 was self-reported and was not confirmed by a physician. Secondly, the list of COVID-19 symptoms was limited to 4 key questions. However, most of the currently available studies on COVID-19 are based on electronic health records of patients with COVID-19. Third, this study was carried out among nonhospitalized patients so the results cannot be generalized to the whole population of patients with COVID-19. We cannot exclude selection bias. Nevertheless, our study is one of the first cross-sectional surveys focusing on nonrespiratory symptoms of COVID-19. Moreover, the sample size is relatively high compared with other currently published studies.

In conclusion, this study demonstrated that olfactory and taste disorders are frequent symptoms in patients with mild-to-moderate COVID-19. Moreover, our study indicates sex differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among nonhospitalized patients with COVID-19. This study suggests that nonrespiratory symptoms should be

considered as potential clinical manifestations of COVID-19 during the diagnostic workup.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT RS, JP, MJ, MG, and ŁS conceived the concept of the survey study, and were responsible for its design, questionnaire development, crude data collection and interpretation. RS, JP, and ŁS conceived the concept of the research questions. RS, MJ, WSZ, and WW were responsible for methodology of advanced data management and statistical analysis. RS, JP, MJ, WSZ, WW, MG, and ŁS edited the manuscript. MG and ŁS were responsible for linguistic correction and adjustment of the manuscript. All authors read and approved the final version of the manuscript.

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REFERENCES

1 Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395: 565-574.

2 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.

3 European Centre for Disease Prevention and Control (ECDC). Case definition and European surveillance for COVID-19, as of 2 March 2020. https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov. Accessed April 28, 2020.

4 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Feb 24. [Epub ahead of print].

5 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382: 1708-1720.

6 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062.

7 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8: 475-481.

8 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507-513.

9 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: 1061-1069.

10 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 Mar 13. [Epub ahead of print].

11 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 Apr 22. [Epub ahead of print].

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: 1002-1009.

13 Lechien JR, Chiesa-Estomba CM, De Siati 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 Apr 6. [Epub ahead of print].

14 Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020 Mar 26. [Epub ahead of print].

15 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr 10. [Epub ahead of print].

16 Pinkas J, Kaleta D, Zgliczyński WS, et al. The prevalence of tobacco and e-cigarette use in Poland: a 2019 nationwide cross-sectional survey. Int J Environ Res Public Health. 2019; 16: E4820.

17 Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicenter PCR-based case-control study. Eur J Neurol. 2020 Apr 22. [Epub ahead of print].

18 Oliveira-Pinto AV, Santos RM, Coutinho RA, et al. Sexual dimorphism in the human olfactory bulb: females have more neurons and glial cells than males. PLoS One. 2014; 9: e111733.

19 Loper HB, La Sala M, Dotson C, Steinle N. Taste perception, associated hormonal modulation, and nutrient intake. Nutr Rev. 2015; 73: 83-91.

Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus responsible for coronavirus disease 2019 (COVID-19).[1,2] The virus enters cells via the angiotensin-converting enzyme 2 receptor, which is present in enterocytes in the ileum and colon.[3] Gastrointestinal (GI) manifestations include diarrhea, nausea, vomiting, and abdominal pain, and the prevalence of GI symptoms varies greatly, with a range between 2% and 57%.[4] In addition, abnormal liver chemistries are reported commonly.[4] As a medical center at the forefront of the early epidemic in the United States, we seek to contribute to the growing body of literature that outlines the gastrointestinal and hepatic manifestations of COVID-19.

Methods

We performed a retrospective review of consecutive adult nonpregnant patients admitted to New York–Presbyterian Queens Hospital in Flushing, NY, for SARS-CoV-2 between March 14, 2020, and April 1, 2020 (Supplementary Methods). The Fisher exact, chi-square, and Wilcoxon rank-sum tests were used to compare groups, and a P value less than .05 was considered statistically significant. This study was approved by the New York–Presbyterian Queens Institutional Review Board.

Results

A total of 892 patients were included. Forty percent were women. The median age was 59 years (interquartile range [IQR], 47–72 y). Twenty-five percent of patients presented with GI symptoms, the most common of which was diarrhea (19.8%) (Table 1). The median aspartate aminotransferase (AST) level on admission was 41 U/L (IQR, 30–61 U/L), and the median peak AST level was 55 U/L (IQR, 36–97 U/L). Forty-three percent of patients had a normal AST level on admission, 40.0% had a borderline increase (1–2 times the upper limit of normal [ULN]), 13.8% had a mild increase (2–5 times the ULN), and 2.8% had a moderate to severe increase (>5 times the ULN). The median alanine aminotransferase (ALT) level on admission was 32 U/L (IQR, 19–56 U/L) and the median peak ALT level was 47 U/L (IQR, 25–91 U/L). Sixty percent of patients had a normal ALT level on admission, 26.5% had a borderline increase (1–2 times the ULN), 11.5% had a mild increase (2–5 times the ULN), and 1.9% had a moderate to severe increase (>5 times the ULN). The median initial total bilirubin level was 0.40 mg/dL (IQR, 0.3–0.6 mg/dL) and 4.3% of patients had an abnormal initial total bilirubin level (>1.2 mg/dL). The median initial alkaline phosphatase level was 75 U/L (IQR, 60–98 U/L) and 11.9% had an abnormal alkaline phosphatase level on admission (>130 U/L). Twenty-four percent of patients had an abnormal international normalized ratio (defined as >1.13) on admission. An abnormal initial total bilirubin level was associated with increased mortality (39% vs 24%; $P = .04$), but not intensive care unit (ICU) admission, rate of intubation, or length of stay (LOS). An abnormal initial international normalized ratio was not associated with ICU admission, intubation, LOS, or mortality. Patients treated with hydroxychloroquine, azithromycin, or tocilizumab were more likely to have abnormal peak ALT and AST levels.

There was no difference between patients with or without GI symptoms on presentation with regard to rate of intubation ($P = .3$), ICU admission ($P = .4$), length of stay ($P = .8$), or mortality ($P = .067$) (Supplementary Table 1).

An abnormal initial AST level compared with a normal initial AST level was associated with higher rates of intubation (18% vs 12%; $P = .01$), ICU admission (18% vs 11%; $P = .005$), and mortality (28% vs 20%; $P = .009$) (Supplementary Table 2).

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal.

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Table 1. Baseline Patient Demographics, Clinical Characteristics, Treatments, and Outcomes

Characteristic	N = 892
Age, *y*	59 (47–72)
Sex	
Female	358 (40.1%)
Race/ethnicity	
African American	57 (6.4%)
Asian	127 (14.2%)
Hispanic or Latino	409 (45.9%)
White	167 (18.7%)
Other	85 (9.5%)
Not available	45 (5.0%)
Comorbidities	
Hypertension	397 (44.5%)
Diabetes	245 (27.5%)
Cardiac disease	185 (20.7%)
Renal disease	89 (10.0%)
Pulmonary disease	113 (12.7%)
Hepatic disease	19 (2.1%)
GI symptoms	
Loss of taste	21 (2.4%)
Loss of appetite	105 (11.8%)
Abdominal pain	70 (7.8%)
Nausea	148 (16.6%)
Vomiting	91 (10.2%)
Diarrhea	177 (19.8%)
Any GI symptom	219 (24.6%)
Duration of symptoms, *d*	4 (3–7) (number available, 251)
Treatment	
Hydroxychloroquine	726 (81.4%)
Azithromycin	770 (86.3%)
Tocilizumab	12 (1.3%)
Remdesivir	9 (1.0%)
Outcome	
ICU admission	131 (14.7%)
Intubation	136 (15.2%)
Length of stay, *d*	6 (3–10) (number available, 876)
Mortality	215 (24.1%)

NOTE. Data are presented as n (%) or as median (interquartile range).
GI, gastrointestinal; ICU, intensive care unit.

Discussion

GI manifestations are common presenting features of COVID-19, occurring in 25% of our patient population. This finding supports the theory of SARS-CoV-2 gastrointestinal entry and infection via the angiotensin-converting enzyme 2 receptor.[3] GI symptoms were not associated with increased rates of ICU admission, intubation, LOS, or mortality, suggesting that they do not portend a more severe disease course.

AST level was increased more often compared with ALT level, which is distinct from other viral-induced liver injuries,[5] and may be a useful indicator of SARS-CoV-2 infection. An increased initial AST level was associated with poorer outcomes including higher rates of ICU admission, intubation, and mortality. AST is located in the cytosol and the mitochondria, and viral damage to mitochondrial components has been postulated as a mechanism for release of AST.[6] In addition, a greater increase of AST could reflect injury to zone 3 of the hepatocyte, which is most susceptible to hypoxia and is the largest hepatic reservoir of AST.[7] An abnormal initial ALT level was not associated with poorer outcomes. This may be owing to wider parenchymal distribution of AST (including skeletal muscle, cardiac, kidney, and lung tissue), which supports multiorgan injury seen in COVID-19. Bilirubin and alkaline phosphatase levels were not increased considerably.

Limitations of our study included its retrospective design. Collection of data was limited by recall bias of both patients and health care professionals involved at the time of intake.

We report a large, single-center analysis of the GI and hepatic manifestations of COVID-19. GI symptoms and an increase in liver chemistries were common in our patient cohort and may be clinically useful in stratifying the risk of disease severity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.05.049.

References

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. Accessed February 12, 2020.
2. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–273.
3. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv 2020 January 30 [Epub ahead of print].
4. Mao R, Qui Y, He J, 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;5:667–678.
5. Kasarala G, Tillmann HL. Standard liver tests. Clin Liver Dis (Hoboken) 2016;8:13–18.
6. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020. Epub ahead of print.
7. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ 2005;172:367–379.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

Follow-up data were extracted until May 1, 2020. Extracted data included patient demographics, comorbidities, clinical symptoms, baseline and peak laboratory value parameters, clinical course (including ICU admission and need for invasive mechanical ventilation), and outcome (discharged, deceased, currently admitted at time of data collection). Race and ethnicity data were collected by patient self-reporting from a set of predetermined categories. Specific laboratory values collected included initial and peak values of ALT, AST, total bilirubin, and alkaline phosphatase. Liver chemistries were defined as normal, borderline (<2 times the ULN), mild (2–5 times the ULN), moderate (5–15 times the ULN), severe (>15 times the ULN), or massive (>10,000 times the ULN). These categories were based on American College of Gastroenterology Clinical Guidelines.[9] Study data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at the Weill–Cornell Clinical and Translational Science Center. Descriptive statistics were generated to describe the study population using N (%) and median and IQR. The Fisher exact, chi-square, and Wilcoxon rank-sum tests were used to compare patients with and without GI symptoms, and those with abnormal and normal AST and ALT values (initial and peak) on key clinical and demographic characteristics of interest.

Supplementary Table 1. Comparison Between the Presence of GI Symptoms at the Time of Admission and Outcomes

Characteristic	N	GI symptoms (N = 219)	No GI symptoms (N = 658)	*P* value[a]
Intubation	874	28 (13%)	105 (16%)	.3
ICU admission	874	28 (13%)	100 (15%)	.4
Length of stay, *d*	861	5 (3–10)	6 (3–10)	.8
Mortality	876	42 (19%)	166 (25%)	.067

NOTE. Data are presented as n (%) or as median (interquartile range).
GI, gastrointestinal; ICU, intensive care unit.
[a]Statistical tests performed included the Fisher exact test and the Wilcoxon rank-sum test.

Supplementary Table 2. Association Between Abnormal Initial and Peak AST and ALT Levels and Outcomes

		Initial AST				Peak AST		
Characteristic	N	Abnormal, N = 491	Normal, N = 376	*P* value[a]	N	Abnormal, N = 623	Normal, N = 230	*P* value[a]
Intubation	865	89 (18%)	44 (12%)	.010	851	125 (20%)	7 (3.0%)	<.001
ICU admission	864	88 (18%)	41 (11%)	.005	850	123 (20%)	5 (2.2%)	<.001
Length of stay, *d*	851	6 (3–11)	5 (3–10)	.12	837	7 (4–12)	4 (2–7)	<.001
Mortality	866	135 (28%)	74 (20%)	.009	852	182 (29%)	24 (10%)	<.001
		Initial ALT				Peak ALT		
		Abnormal, N = 347	Normal, N = 520			Abnormal, N = 503	Normal, N = 348	
Intubated	865	57 (16%)	75 (14%)	.4	849	103 (21%)	27 (7.8%)	<.001
ICU admission	864	57 (17%)	71 (14%)	.3	848	102 (20%)	25 (7.2%)	<.001
Length of stay, *d*	851	6 (3–10)	6 (3–10)	.5	835	7 (3–12)	5 (3–9)	<.001
Mortality	866	71 (21%)	138 (27%)	.052	850	129 (26%)	76 (22%)	.2

NOTE. Data are presented as n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit.
[a]Statistical tests performed included the Fisher exact test and the chi-square test of independence.

Stomach and Duodenum: Research Article

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Gastrointestinal Symptoms and Outcomes in Hospitalized Coronavirus Disease 2019 Patients

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Keywords
COVID-19 · Gastrointestinal manifestations · Gastrointestinal symptoms · Severe acute respiratory syndrome coronavirus 2 · Coronavirus · Outcomes · Mortality · Length of stay

Abstract
Introduction: Gastrointestinal (GI) symptoms are increasingly being recognized in coronavirus disease 2019 (COVID-19). It is unclear if the presence of GI symptoms is associated with poor outcomes in COVID-19. We aim to assess if GI symptoms could be used for prognostication in hospitalized patients with COVID-19. ***Methods:*** We retrospectively analyzed patients admitted to a tertiary medical center in Brooklyn, NY, from March 18, 2020, to March 31, 2020, with COVID-19. The patients' medical charts were reviewed for the presence of GI symptoms at admission, including nausea, vomiting, diarrhea, and abdominal pain. COVID-19 patients with GI symptoms (cases) were compared with COVID-19 patients without GI symptoms (control). ***Results:*** A total of 150 hospitalized COVID-19 patients were included, of which 31 (20.6%) patients had at least 1 or more of the GI symptoms (cases). They were compared with the 119 COVID-19 patients without GI symptoms (controls). The average age among cases was 57.6 years (SD 17.2) and control was 63.3 years (SD 14.6). No statistically significant difference was noted in comorbidities and laboratory findings. The primary outcome was mortality, which did not differ between cases and controls (41.9 vs. 37.8%, $p = 0.68$). No statistically significant differences were noted in secondary outcomes, including the length of stay (LOS, 7.8 vs. 7.9 days, $p = 0.87$) and need for mechanical ventilation (29 vs. 26.9%, $p = 0.82$). ***Discussion:*** In our study, the presence of GI manifestations in COVID-19 at the time of admission was not associated with increased mortality, LOS, or mechanical ventilation.

Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was started as an epidemic in Wuhan,

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China. It was later declared as a global pandemic with New York as the current epicenter [1]. The SARS-CoV-2 mainly spreads through direct exposure (droplets, person to person). However, it is also assumed to be transmitted by contaminated objects, airborne transmission, and fecal-oral transmission [2]. The COVID-19 is predominantly a respiratory disease manifested by fever, fatigue, dry cough, anorexia, myalgia, and dyspnea [3]. However, gastrointestinal (GI) manifestations such as nausea, vomiting, diarrhea, and abdominal pain are increasingly being recognized as important manifestations of COVID-19 [4–8]. Other symptoms such as dysgeusia and anosmia are also gaining attention as important symptoms of COVID-19 [9, 10].

The spectrum of COVID-19 infection ranges from mild to critical. Most of the patients (81%) have mild disease, 14% of the patients have severe disease, and 5% of the patients have a critical disease [1, 11]. The factors associated with severe COVID-19 infection include advanced age >65 years, chronic respiratory diseases, hypertension, diabetes mellitus (DM), malignancy, and cardiovascular disease [12–14]. In a recent study published from the USA, about 12% of the patients required mechanical ventilation, and the mortality rate of patients on mechanical ventilation was 88% [15]. In a study by Pan et al. [7], the presence of GI symptoms was associated with higher liver enzymes, lower monocyte count, and longer prothrombin time. The overall pooled prevalence of GI symptoms in COVID-19 based on a systematic review was reported to be 18% [16]. The most common GI symptom reported is diarrhea (13%), followed by nausea or vomiting (10%) and abdominal pain [16]. SARS-CoV-2 has also been found in the fecal samples of COVID-19 patients even after the complete resolution of symptoms [13, 17]. Therefore, the fecal-oral transmission is also considered as a potential mode of transmission [17]. The occurrence of GI symptoms is probably from the intestinal tropism of the SARS-CoV-2 [18]. Moreover, GI symptoms can coexist or even precede respiratory manifestations [19]. Rarely, COVID-19 patients can present with only GI symptoms without respiratory symptoms [7].

Hence, there has been an increasing interest in whether GI symptoms are associated with severe disease. There are conflicting reports in terms of whether GI symptoms are associated with severe COVID-19 or not [7, 20]. Therefore, in this study, we aimed to analyze if the presence of GI symptoms at the time of hospitalization is associated with mechanical ventilation or mortality when compared to those who did not have GI symptoms.

Table 1. Prevalence of gastrointestinal (GI) system in the entire cohort

GI symptoms	*N* (%)
No gastrointestinal symptoms	119 (79.3)
Nausea/vomiting	6 (4)
Diarrhea	15 (10)
Nausea/vomiting + diarrhea	7 (4.7)
Nausea/vomiting + abdominal pain	3 (2)

Methods

Study Design and Data Source

This is a retrospective cohort study conducted in a cohort of COVID-19 patients who were admitted to the Brookdale University Hospital Medical Center (BHMCNY), a tertiary care academic medical center in Brooklyn, New York. BHMCNY is a non-profit medical service provider servicing almost 1 million residents of Eastern Brooklyn. The BHMCNY's Institutional Review Board approved this study as minimal-risk research while utilizing anonymized and de-identified retrospective data collection and waived the requirement for informed consent. We included consecutive patients who were admitted to the hospital with a confirmed diagnosis of COVID-19 on nasopharyngeal polymerase chain reaction testing for SARS-CoV-2 from March 18, 2020, to March 31, 2020. Patients were excluded if they were younger than 18 years, who were not hospitalized and managed on an ambulatory basis, pregnant patients, unavailability of results of SARS-CoV-2 nasopharyngeal testing, and missing data on mortality or disposition.

Data related to patients' demographics, clinical symptoms, comorbidities, home medications, vitals at presentation, admission laboratory tests, inpatient medications, and outcomes were collected (Table 1). Demographic variables such as age, sex, race, smoking status, and BMI were obtained. Data on multiple comorbid conditions such as the history of hypertension, dyslipidemia, coronary artery disease, DM, history of any cancer, chronic obstructive pulmonary disease, and asthma were obtained. Medication history of the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, non-steroidal anti-inflammatory drugs, aspirin, or statin use was collected. Furthermore, initial laboratory data such as hemoglobin level, WBC, absolute lymphocyte count, platelet count, ferritin, C-reactive protein (CRP), d-dimer, lactic acid, aspartate aminotransferase, and alanine aminotransferase were noted. If a particular laboratory test was not performed at the time of admission, then the first laboratory values within 24 h of the admission were used.

Stratification of Study Cohort and Outcomes

In our study, the GI symptoms were defined as the presence of nausea, vomiting, diarrhea, or abdominal pain at the time of admission. The study cohort was stratified into 2 groups based on the presence of GI symptoms: COVID-19 with GI symptoms (cases) and COVID-19 without GI symptoms (controls). The primary outcome was death from any cause. Secondary outcomes were identified as total hospital length of stay (LOS) and need for mechanical ventilation during that hospitalization.

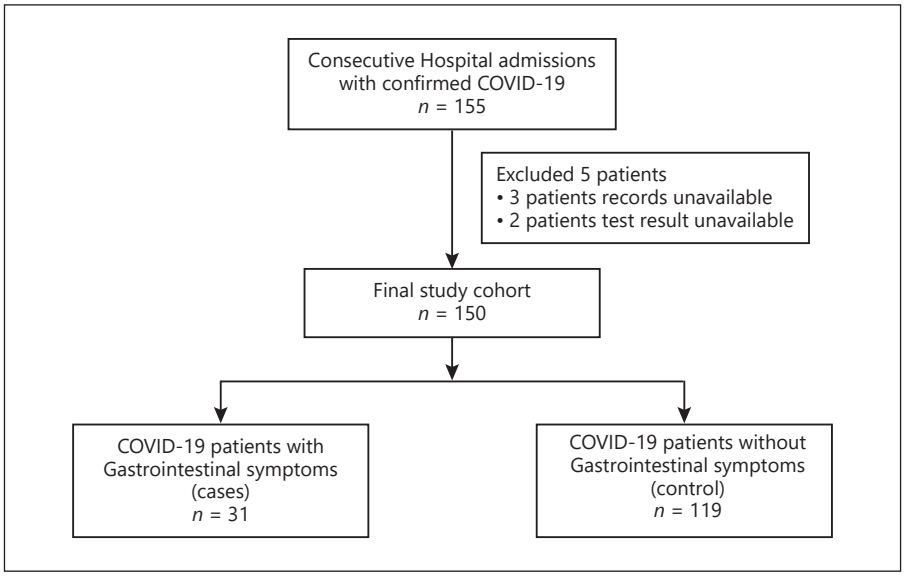

Fig. 1. Study flowchart.

Table 2. Prevalence of individual gastrointestinal (GI) symptoms in the COVID-19 cohort with GI symptoms (cases)

GI symptoms	*N* (%)
Nausea/vomiting	6 (19.4)
Diarrhea	15 (48.4)
Nausea/vomiting + diarrhea	7 (22.6)
Nausea/vomiting + abdominal pain	3 (9.7)

Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 26 (SPSS Inc., Armonk, NY, USA). Descriptive summary statistics are presented as means and SD for continuous variables and frequencies with percentages for categorical variables. Categorical and continuous variables were tested for statistical significance using χ^2 tests and *t* tests, respectively. If the continuous variable is not normally distributed, we utilized the nonparametric test such as the Mann-Whitney *U* test to compare the groups.

Results

Study Population and Baseline Demographics

A total of 155 patients were hospitalized with confirmed COVID-19 during the study period. Five patients were excluded based on the exclusion criteria. A total of 150 patients met the inclusion criteria and formed our final study population (Fig. 1). Of these, 31 (20.6%) patients had GI symptoms (cases), and 119 patients had no GI symptoms (controls) (Table 1). Diarrhea was the most common GI symptom, which was reported in 14.7% of the cohort, followed by nausea or vomiting, reported in 10.7% of the patients, and only 2% of the patients had abdominal pain (Table 2). Demographic variables are noted in Table 3. The mean age was 57 years (SD ± 17) in cases as compared to 63 years (SD ± 15 years) in controls. The mean BMI was 31.7 and 30.7 in cases and controls, respectively. Comorbidities such as hypertension, dyslipidemia, chronic obstructive pulmonary disease, asthma, coronary artery disease, DM, and cancer were similarly distributed between 2 groups (Table 3). There was no difference in the presence of other symptoms such as fever, cough, dyspnea, fatigue, and myalgia between the 2 groups.

Laboratory Data

There was no statistical difference between the 2 groups in values of laboratory data such as mean hemoglobin, WBC, lymphocyte, and platelet counts. The mean ferritin level was lower in the cases than in controls but did not reach statistical significance (777 vs. 951 ng/mL, $p = 0.61$). Mean CRP, creatinine, and lactic acid levels were higher but not statistically significant in both groups, as noted in Table 4.

Outcomes

The outcomes of the study are outlined in Table 5. The patients with the GI symptoms (cases) had higher mortality of 41.9% (13/31 patients) when compared to controls, 37.8% (45/119 patients), but it did not reach statistical

Table 3. Baseline demographics of the study population

Characteristic	COVID-19 patients with GI symptoms (N = 31)	COVID-19 patients without GI symptoms (N = 119)	p value
Age, mean (SD)	57.6 (17.2)	63.3 (14.6)	0.06
Age >60 years, *n* (%)	16 (53.3)	74 (64.3)	0.29
Female gender, *n* (%)	12 (38.7)	55 (46.2)	0.54
BMI, mean (SD)	31.7 (8.8)	30.7 (7.6)	0.57
Race, *n* (%)			
White	3 (9.7)	3 (2.5)	
African American	23 (74.2)	90 (75.6)	
Hispanic	1 (3.2)	12 (10.1)	0.29
Asian	1 (3.2)	6 (5)	
Unknown	3 (9.7)	8 (6.7)	
Comorbidities, *n* (%)			
Hypertension	22 (14.7)	79 (66.4)	0.67
Dyslipidemia	10 (32.3)	44 (37)	0.68
CAD	7 (22.6)	20 (16.8)	0.44
DM	12 (38.7)	52 (43.7)	0.69
Cancer	4 (12.9)	11 (9.2)	0.51
COPD	1 (3.2)	13 (10.9)	0.30
Asthma	6 (19.4)	17 (14.4)	0.58
Smoker	4 (12.9)	13 (10.9)	0.75
Medications, *n* (%)			
ACEI/ARB	11 (35.5)	38 (31.9)	0.83
NSAID	6 (19.4)	28 (23.5)	0.81
Aspirin	6 (19.4)	42 (35.3)	0.13
Statin	12 (38.7)	58 (48.7)	0.42
Symptoms, *n* (%)			
Cough	23 (74.2)	76 (63.9)	0.39
Fever	22 (71)	79 (66.4)	0.67
Dyspnea	17 (54.8)	82 (68.9)	0.20
Fatigue	19 (61.3)	61 (51.3)	0.42
Myalgia	12 (38.7)	47 (39.5)	1.00
Pneumonia	29 (93.5)	119 (100)	0.04

COVID-19, coronavirus disease 2019; GI, gastrointestinal; CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

significance (p = 0.68). No significant differences were noted in the secondary outcomes – mean LOS (7.8 [SD 4.4] vs. 7.9 days [SD 4.7 days], p = 0.87) and need for mechanical ventilation (29 vs. 26.9%, p = 0.82).

Discussion

In this study, we found that 20.6% of the patients hospitalized with COVID-19 presented with at least 1 GI symptom such as diarrhea, nausea, vomiting, or abdominal pain. Diarrhea was the most common GI symptom, followed by nausea/vomiting and abdominal pain. There were no significant differences in terms of patient demographics, comorbid conditions, and presenting laboratory evaluations between patients with and without GI symptoms. Furthermore, there was no association between the GI symptoms and other symptoms such as fever, cough, fatigue, and myalgia.

Our study shows that the prevalence of GI symptoms in COVID-19 patients is 20.6%, which is lower than the prevalence of GI symptoms reported by other studies in the USA and China in the range of 50.5–61.3% [7, 21]. The higher reported rate of GI symptoms in those studies could probably be due to the inclusion of anorexia as one of the GI symptoms. Anorexia is a nonspecific symptom

Table 4. Laboratory data of both cohorts at the time of admission[a]

Laboratory test	COVID-19 patients with GI symptoms (N = 31)	COVID-19 patients without GI symptoms (N = 119)	p value
Hemoglobin	12.6 (2.2)	13 (1.8)	0.28
Ferritin	776.9 (961)	951.8 (1,253.1)	0.61
d-dimer	901.6 (1,380)	10,661.9 (22,910.3)	0.36
WBC	7,200 (2,100)	7,400 (3,700)	0.78
Lymphocyte count	1,000 (617)	1,168 (681.5)	0.22
Platelet count	211,870 (60,531)	202,190 (76,669)	0.52
Creatinine	2.5 (3.7)	1.8 (2.1)	0.28
Albumin	3.9 (0.5)	3.7 (0.5)	0.07
CPK	391.8 (602.8)	924.5 (3,143.9)	0.48
Lactate	2.1 (2.2)	1.99 (1.7)	0.78
LDH	1,134.4 (702.9)	1,208.1 (734.8)	0.65
CRP	13.7 (8.1)	10.8 (8.1)	0.15
AST	71.4 (77.3)	70.9 (64.1)	0.97
ALT	52.1 (63.3)	51.8 (44.4)	0.98

COVID-19, coronavirus disease 2019; GI, gastrointestinal; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a] All the laboratory values are represented as mean (SD).

Table 5. Outcome data of both cohorts at the time of admission

Characteristic	COVID-19 patients with GI symptoms (N = 31)	COVID-19 patients without GI symptoms (N = 119)	p value
Mortality, n (%)	13 (41.9)	45 (37.8)	0.68
Length of stay, mean (SD)	7.8 (4.4)	7.9 (4.7)	0.87
Mechanical ventilation, n (%)	9 (29)	32 (26.9)	0.82

COVID-19, coronavirus disease 2019; GI, gastrointestinal.

that could be related to an overall infectious or inflammatory process and hence was not included as a specific GI symptom in our study. In a US study by Redd et al. [20], the prevalence of GI symptoms in COVID-19 patients was reported to be as high as 61.3%. In that study, anorexia was reported in 34.8% cases, diarrhea in 33.7%, and nausea in 26.4% cases. In a study by Pan et al. [7] from Wuhan, China, even though about 50% reported having GI symptoms, the majority of these patients had anorexia (78.6%). When anorexia was excluded from the analysis, only 18.6% had specific GI symptoms. A trend of increasing recognition of GI manifestations among COVID-19 patients is noted since its outbreak in Wuhan, China. During the original outbreak in Wuhan, diarrhea was reported in only 3% of the cases [1]. This number increased to 10% in a subsequent study from Wuhan and 25% in a study from Singapore [3, 22]. As awareness is increasing among the health-care workers about the GI manifestations in COVID-19 patients, the reports of the presence of GI symptoms increased in the studies.

In our study, there was no association between the GI symptoms and poor outcomes in COVID-19 patients. Previous studies have reported conflicting findings concerning the presence of GI symptoms and poor outcomes. In the study by Pan et al. [7] from Wuhan, China, patients with digestive symptoms had longer LOS (9 vs. 7.3 days, p = 0.013). Furthermore, this study noted that as the severity and duration of COVID-19 increase, GI symptoms increase as well. In a multicenter study of 191 patients by Zhou et al. [14], the presence of GI symptoms was associated with elevated CRP (7.3 vs. 3.8 mg/L, p = 0.021), elevated alanine aminotransferase (64.1 vs. 46.6

units/L, $p = 0.049$), and lower hemoglobin levels when compared to patients without GI symptoms. However, in the study by Redd and colleagues [20], there were no differences in clinical outcomes in patients with or without GI symptoms. Also, they reported no significant differences in the leukocyte count, hemoglobin, platelets, coagulation, or liver tests in groups with or without GI symptoms.

Although the specific mechanisms causing GI manifestations in COVID-19 are not entirely known, there are several proposed theories. Intestinal tropism has been noted with SARS-CoV-2, which could be due to its strong affinity to angiotensin-converting enzyme-2 receptors, and angiotensin-converting enzyme-2 receptors are highly expressed in the esophagus and intestinal epithelial cells [23]. Hence, there is a strong possibility of direct small bowel involvement, resulting in direct cytopathic effects causing GI symptoms. Furthermore, Redd et al. [20] noted that loss of smell (anosmia) and loss of taste (ageusia) were commonly associated with nausea (adjusted OR 2.71, 95% CI: 1.21–6.20; $p = 0.015$) and anorexia (adjusted OR 3.70, 95% CI: 1.49–9.16; $p = 0.0048$) after controlling for potential confounders. While the exact cause of this association is unclear, it could be due to damage to olfactory and gustatory receptors during viral entry through nasal and oral routes [24]. Additionally, in a study from Hong Kong, patients with diarrhea on presentation had higher rates of stool RNA positivity when compared to those without diarrhea (38.5 vs. 8.7%, $p = 0.02$). This is suggestive of the direct effects of the SARS-CoV-2 on the GI tract [16]. Also, the viral infection can cause altered intestinal permeability, resulting in malabsorption [25]. Finally, the inflammatory response from a cytokine storm in severe COVID-19 patients can cause hypoxia-induced bowel ischemia and contribute to diarrhea.

Specific limitations to this study include the retrospective design, relatively small sample, single-center hospital-based study, and lack of validated symptom instruments. This could introduce selection bias and limit the reliability and generalizability of the results. We could not correlate the presence of SARS-CoV-2 RNA with GI symptoms since this test was not routinely performed in our institution. Despite these limitations, the main strengths of this study are that it has validated the findings of another US study by Redd et al. [20] on GI manifestations in COVID-19. Our study also presents data from New York with a significantly higher proportion of African American patients. We also included data on home medications such as non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, which has not been presented in previous studies.

Conclusion

GI symptoms are commonly encountered in hospitalized COVID-19 patients. In our study, GI symptoms were not associated with poorer outcomes such as increased mortality, longer hospital LOS, and increased mechanical intubation in COVID-19 patients. It appears that the GI symptoms could potentially be a bystander in patients with COVID-19. Further, more extensive studies are needed to evaluate the effects of GI symptoms on outcomes in COVID-19.

Statement of Ethics

The BHMCNY's Institutional Review Board approved this study as minimal-risk research while utilizing anonymized and de-identified retrospective data collection and waived the requirement for informed consent.

Conflict of Interest Statement

All authors have no conflicts of interest or financial ties to disclose.

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Author Contributions

P.R., A.P., and H.G.: Conception and design. P.R., I.O., and S.G.: Data collection. A.P. and M.G.: Drafting manuscript. P.R., I.O., S.G., M.G., A.A., H.G., and A.A.: Literature review, critical revision, and final approval of the manuscript.

Availability of Data and Material

This own work has been deposited in a pre-print repository [26].

References

1 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497–506.
2 Santarpia JL, Rivera DN, Herrera V, Morwitzer MJ, Creager H, Santarpia GW, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center.
3 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7;323(11):1061–9.
4 Aloysius M, Thatti A, Gupta A. COVID-19 presenting as acute pancreatitis. Pancreatology. 2020;S1424–3903(20):30154.
5 Gao QY, Chen YX, Fang JY. 2019 novel coronavirus infection and gastrointestinal tract. J Dig Dis. 2020 Mar;21(3):125–6.
6 Kopel J, Perisetti A, Gajendran M, Boregowda U, Goyal H. Clinical insights into the gastrointestinal manifestations of COVID-19. Dig Dis Sci. 2020 Jul;65(7):1932–9.
7 Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020 Apr 14; 115(5):766–73.
8 Perisetti A, Gajendran M, Goyal H. Putative mechanisms of diarrhea in COVID-19. Clin Gastroenterol Hepatol. 2020 Jun 11;S1542–3565(20):30708–1.
9 Aziz M, Perisetti A, Lee-Smith W, Gajendran M, Bansal P, Goyal H. Taste changes (dysgeusia) in COVID-19: a systematic review and metaanalysis. Gastroenterology. 2020 May 5; S0016–5085(20):30595–3.
10 Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020 Mar 26:ciaa330.
11 Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507–13.
12 Worldometer-age, sex, existing conditions of COVID-19 cases and deaths. https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/.
13 Perisetti A, Gajendran M, Boregowda U, Bansal P, Goyal H. COVID-19 and gastrointestinal endoscopies: current insights and emergent strategies. Dig Endosc. 2020 Apr 13.
14 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054–62.
15 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA. 2020;323(20):2052–9.
16 Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology. 2020 Apr 3;S0016–5085(20): 30448–0.
17 Perisetti A, Garg S, Inamdar S, Tharian B. Role of face mask in preventing bacterial exposure to the endoscopist's face. Gastrointest Endosc. 2019 Nov;90(5):859.
18 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–20.
19 Liang W, Feng Z, Rao S, Xiao C, Xue X, Lin Z, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020 Jun;69(6):1141–3.
20 Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, 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 Apr 22; S0016–5085(20):30564–3.
21 Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol. 2020 Jun; 115(6):916–23.
22 Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020 Mar 3;323(15):1488–94.
23 Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020 Apr; 14(2):185–92.
24 Vaira L, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. Laryngoscope. 2020 Jul; 130(7):1787.
25 Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020 Mar 3; 158(6):1518–9.
26 Ramachandran P, Onukogu I, Ghanta S, Gajendran M, Perisetti A, Goyal H, et al. Gastrointestinal Symptoms and outcomes in hospitalized COVID-19 patients.

Association of Digestive Symptoms and Hospitalization in Patients With SARS-CoV-2 Infection

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INTRODUCTION: **High rates of concurrent gastrointestinal manifestations have been noted in patients with corona virus disease 2019 (COVID-19); however, the association between these digestive manifestations and need for hospitalization has not been established.**

METHODS: **This is a retrospective review of consecutive patients diagnosed with COVID-19. A total of 207 patients were identified; 34.5% of patients noted concurrent gastrointestinal symptoms, with 90% of gastrointestinal symptoms being mild.**

RESULTS: **In a multivariate regression model controlled for demographics and disease severity, an increased risk of hospitalization was noted in patients with any digestive symptom (adjusted odds ratio 4.84, 95% confidence interval: 1.68–13.94).**

DISCUSSION: **The presence of digestive symptoms in COVID-19 is associated with a need for hospitalization.**

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INTRODUCTION

The current pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 continues to spread globally, and as of April 13, 2020, more than 1.7 million cases have been reported worldwide (1). Although respiratory manifestations preponderate in patients with SARS-CoV-2 infection (2,3), emerging data suggest a significant prevalence of concurrent gastrointestinal symptomology (4). Our aim was to examine the association between clinical and disease characteristics, including concurrent digestive manifestations, and need for hospitalization in patients with confirmed corona virus disease 2019 (COVID-19).

METHODS

After expedited approval from our Institutional Review Board, we analyzed retrospectively collected data from consecutive patients with confirmed COVID-19 based on a positive polymerase chain reaction testing at our institution from March 3, 2020, to April 7, 2020. Baseline demographic, clinical, laboratory, and patient-reported symptom data were collected at presentation. Multivariable logistic regression analyses were performed to assess likelihood for hospitalization with digestive symptoms (nausea/vomiting, diarrhea, abdominal pain, and loss of appetite) after adjusting for clinical demographics (age, sex, and race/ethnicity), chronic comorbidities, duration of symptoms, oxygen status, and respiratory symptoms at presentation. Patients with missing covariate data were excluded from the regression model.

RESULTS

Clinical demographics and characteristics of 207 patients with confirmed COVID-19 are listed in Table 1. Of these 207 patients, 60 patients (29.0%) were hospitalized, with 17 patients (8.2%) requiring intensive care unit level of care. To date, there have been 4 COVID-19–related deaths. Overall, a higher prevalence of men, hypertension, and diabetes mellitus were seen in patients who were hospitalized ($P < 0.05$). Respiratory viral coinfection was found in 14 of 146 (9.1%) tested patients, of whom 2 patients were hospitalized, and 3 patients had digestive symptoms. Concurrent digestive symptoms were noted in more than one-third of all patients, with a higher prevalence observed in those hospitalized to the medical floor and intensive care unit compared with those seen only in the emergency room (Table 2); 90% of all digestive symptoms were characterized as mild in severity. Prevalence of acute renal insufficiency was observed to be higher in patients with digestive symptoms than those without digestive symptoms (9.3% vs 3.1%).

After adjusting for confounders and clinical covariates, patients experiencing any digestive symptoms had a more than 4-fold higher odds for hospitalization (adjusted odds ratio [OR] 4.84, 95% confidence interval [CI]: 1.68–13.94, $P < 0.001$). Diarrhea was associated with a 7-fold higher likelihood for hospitalization (adjusted OR = 7.58, 95% CI: 2.49–20.02, $P < 0.001$), and nausea or vomiting had a 4 times higher odds (adjusted OR 4.39, 95% CI: 1.61–11.4, $P = 0.005$).

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Table 1. Clinical demographics and characteristics of patients with confirmed SARs-CoV-2 infection at Stanford Hospital and Clinics median (IQR) or n (%)

	All patients, N = 207	Not hospitalized, N = 147	Hospitalized, N = 60	Level of hospitalization	
				Medical floor, N = 43	Intensive care unit, N = 17
Age (yr)	49 (34–65)	43 (31–58)[a]	62 (43–77)	65 (45–77)	55 (42–70)
Men	104 (50.2)	72 (49.0)[a]	32 (53.3)	22 (51.2)	10 (58.8)
Women	103 (49.8)	75 (51.0)[a]	28 (46.7)	21 (48.8)	7 (41.2)
Race/ethnicity					
White	87 (42.4)	66 (44.9)	21 (36.2)	18 (41.9)	3 (20.0)
Asian	42 (20.5)	27 (18.4)	15 (25.9)	11 (25.6)	4 (26.7)
Hispanic	62 (30.2)	45 (30.6)	17 (29.3)	9 (20.9)	8 (53.3)
Black	2 (1.0)	1 (0.7)	1 (1.7)	1 (2.3)	0 (0.0)
Other	12 (5.9)	8 (5.4)	4 (6.9)	4 (9.3)	0 (0.0)
Body mass index (kg/m^2)	26.3 (23.2–31.0)	25.4 (23.1–30.8)	28.0 (24.0–32.5)	27.0 (23.8–31.2)	29.5 (27.5–33.8)
Current smoker	3 (1.6)	1 (0.7)	2 (3.5)	2 (4.8)	0 (0.0)
History of recent travel					
Domestic	20 (10.1)	16 (11.4)	4 (6.8)	1 (2.3)	3 (18.8)
International	20 (10.1)	16 (11.4)	4 (6.8)	4 (9.3)	0 (0.0)
Cruise	6 (3.0)	4 (2.9)	2 (3.4)	1 (2.3)	1 (6.3)
Healthcare worker	22 (10.6)	16 (10.8)	6 (10.2)	3 (7.0)	3 (17.6)
Known exposure to COVID-19	73 (36.8)	52 (37.1)	21 (36.2)	14 (33.3)	7 (43.8)
Medical history					
Chronic liver disease	5 (2.7)	4 (3.1)	1 (1.7)	1 (2.3)	0 (0.0)
Chronic pulmonary disorder	42 (20.3)	25 (17.0)	17 (28.3)	13 (30.2)	4 (23.5)
Hypertension	52 (25.5)	30 (20.7)[a]	22 (37.3)	14 (33.3)	8 (47.1)
Diabetes	33 (16.0)	16 (11.0)[a]	17 (28.3)	10 (23.3)	7 (41.2)
Cardiovascular disease	24 (11.7)	13 (8.9)	11 (18.3)	10 (23.3)	1 (5.9)
Metabolic syndrome	19 (9.2)	8 (5.5)[a]	11 (18.3)	8 (18.6)	3 (17.7)
Chronic kidney disease	10 (4.4)	2 (1.4)	8 (13.3)	7 (16.3)	1 (5.9)
Medication use					
Angiotensin-converting enzyme inhibitors/ angiotensin-receptor blockers	23 (11.2)	14 (9.6)	9 (15.0)	5 (11.6)	4 (23.5)
Chronic immunosuppression	7 (3.4)	4 (2.7)	3 (5.0)	3 (7.0)	0 (0.0)
Immunotherapy	5 (2.4)	3 (2.1)	2 (3.33)	1 (2.3)	1 (5.9)

COVID-19, corona virus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Clinical presentation of respiratory and gastrointestinal symptoms and laboratory findings at initial evaluation in patients with confirmed SARS-CoV-2 infection

	All patients N = 207	Not hospitalized N = 147	Hospitalization N = 60	Level of hospitalization	
				Medical floor N = 43	Intensive care unit N = 17
Respiratory or viral symptoms					
Fever	142 (68.6)	92 (62.6)[a]	50 (83.3)	36 (83.7)	14 (82.4)
Cough	175 (85.4)	118 (80.8)[a]	57 (96.6)	41 (95.6)	16 (94.1)
Shortness of breath	108 (52.2)	58 (39.5)[a]	50 (83.3)	34 (79.0)	16 (94.1)
Sore throat	54 (26.2)	43 (29.3)	11 (18.6)	6 (14.3)	5 (29.4)
Myalgias	105 (51.0)	68 (46.6)	37 (61.7)	23 (53.5)	14 (82.4)
Duration of respiratory viral symptoms, d	5 (3–7)	5 (3–7)[a]	7 (3.5–9)	7 (3–9)	7 (6–8)
Gastrointestinal symptoms					
Any gastrointestinal symptom[b]	70 (34.5)	34 (23.5)[a]	36 (60)	26 (63.1)	10 (58.2)
Nausea or vomiting only	22 (10.8)	14 (9.6)[a]	8 (13.8)	6 (14.6)	2 (11.8)
Diarrhea only	22 (10.8)	10 (6.9)[a]	12 (20.7)	8 (19.5)	4 (23.5)
Nausea or vomiting and diarrhea	10 (4.9)	3 (2.1)	7 (12.1)	5 (12.2)	2 (11.8)
Abdominal pain	14 (7.1)	10 (7.1)	4 (7.0)	4 (10.0)	0
Duration of gastrointestinal symptoms, d	1 (0–4)	1 (0–3)	2 (1–4)	2 (1–4)	4 (2–7)
Laboratory values n = 115					
White blood cell count (K/μL)	5.6 (4.1–7.3)	5.8 (4.5–7.2)	5.4 (3.9–7.8)	5.2 (3.8–8.2)	5.3 (3.9–7.0)
Absolute lymphocyte count (K/μL)	0.9 (0.7–1.5)	1.1 (0.8–1.7)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.6 (0.4–1.0)
Platelet count (K/μL)	190 (159–241)	203 (169–244)	182 (153–241)	183 (142–241)	181 (157–250)
Serum sodium (mmol/L)	138 (135–141)	139 (136–141)[a]	136 (133.5–139)	136 (132–139)	136 (134–138)
Serum creatinine (mg/dL)	0.8 (0.6–1.0)	0.8 (0.6–0.9)[a]	0.9 (0.7–1.1)	0.9 (0.8–1.1)	0.8 (0.5–1.0)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]$P < 0.05$ not hospitalized vs hospitalized.
[b]Gastrointestinal symptoms include nausea or vomiting, diarrhea, abdominal pain, or loss of appetite.

DISCUSSION

We demonstrate that a significant portion of COVID-19 patients have concurrent mild gastrointestinal symptoms and that the presence of these digestive symptoms is associated with a need for hospitalization. The pathogenesis for gastrointestinal involvement related to SARS-CoV-2 is unknown. However, a critical cellular receptor in the SAR-CoV-2 lifecycle, angiotensin-converting enzyme 2, is abundantly expressed throughout the gastrointestinal tract (5) and might play a role in worsening digestive symptoms as COVID-19 progresses (6). Whether digestive symptoms are a surrogate clinical marker for higher levels of viremia or from an alternative pathophysiologic process remains unknown.

There are several limitations to our findings. Because this is a retrospective single institution study, our findings might not be broadly generalizable. In addition, because this series represents our initial experience treating COVID-19, it is unclear whether these results should be viewed on a continuum with changing demographic and clinical information with time. Moreover, because of the short study duration, we were unable to further assess hospitalization outcomes.

In conclusion, while analyzing our initial clinical and demographic data in patients with COVID-19, we identified the presence of gastrointestinal symptoms as a risk factor of higher severity of overall illness and need for hospitalization. With the current focus on streamlining triaging efforts, first responders and frontline providers should consider assessing for digestive symptoms in their initial clinical evaluation and decision making. Larger prospective studies are needed to validate these observations.

CONFLICTS OF INTEREST

Guarantor of the article: Alexander Podboy, MD and George Cholankeril, MD, MS.

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REFERENCES

1. World Health Organization (WHO). Coronavirus Disease 2019 (COVID-19) Situation Report–78. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200326-sitrep-78-covid-19.pdf?sfvrsn=9e5b8b48_2. Accessed April 8, 2020.
2. 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(11):1061–9.
3. Guan WJ, Ni ZY, Hu Y et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020;382:1708–20.
4. Cholankeril G, Podboy A, Aivaliotis VI, et al. High prevalence of concurrent gastrointestinal manifestations in patients with SARS-CoV-2: Early experience from California. Gastroenterology 2020. [Epub ahead of print April. 2020.]
5. Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444–8.
6. Pan L, Mu M, Penchcheng Y, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–73.

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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].

RESEARCH CORRESPONDENCE

COVID-19 Digestive System Involvement and Clinical Outcomes in a Large Academic Hospital in Milan, Italy

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Since February 2020, the COVID-19 pandemic has spread to Italy affecting more than 100,000 people. Several studies have reported a high prevalence of gastrointestinal (GI) symptoms, and investigated their potential association with clinical outcomes.[1] The timing, clinical significance, and possible impact on viral spread of GI symptoms presentation have not been fully elucidated. Elevation of liver function tests and other laboratory values has also been reported; however, their prognostic significance has not been clearly established.[2]

We analyzed a cohort of reverse-transcriptase polymerase chain reaction–confirmed COVID-19 patients[3] consecutively admitted to Humanitas Hospital, Milan, Italy, to describe the prevalence of GI symptoms and GI/liver tests abnormalities, and their association with clinical outcomes.

Methods

Clinical and laboratory data were extracted from electronic medical records. Presence of vomit and diarrhea (defined as passing of 3 or more loose stools per day) as reported at admission or during the week preceding admission were recorded as per electronic medical records. To explore the associations between GI clinical and laboratory parameters with clinical deterioration we used survival model for censored observations. The composite study end point was clinical deterioration defined as intensive care unit (ICU) transfer or death within 20 days of hospital admission. Time to event was defined as the time from hospital admission until the date of event or censoring. We used log-rank tests and Cox regression analysis. Missing data were not imputed. We presented hazard ratios with 95% confidence intervals (CI).

Results

From February 22 to March 30, 2020, 325 reverse-transcriptase polymerase chain reaction–confirmed COVID-19 patients had been admitted to the Humanitas Research Hospital. The analysis was restricted to 292 patients, after excluding those who were transferred to the ICU, or died, within the first day. Patients were predominantly males (68.2%) with a mean age of 65.0 ± 14.1 years. Diarrhea (27.1%) was the most frequent GI symptom. Patients' characteristics are summarized in Table 1.

As of March 30, 129 patients (44.2%) had been discharged, and 107 (36.6%) were still hospitalized. Clinical deterioration occurred in 82 patients (28.1%), including 27 (9.2%) patients who were transferred to ICU, and 56 (19.2%) who died.

Among admission parameters, the presence of any GI symptom (ie, diarrhea or vomit), and alkaline phosphatase, total bilirubin, direct bilirubin, and lipase levels were significantly associated with ICU transfer or death in the univariable analyses (Supplementary Table 1). Of these, the occurrence of any GI symptom (adjusted hazard ratio [aHR], 0.47; 95% CI, 0.23–0.97; $P = .041$), alkaline phosphatase levels (aHR, 1.14; 95% CI, 1.05–1.23, per 100 U/L increase; $P = .001$) and high lipase

[a]A list of investigators in the Humanitas COVID-19 Task Force is provided in the Supplementary Appendix

Abbreviations used in this paper: aHR, adjusted hazard ratio; CI, confidence interval; GI, gastrointestinal; ICU, intensive care unit.

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Table 1. Association Between Clinical and Laboratory Gastrointestinal Parameters of Hospitalized COVID-19 Patients (n = 292) and Clinical Deterioration Leading to ICU Transfer or Death Adjusted by Age and Gender

		Cox proportional hazards analysis		
	Mean ± SD or n (%)	Adjusted[a] HR	95% CI	*P* value
Demographic characteristics				
Age, *y*	65.0 ± 14.1	—	—	—
≥65	161/292 (55.1)			
<65	131/292 (44.9)			
Gender		—	—	—
Female	93/292 (31.8)			
Male	199/292 (68.2)			
Gastrointestinal symptoms				
Diarrhea	69/255 (27.1)	0.79	0.42–1.46	.45
Vomit	11/274 (4.0)	—	—	—
Any gastrointestinal symptom (ie, diarrhea or vomit)	69/245 (28.2)	0.47	0.23–0.97	**.041**
Blood biochemistry				
Alanine aminotransferase ≥50 *U/L*	54/292 (18.5)	1.11	0.60–2.04	.74
Aspartate aminotransferase ≥50 *U/L*	78/292 (26.7)	1.30	0.81–2.08	.28
γ-Glutamyl transpeptidase ≥55 *U/L*	102/282 (36.2)	1.45	0.91–2.30	.12
Alkaline phosphatase ≥150 *U/L*	27/280 (9.6)	1.62	0.87–3.00	.13
Total bilirubin ≥1.2 *mg/dL*	31/292 (10.6)	1.39	0.76–2.56	.29
Direct bilirubin ≥0.3 *mg/dL*	70/283 (24.7)	1.52	0.94–2.44	.084
Indirect bilirubin ≥1.1 *mg/dL*	16/269 (6.0)	1.28	0.51–3.20	.60
Amylase ≥100 *U/L*	43/288 (14.9)	1.54	0.88–2.72	.13
Lipase ≥68 *U/L*	28/249 (11.2)	2.02	1.08–3.80	**.028**

NOTE. Boldface indicates statistically significant P values.
CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; SD, standard deviation.
[a]Adjusted for age and gender.

levels (aHR, 2.02; 95% CI, 1.08–3.80; $P = .028$) remained significant after adjustment for age and sex (Supplementary Table 1). Importantly, the presence of GI symptoms was inversely associated with the risk of clinical deterioration, whereas higher levels of alkaline phosphatase and lipase predicted a poor prognosis.

Discussion

In a cohort of COVID-19 admitted patients, we found a high prevalence of GI symptoms. Interestingly, the presence of diarrhea or vomit was associated with a better prognosis, independently of patient age and sex. It is worth noting that we excluded patients admitted in critical conditions in whom a detailed medical history about GI symptoms was not adequately assessed. Our findings could be explained by a prevalent GI viral localization rather than respiratory. GI tropism of SARS-CoV2 has been demonstrated in a recent study that detected SARS-CoV2 more frequently in the stools of patients presenting with diarrhea.[4,5]

We also found that elevated lipase and alkaline phosphatase levels were associated with poor prognosis; whether this reflects a greater systemic inflammatory response or an early sign of multiorgan failure needs to be ascertained.[6] Because angiotensin-converting enzyme-2 receptors are highly expressed by pancreatic islets, a possible direct cytopathic injury seems likely.[6] The action of Sars-CoV on the pancreas through these receptors can induce acute hyperglycemia and transient type-2-diabetes,[7] possibly leading to further complications and poor prognosis. The correlation we observed with alkaline phosphatase is intriguing because angiotensin-converting enzyme-2 receptors are also abundantly expressed on endothelial liver cells, which makes liver a potential target for SARS-CoV.[8] However, liver biopsies of patients with COVID-19 have not shown signs of biliary tract damage or cholestasis, thus we cannot exclude that high alkaline phosphatase reflects bone diseases and systemic frailty.

In conclusion, we observed that biochemical elevations of liver and GI tests and GI symptoms are common at presentation in hospitalized patients with COVID-19, with high lipase and alkaline phosphatase levels and the absence of vomit/diarrhea predicting poor clinical outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.05.011.

References

1. Zhou Z, Zhao N, Shu Y, et al. Journal pre-proof effect of gastrointestinal symptoms on patients infected with COVID-19. 2020. Available at: https://doi.org/10.1053/j.gastro.2020.03.020. Accessed April 6, 2020.

2. Zhang C, Shi L, Wang F. Liver injury in COVID-19: management and challenges. Lancet 2020;10:2019–2021. Available at: https://doi.org/10.1016/S2468-1253(20)30057-1. Accessed April 6, 2020.
3. Cecconi M, Piovani D, Brunetta E, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for COVID-19 infection in Lombardy, Italy. J Clin Med 2020; 9:E1548.
4. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/32142773. Accessed April 6, 2020.
5. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong Cohort and systematic review and meta-analysis. Gastroenterology 2020:pii:S0016-5085(20)30448-0.
6. Wang F, Wang H, Fan J, et al. Pancreatic injury patterns in patients with COVID-19 pneumonia. Gastroenterology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/32247022. Accessed April 6, 2020.
7. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–199.
8. Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int. https://doi.org/10.1111/liv.14435. Accessed April 6, 2020.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Appendix. Humanitas Covid-19 Task Force

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Supplementary Table 1. Association of Gastrointestinal Clinical and Laboratory Parameters With Clinical Deterioration Leading to ICU Transfer or Death in Hospitalized COVID-19 Patients

	Log-rank test		Cox proportional hazards analysis					
Gastrointestinal characteristics at admission	Chi-square (d.f.)	*P* value	Crude HR	(95% CI)	*P* value	Adjusted[a] HR	(95% CI)	*P* value
Gastrointestinal symptoms								
Diarrhea	2.88 (1)	.089	0.60	0.33–1.10	.097	0.79	0.42–1.46	.45
Vomit	3.62 (1)	.057	—	—	—	—	—	—
Any gastrointestinal symptom (ie, diarrhea or vomit)	8.53 (1)	**.004**	0.37	0.18–0.75	**.006**	0.47	0.23–0.97	**.041**
Blood biochemistry								
Alanine aminotransferase (per 10 *U/L* increase)	—	—	1.01	0.95–1.07	.87	1.03	0.98–1.08	.19
Alanine aminotransferase (≥50 vs <50 *U/L*)	0.36 (1)	.55	0.84	0.46–1.51	.56	1.11	0.60–2.04	.74
Aspartate aminotransferase (per 10 *U/L* increase)	—	—	1.03	0.99–1.08	.12	1.04	0.997–1.09	.065
Aspartate aminotransferase (≥50 vs <50 *U/L*)	1.22 (1)	.27	1.30	0.81–2.08	.28	1.30	0.81–2.08	.28
γ-Glutamyl transpeptidase (per 100 *U/L* increase)	—	—	1.16	0.96–1.41	.13	1.20	0.98–1.46	.074
γ-Glutamyl transpeptidase (≥55 vs <55 *U/L*)	1.11 (1)	.29	1.27	0.81–2.01	.30	1.45	0.91–2.30	.12
Alkaline phosphatase (per 100 *U/L* increase)	—	—	1.14	1.06–1.23	**< .001**	1.14	1.05–1.23	**.001**
Alkaline phosphatase (≥150 vs <150 *U/L*)	3.90 (1)	**.048**	1.83	0.99–3.39	.055	1.62	0.87–3.00	.13
Total bilirubin (per 1 *mg/dL* increase)	—	—	1.11	1.00–1.23	**.048**	1.12	0.998–1.25	.054
Total bilirubin (≥1.2 vs <1.2 *mg/dL*)	3.26 (1)	.071	1.70	0.94–3.08	.079	1.39	0.76–2.56	.29
Direct bilirubin (per 1 *mg/dL* increase)	—	—	1.16	0.96–1.40	.12	1.18	0.96–1.44	.11
Direct bilirubin (≥0.3 vs <0.3 *mg/dL*)	9.04 (1)	**.003**	1.96	1.25–3.09	**.004**	1.52	0.94–2.44	.084
Indirect bilirubin (per 1 *mg/dL* increase)	—	—	1.04	0.63–1.72	.87	1.08	0.65–1.78	.76
Indirect bilirubin (≥1.1 vs <1.1 *mg/dL*)	0.02 (1)	.88	1.07	0.43–2.65	.89	1.28	0.51–3.20	.60
Amylase (per 10 *U/L* increase)	—	—	1.04	0.98–1.10	.23	1.04	0.98–1.11	.17
Amylase (≥100 vs <100 *U/L*)	2.52 (1)	.11	1.56	0.89–2.74	.12	1.54	0.88–2.72	.13
Lipase (per 10 *U/L* increase)	—	—	1.06	1.00–1.13	.051	1.07	1.002–1.15	**.042**
Lipase (≥68 vs <68 *U/L*)	4.89 (1)	**.027**	1.98	1.06–3.71	**.033**	2.02	1.08–3.80	**.028**

NOTE. Boldface indicates statistically significant *P* values.
CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; SD, standard deviation.
[a]Adjusted for age and gender.

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ORIGINAL RESEARCH

Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms

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ABSTRACT

Objective The SARS-CoV-2-infected disease (COVID-19) outbreak is a major threat to human beings. Previous studies mainly focused on Wuhan and typical symptoms. We analysed 74 confirmed COVID-19 cases with GI symptoms in the Zhejiang province to determine epidemiological, clinical and virological characteristics.

Design COVID-19 hospital patients were admitted in the Zhejiang province from 17 January 2020 to 8 February 2020. Epidemiological, demographic, clinical, laboratory, management and outcome data of patients with GI symptoms were analysed using multivariate analysis for risk of severe/critical type. Bioinformatics were used to analyse features of SARS-CoV-2 from Zhejiang province.

Results Among enrolled 651 patients, 74 (11.4%) presented with at least one GI symptom (nausea, vomiting or diarrhoea), average age of 46.14 years, 4-day incubation period and 10.8% had pre-existing liver disease. Of patients with COVID-19 with GI symptoms, 17 (22.97%) and 23 (31.08%) had severe/critical types and family clustering, respectively, significantly higher than those without GI symptoms, 47 (8.14%) and 118 (20.45%). Of patients with COVID-19 with GI symptoms, 29 (39.19%), 23 (31.08%), 8 (10.81%) and 16 (21.62%) had significantly higher rates of fever >38.5°C, fatigue, shortness of breath and headache, respectively. Low-dose glucocorticoids and antibiotics were administered to 14.86% and 41.89% of patients, respectively. Sputum production and increased lactate dehydrogenase/glucose levels were risk factors for severe/critical type. Bioinformatics showed sequence mutation of SARS-CoV-2 with m^6A methylation and changed binding capacity with ACE2.

Conclusion We report COVID-19 cases with GI symptoms with novel features outside Wuhan. Attention to patients with COVID-19 with non-classic symptoms should increase to protect health providers.

Significance of this study

What is already known on this subject?

- The national spread and global sporadic appearance of the novel coronavirus (SARS-CoV-2)-infected disease (COVID-19) have become an enormous threat to human beings.
- Our understanding of COVID-19 has been greatly increased after efforts to study its gene homology with bat coronavirus, varied transmission capacity, potential effective drugs such as Remdesivir and other transmission routes such as faeces.
- Most of the current data are focused on Wuhan, which may have selection bias, since more severely affected patients were admitted to hospitals due to the region's insufficient healthcare resources.
- In addition, respiratory symptoms and fevers have been overemphasised at times, while some non-classical symptoms have been overlooked, posing a threat to the public.

INTRODUCTION

The outbreak of novel coronavirus (SARS-CoV-2)-infected disease (COVID-19) began in Wuhan, Hubei province in December 2019[1] and spread throughout China,[2] increasing the risk of global dissemination.[3] Although the Chinese government provided a quick response and took drastic measures, including quarantining Wuhan City on January 23, COVID-19 has become a major public health threat and economic burden on China. On 9 February 2020, the date we finished data collection and started analysis, there were a total of 37 251 confirmed, 28 942 suspected and 6188 severe/critical cases, with 812 deaths and 2731 hospital

Significance of this study

What are the new findings?

- In this study, we report for the first time on the largest cohort of patients with COVID-19 outside Wuhan with GI symptoms.
- We found that the percentage of patients with COVID-19 with GI symptoms was also higher than that in Wuhan.
- We uncovered novel characteristics of COVID-19, including increased family clustering and liver injury, severe/critical type tendency and higher rate of body temperature >38.5°C.
- The findings of novel m^6A methylation loci in the S protein of SARS-CoV-2 may provide underlining mechanisms for its change of virulence and transmission capacity during the spread.

How might it impact on clinical practice in the foreseeable future?

- Our results indicated that global authorities should pay more attention to patients with COVID-19 with GI symptoms and its novel features, as those presentations may change the treatment strategy.
- GI doctors and other health professionals treating suspected patients with COVID-19 without respiratory symptoms and fever should take precautions.

discharges, according to official reports from the National Health Commission. The epidemiological and clinical characteristics of COVID-19 in Wuhan have been reported elsewhere,[4 5] with estimated early transmission dynamics presented as the varied basic reproductive numbers (R_0) of 2.2[6] and 2.68,[7] indicating a high virus transmission capacity.

SARS-CoV-2 was the seventh coronavirus identified with human infection capacity by the Chinese authorities. Its genomic features were revealed in a Wuhan patient, showing 89% and 82% nuclear acid sequence similarity with Bat SARS-CoVZXC21 and human SARS-CoV,[8] respectively. Further functional studies indicated that the spike (S) protein of 2019-nCoV had a high affinity to ACE2, which is responsible for the virus invasion.[9] It is well-known that viral mutations occur during transmission and spreading. Therefore, we would like to know the mutation and transmission ability, virulence change and associated clinical features of SARS-CoV-2 during its spread.

Currently, most published data focus on Wuhan, reporting an approximately 11% fatality rate caused by various complications such as acute respiratory distress syndrome (ARDS) and acute respiratory failure.[4] However, since Wuhan is the original location of the SARS-CoV-2 outbreak, the disease outburst caused a shortage of healthcare resources; hence, the hospitals only admitted patients with severe/critical disease. In addition, 'spring festival travel', especially train transportation, greatly increased the risk of spreading the virus.[10] Therefore, it is necessary to explore specific features of COVID-19 in areas outside Wuhan. Starting from January 17, SARS-CoV-2 was first identified in Zhejiang province, eventually reaching 1117 cases by February 11, with 10.54% of cases having a lower severe/critical type of COVID-19 and zero death cases.

Since the latest study reported the finding of SARS-CoV-2 nucleic acid in patient faeces[11] and single cell analysis revealed the digestive system as a potential route for the virus infection,[12] it is theoretically plausible that a portion of patients may present with GI tract symptoms. We should be very cautious about this speculation since the outpatient centres of GI endoscopy may become high-risk places. More formidably, doctors serving in these centres may behave less vigilantly, with lower levels of protective personal equipment compared with those doctors working in clinics serving those with fevers, unknowingly putting the GI practitioners under high exposure risk. Therefore, in this study, we provide the first report on the epidemiological, clinical and virological characteristics of patients with COVID-19 with GI symptoms outside Wuhan, which is helpful for disease control and medical staff protection.

METHODS

Data sources and ethics

A retrospective study investigating the epidemiological, clinical and virological characteristics of COVID-19 between 17 January 2020 and 8 February 2020 was performed. The data were uniformly collected by the Health Commission of Zhejiang province in designated hospitals, with all successfully enrolled patients diagnosed as having COVID-19 according to WHO interim guidance.[13] Our preliminary data were reported to the authority of Zhejiang province and open for sharing with WHO. Written informed consent was waived by the ethics commission of the designated hospital, as this study was carried out for emerging infectious disease purposes and is part of a continuing public health outbreak investigation under national authorisation.

The definition of positive GI symptoms required that the patients have at least one of the following symptoms: nausea, vomiting and diarrhoea. GI symptoms were recorded on admission, precluding the influence of other medical therapy and external factors. The definition of diarrhoea was the passing of loose stools >3 times per day. A stool culture was performed with negative results for all patients with COVID-19 with GI symptoms. Since the diarrhoea was diagnosed on admission, those patients had no history of recent antibiotic use. Therefore, *Clostridium difficile* was not detected in the stools. Patients with COVID-19 were divided into four subtypes according to the degree of disease severity, based on the diagnosis and treatment scheme for SARS-CoV-2 of Chinese (sixth edition). The mild type is defined as having slight clinical symptoms without pneumonia on radiography. The common type is defined as presenting with fever and/or respiratory symptoms plus pneumonia on radiography. The severe type was diagnosed according to dyspnoea (respiratory rate (RR) ≥30 times/min), resting finger oxygen saturation ≤93%, artery $PaO_2/FiO_2 \leq 300$ mm Hg (1 mm Hg=0.133 kPa). The critical type is defined as respiratory failure with shock and multiorgan failure requiring mechanical ventilation and intensive care unit (ICU) admission. The definition of liver damage was alanine aminotransferase (ALT) >50 U/L or aspartate aminotransferase (AST) >40 U/L. The incubation period was calculated from the specific date of contact of the confirmed patient with COVID-19 to the time of onset of illness.

Procedures

Epidemiological, clinical, laboratory, therapeutic and outcome data were collected from patients' medical records, with verification by independent doctors. Clinical outcomes were followed up to 8 February 2020, when specimens were obtained from throat swabs and sputum. For missing or vague data, direct communications with attending doctors and other healthcare providers were performed. Laboratory confirmation of SARS-CoV-2 was performed in our hospital and the Centre for Disease Control and Prevention of Zhejiang province/city level under authorisation by previously reported real-time RT-PCR.[5] All patients

received chest radiography or CT at admission, while other respiratory viruses were excluded, such as influenza A (H1N1, H3N2 and H7N9), influenza B, respiratory syncytial virus, parainfluenza virus, adenovirus, SARS-CoV and MERS-CoV.

Outcomes

In this study, we collected and calculated epidemiological data (exposure to infected area, contact with confirmed/suspected patients with COVID-19, cluster situation and median incubation period) and other anthropometrics, demographics, symptoms and signs on admission. Laboratory and chest X-ray/CT results, comorbidities, treatments (including drugs, intensive care and mechanical ventilation) and clinical outcomes were also summarised.

Sequence alignment, transcriptional methylation site prediction and protein model electrostatic analysis

Gene sequences of SARS (AAS00003.1 and AY278489.2) and Wuhan-Hu-1 (MN908947.3) were obtained from the NCBI viral genome database (https://www.ncbi.nlm.nih.gov/). ZJ01 was separated and named from a Zhejiang patient (online supplementary material—ZJ01 sequence). SRAMP (http://www.cuilab.cn/sramp) was used to analyse gene sequences and predict post-transcriptional methylation (N6-methyladenosine) modification sites. According to the results, the relevant predicted m^6A sites can be divided into four levels: very high, high, medium and low confidence. Multalin (http://multalin.toulouse.inra.fr/multalin/multalin.html) was used to compare the differences among these sequences. The SWISS-MODEL online server (https://swissmodel.expasy.org/) was used to reconstruct the three-dimensional structure of proteins according to gene or amino sequence. The Poisson-Boltzmann equation can be used to calculate the electrostatic behaviour of S protein in aqueous solution through the vacuum electrostatics function of PyMol. Further analysis of the power of the protein model showed a difference in the electrostatic power distribution on the protein surface of the three virus strains.

Statistical analysis

For continuous variables, mean (SD) and median (IQR) were used for normally and abnormally distributed data, followed by unpaired t-test and non-parametric test when appropriate. Categorical variables were expressed as number (%) and compared using the χ^2 test. Univariate logistic regression analysis was used to identify the risk factors of severe/critical type patients. All significant variables achieved from univariate analysis were included in a multivariate logistic regression model with the forward method to identify independent predictors of the severe/critical type. No adjustment for multiple testing was performed. A two-sided α of <0.05 was considered statistically significant and SPSS (V.26.0) was used for all analyses.

RESULTS

Demographic and epidemiological characteristics

This study enrolled 651 patients with confirmed COVID-19 from 17 January 2020 to 8 February 2020 in Zhejiang province, among which 74 (11.4%) patients presented with at least one GI tract symptom (nausea, vomiting and diarrhoea), which was higher than previous Wuhan data (table 1). In detail, of 74 patients with COVID-19 with GI symptoms, 53 patients had only the symptom of diarrhoea, 11 patients had only the symptom of vomiting and 10 patients had only the symptom of nausea. In addition, only three patients had all the GI symptoms of diarrhoea, vomiting and nausea, while four patients had the symptoms of both nausea and vomiting. Diarrhoea was the most common GI symptom in this study and accounted for 8.14% of the total enrolled 651 patients with COVID-19, which was higher than the rate of 3.8% reported previously.[14] Of 53 patients with COVID-19 with diarrhoea, the median duration period was 4 days (IQR: 3–6 days), with the shortest duration of 1 day and longest of 9 days. Most diarrhoea was self-limiting.

Table 1 Demographic and epidemiological characteristics of patients with COVID-19 with and without GI symptoms

Characteristic	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Age	46.14±14.19	45.09±14.45	0.559
Sex (male)	37/74 (50.0%)	294/577 (50.95%)	0.902
Current smoker	3/74 (4.23%)	38/577 (6.59%)	0.610
Pre-existing conditions			
Any	25/74 (33.78%)	153/577 (26.52%)	0.212
Hypertension	12/74 (16.22%)	88/577 (15.25%)	0.864
Diabetes	7/74 (9.46%)	41/577 (7.11%)	0.477
Chronic liver disease	8/74 (10.81%)	17/577 (2.95%)	0.004
Cancer	0/74 (0%)	6/577 (1.04%)	1.00
Chronic renal disease	0/74 (0%)	6/577 (1.04%)	1.00
Heart disease	1/74 (1.35%)	4/577 (0.69%)	0.454
Pregnancy	0/74 (0%)	3/577 (0.52%)	1.00
COPD	0/74 (0%)	1/577 (0.17%)	1.00
Immunosuppression	0/74 (0%)	1/577 (0.17%)	1.00
Exposure history			
From Wuhan	38/74 (51.35%)	347/577 (60.14%)	0.167
Contact with patients	32/74 (43.24%)	230/577 (39.86%)	0.615
Family cluster	23/74 (31.08%)	118/577 (20.45%)	0.037
Clinical type on admission			
Severe/Critical type (%)	17/74 (22.97%)	47/577 (8.14%)	<0.001

Data are presented as medians (IQR), n (%) and n/N (%).
COPD, chronic obstructive pulmonary disease.

The average age of the patients with GI symptoms was 46.14±14.19 years and the male:female ratio was 1:1. There were no coexisting conditions of cancer, chronic renal disease, pregnancy, chronic obstructive pulmonary disease or immunosuppression. Thirty-eight (51.35%) patients had a Wuhan exposure history and 32 (43.24%) patients had a history of contact with patients with COVID-19. Intriguingly, the rate of chronic liver disease was 10.81% in patients with COVID-19 with GI symptoms, which was significantly higher than that of 2.95% in those without GI symptoms (p=0.004). More importantly, the rate of the severe/critical type was also markedly increased in patients with COVID-19 with GI symptoms than in those without GI symptoms (22.97% vs 8.14%, p<0.001). Family clustering is another pivotal phenomenon of COVID-19. We identified that 23 (31.08%) patients with GI symptoms had family clustering, which was prominently higher than that in patients without GI symptoms (20.45%, p=0.037). Twenty-one patients with COVID-19 with GI symptoms and 195 without them had definite exposure times, with the median calculated incubation period as 4 days (IQR 3–7 days) and 5 days (IQR 3–8 days), respectively.

Clinical features and laboratory abnormalities

The clinical characteristics of patients with GI symptoms are shown in table 2. Fever, cough and sputum production were the most common symptoms. Of the aforementioned symptoms, 29

Table 2 Clinical characteristics and selected laboratory abnormalities of patients with COVID-19 with and without GI symptoms

Characteristic	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Fever (Y)			
Any	63/74 (85.14%)	482/577 (83.54%)	0.867
>38.5°C	29/74 (39.19%)	101/577 (17.50%)	<0.001
Cough (Y)	53/74 (71.62%)	382/577 (66.20%)	0.431
Sputum production (Y)	29/74 (39.19%)	198/577 (34.32%)	0.438
Haemoptysis (Y)	3/74 (4.05%)	8/577 (1.39%)	0.119
Sore throat (Y)	6/74 (8.11%)	93/577 (16.12%)	0.085
Nasal obstruction (Y)	2/74 (2.70%)	35/577 (6.07%)	0.419
Muscle ache (Y)	10/74 (13.51%)	61/577 (10.57%)	0.430
Fatigue (Y)	23/74 (31.08%)	96/577 (16.64%)	0.004
Shortness of breath (Y)	8/74 (10.81%)	19/577 (3.30%)	0.007
Headache (Y)	16/74 (21.62%)	51/577 (8.84%)	0.002
Blood tests (Y)			
Leucocytes ($\times10^9$/L; normal range 4–10)	4.85 (3.80–6.34)	4.70 (3.76–5.90)	0.406
Neutrophils ($\times10^9$/L; normal range 2–7)	3.14 (2.60–4.70)	2.90 (2.13–3.91)	0.014
Lymphocytes ($\times10^9$/L; normal range 0.8–4)	0.97 (0.73–1.30)	1.20 (0.90–1.60)	0.001
Platelets ($\times10^9$/L; normal range 83–303)	183 (141–216)	177 (146–218)	0.559
Haemoglobin (g/L; normal range: male 131–172, female 113–151)	135.5 (127.0–149.3)	138.0(128.0–151.0)	0.395
Haematocrit (%; normal range: male 38–50.8, female 33.5–45)	39.40 (37.60–43.60)	40.50 (37.35–43.95)	0.339
Coagulation function			
International normalised ratio (normal range 0.85–1.15)	1.03 (0.97–1.15)	1.02 (0.97–1.08)	0.145
Blood biochemistry			
Albumin (g/L; normal range 40–55)	40.13 (35.95–42.60)	41.50 (38.63–43.76)	0.039
Alanine aminotransferase (U/L; normal range 9–50)	25.0 (15.75–38.47	21.5 (15.0–32.8)	0.203
Aspartate aminotransferase (U/L; normal range 15–40)	29.35 (20.87–38.62)	24.4 (19.0–32.0)	0.02
Total bilirubin (umol/L; normal range 0–26)	10.0 (7.15–13.8)	9.6 (7.0–13.1)	0.398
Serum sodium (mmol/L; normal range 137–147)	137.65 (134.98–139.30)	138.33 (136.18–140.15)	0.016
Serum potassium (mmol/L; normal range 3.5–5.3)	3.78 (3.50–4.10)	3.83 (3.60–4.11)	0.145
Blood urea nitrogen (mmol/L; normal range 3.1–8)	3.35 (2.75–4.50)	3.80 (3.04–4.60)	0.074
Serum creatinine (umol/L; normal range: male 57–97, female 41–73)	66.0 (56.20–75.25)	66.0 (56.0–78.0)	0.577
Creatine kinase (U/L; normal range 50–310)	73.0 (52.75–106.25)	70.0 (47.0–107.0)	0.287
Lactate dehydrogenase (U/L; normal range 120–250)	229.0 (170.0–316.75)	210.0 (169.0–257.50)	0.127
Glucose (mmol/L; normal range 3.9–6.1)	5.95 (5.19–7.92)	5.80 (5.0–7.04)	0.144
Infection-related biomarkers			
Procalcitonin (ng/mL; normal range 0–0.5)	0.06 (0.03–0.09)	0.05 (0.04–0.07)	0.589
C reactive protein (mg/L; normal range 0–8)	15.69 (4.81–23.95)	7.90 (2.60–19.55)	0.003
Chest X-ray/CT findings			
Normal	8/74 (10.81%)	64/577 (11.09%)	0.942
Unilateral pneumonia	9/74 (12.16%)	134/577 (23.22%)	0.030
Bilateral pneumonia	31/74 (41.89%)	217/577 (37.61%)	0.525
Multiple mottling and ground-glass opacity	26/74 (35.14%)	162/577 (28.08%)	0.221

Data are presented as medians (IQR), n (%) and n/N (%). Y indicates yes for the symptoms.

(39.19%), 23 (31.08%), 8 (10.81%) and 16 (21.62%) patients with COVID-19 with GI symptoms had >38.5°C fever, fatigue, shortness of breath and headache, respectively, substantially higher than their respective counterparts without GI symptoms. Of 74 patients with COVID-19 with GI symptoms, 63 (85.14%) had fever, with the highest temperature of 40.3°C. Additionally, 21 patients (28.38%) lacked respiratory symptoms of coughing and sputum production and presented only with GI symptoms of nausea, vomiting and diarrhoea. Moreover, the rate of increased AST, but not ALT, was significantly higher in patients with COVID-19 with GI symptoms than in those without GI symptoms (29.35 vs 24.4, p=0.02). Finally, although most radiographic presentations were similar between patients with COVID-19 with and without GI symptoms, the rate of unilateral pneumonia was 12.16% in patients with GI symptoms, much lower than 23.22% in those without GI symptoms (p=0.030). Concerning infection-related markers, there was no significant difference in both procalcitonin and C reactive protein (CRP) between patients with COVID-19 with and without GI symptoms.

Complications and treatment

As shown in table 3, 5 (6.76%), 13 (17.57%) and 1 (1.35%) patient with COVID-19 with GI symptoms had complications of ARDS, liver injury and shock, respectively, where the former two were significantly higher than their counterparts of 2.08% and 8.84% in patients with COVID-19 without GI symptoms, respectively (p=0.034; p=0.035). All 74 patients with COVID-19 with GI symptoms were treated in isolation with

Table 3 Complications and treatment in patients with COVID-19 with and without GI symptoms

Variable	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Complications			
Acute respiratory distress syndrome	5/74 (6.76%)	12/577 (2.08%)	0.034
Shock	1/74 (1.35%)	1/577 (0.17%)	0.215
Liver injury	13/74 (17.57%)	51/577 (8.84%)	0.035
Treatment			
Anticoronavirus treatment	66/74 (89.19%)	480/577 (83.19%)	0.239
Timing from onset of illness to antiviral therapy	5 (3–6)	4 (2–6)	0.062
Mechanical ventilation	5/74 (6.76%)	12/577 (2.08%)	0.034
CRRT	0	0	
ECMO	0	0	
Glucocorticoids	11/74 (14.86%)	63/577 (10.92%)	0.443
Antibiotic treatment	31/74 (41.89%)	246/577 (42.63%)	0.903
Admission to intensive care unit	5/74 (6.76%)	12/577 (2.08%)	0.034

Data are presented as medians (IQR), n (%) and n/N (%).
CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation .

supportive and empiric medication, while 66 (89.19%) patients received antiviral treatment, including interferon-α sprays, arbidol hydrochloride capsules (two tablets three times daily), lopinavir and ritonavir two tablets (500 mg) twice daily, via the oral route. Furthermore, the average time from illness onset to antiviral therapy was 5.56±4.09 days. Compared with Wuhan data, we had lower rates of glucocorticoid and antibiotic use, 14.86% and 41.89%, respectively. No patients received continuous blood purification due to renal failure, and no patients were treated with extracorporeal membrane oxygenation. Until now, only one patient has died. Five (6.76%) patients with COVID-19 with GI symptoms were treated with mechanical ventilation and transferred to the ICU, which was a significantly higher rate than that of 2.08% in the patients with COVID-19 without GI symptoms (p=0.034).

Prediction of risk factors for severe/critical COVID-19 in patients with GI symptoms

Of severe/critical patients with COVID-19, 22.97% presented with GI symptoms in this study. When compared with mild and common COVID-19, initial univariate analysis of epidemiological, clinical and laboratory variables identified 11 significantly changed risk factors for severe/critical COVID-19, including increased ORs of age, age ≥50 years, period between illness onset and hospital visit, sputum production, any existing medical condition, multiple lung infection, ALT, lactate dehydrogenase (LDH), glucose and CRP, as well as decreased OR of the infected area (online supplementary table 1). Based on these variables, further multivariate analysis using the forward method was performed, and we found that sputum production of patients from infected areas such as Wuhan and increased LDH/glucose levels were the independent risk factors for severe/critical COVID-19 in patients with GI symptoms (table 4).

Sequence alignment and protein model structure analysis

ZJ01 is a strain of SARS-CoV-2 with 29 381 bases. The results of the potential methylation sites of S protein sequences of SARS, Wuhan-Hu-1 and ZJ01 indicated that there were significant differences between SARS-CoV-2 and SARS. These coronaviruses can infect host cells through using the S protein to bind to

Table 4 Multivariate analysis of risk factors for the severe/critical patients with COVID-19 with GI symptoms

Risk factor	OR (95% CI)	P value
Sputum production	11.40 (1.89 to 68.73)	0.008
From infected area	0.09 (0.02 to 0.54)	0.008
Increased LDH	24.77 (4.60 to 133.33)	0.000
Increased glucose	2.42 (1.43 to 4.10)	0.001

LDH, lactate dehydrogenase.

the host cell surface receptor ACE2. During virus maturation, S proteins are glycosylated and divided into the parts S1 and S2. S1 is spherical and mainly involved in the recognition and binding of viruses to host cells. S2 is stalked and able to promote the fusion of the virus into host cells. The comparison results of three virus strains showed that ZJ01 and Wuhan-Hu-1 had one high-confidence site, two moderate-confidence sites and four low-confidence sites. SARS has three high-confidence sites, three moderate-confidence sites and five low-confidence sites. From the perspective of high-confidence sites (figure 1A, red arrow), the potential methylation points of SARS-CoV-2 (n=1) and SARS (n=3) are predominantly concentrated in the S1 and S2 segments of the S protein. The positions of two low-confidence sites and one medium-confidence site on S2 are relatively fixed among the three virus strains (blue arrow). These results suggest that the S proteins of the two viruses may have structural and functional differences due to m^6A methylation during transcription and translation.

Additionally, the results of gene sequence alignment (figure 1B) showed that the variation in S protein sequences between ZJ01 and Wuhan-Hu-1 was subtle, and these variations were highly concentrated in the S2 segment. These variations resulted in five amino acid substitutions and two amino acid deletions. However, from the perspective of the simulated three-dimensional protein structure, the effect of these variations on the overall S protein structure is relatively limited. The difference between SARS-CoV-2 and SARS is significant, especially at the specific recognition point position in segment S1 (figure 1C, red circle). On the one hand, this change may affect the viral binding force on host cells. On the other hand, the electrostatic changes between ZJ01 and Wuhan-Hu-1 are largely concentrated in the mutation zone of S2 (figure 1C, green ellipse), where the detailed mechanisms need further exploration.

DISCUSSION

The national spread and global sporadic appearance of SARS-CoV-2 have become an enormous threat to human beings, and the threat is not restricted to China. An endeavour has been made by scientists to reveal the epidemiological, clinical and virological characteristics of SARS-CoV-2 with over 30 publications published in PubMed by 5 February 2020.[2 4–7] Nevertheless, most of these studies focused on the situation in Wuhan, China. In addition, the initiative for SARS-CoV-2 screening started from fever clinics, while fever, cough and shortness of breath were the most emphasised symptoms, which increases the risk of omitting those patients with other symptoms and normal body temperature. It is theoretically plausible that one characteristic of a viral spread is an increased transmission capacity at the cost of decreased virulence, which is also true for SARS-CoV-2.[15] Therefore, caution should be exercised for suspected patients with COVID-19 who had normal body temperatures and visited various outpatient clinics for non-respiratory symptoms.

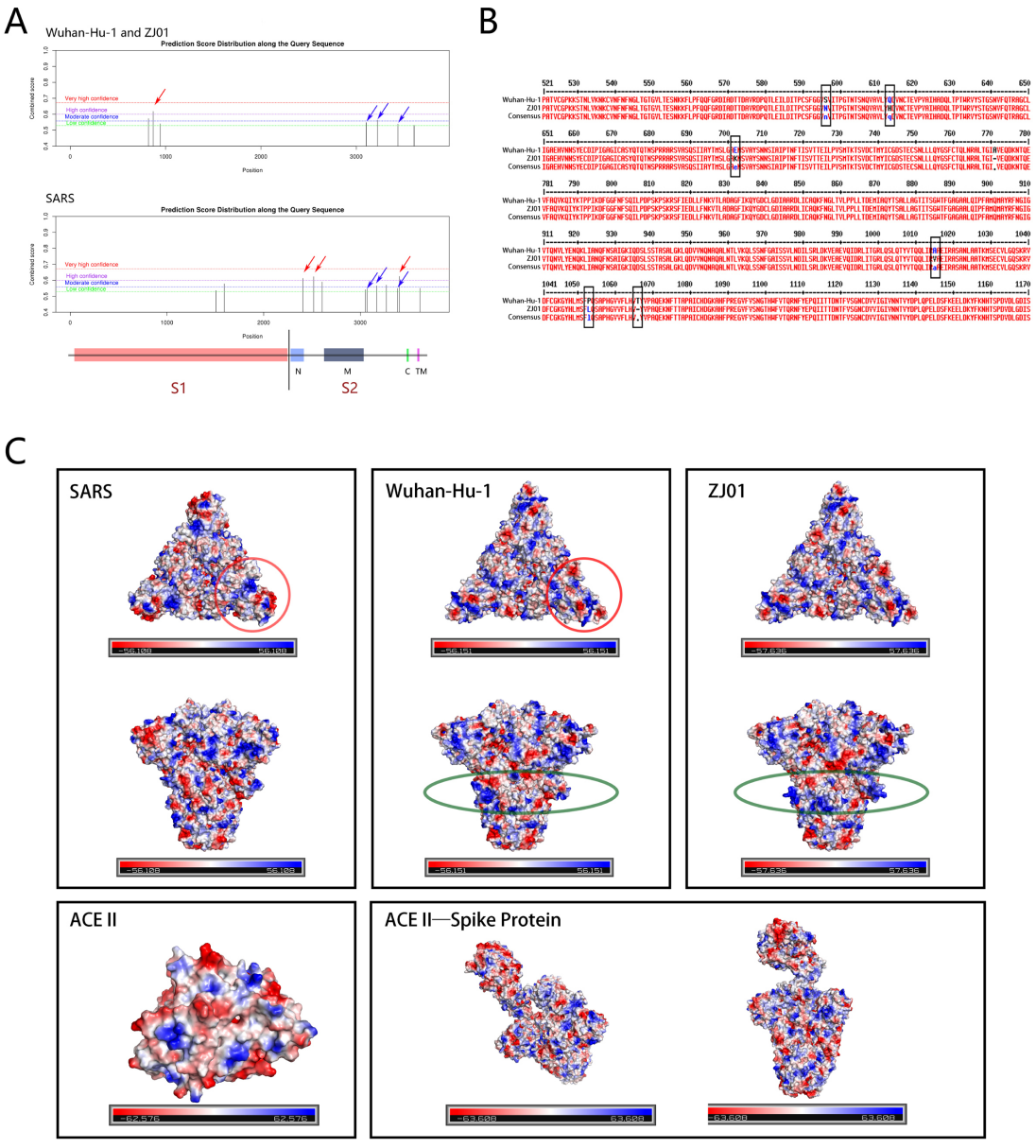

Figure 1 Sequence and protein model structure analysis of three virus strains. (A) The potential methylation sites of S protein gene sequences of SARS, Wuhan-Hu-1 and ZJ01 were analysed. The red arrows represent the positions of high-confidence methylation sites in the S protein gene sequences. Blue arrows represent conserved methylation sites in the three strains. (B) The amino acid sequences of Wuhan-Hu-1 and ZJ01 S protein are aligned. The black box marks the mutation sites. (C) The red circle marks the difference of electrostatic power distribution in receptor binding domain (RBD) region between SARS and Wuhan-Hu-1. The green ellipse indicates the change in the electrostatic distribution of the S proteins due to the mutation of the ZJ01 S protein.

The suspected patients with COVID-19 with GI symptoms, such as nausea, vomiting and diarrhoea, should be seriously considered, since accumulated evidence supports SARS-CoV-2 transmission through faeces[11] and tears[16] and its ability to bind to ACE2 of the GI tract has been identified.[9 12] In this study, we reported the epidemiological, clinical and virological features of 74 patients with COVID-19 with GI symptoms from Zhejiang province. To our knowledge, this is the first report that describes the situation of patients with COVID-19 GI symptoms and is the largest group of cases outside Wuhan. Our novel findings are valuable for disease prevention by emphasising suspected patients with COVID-19 with GI symptoms and their specific clinical characteristics.

Among the 651 total patients with COVID-19 we investigated, the rate of patients with GI symptoms was 11.4%, which is higher than in the previously reported data of 3% from Wuhan.[4] However, a recent report from Wuhan revealed that 10.1% experienced nausea/diarrhoea and 3.6% vomiting.[17] Additionally, the latest data from Wuhan revealed that 79.1% of patients with COVID-19 presented GI symptoms, but such data were collected during 1–10 days after illness onset and reported in a Chinese domestic journal,[18] differing from our strategy of collecting GI symptom data on admission that may be less biassed by various influencing factors, including drugs. More importantly, nationwide data showed GI symptoms in 8.7% of 1099 confirmed patients with SARS-CoV-2,[14] reinforcing our data. All these data indicated that there were symptom changes in patients with COVID-19. We suspect that SARS-CoV-2 may cause acute gastritis and enteritis, as evidenced by the vomiting, nausea and diarrhoea. Since previous studies

indicated high ACE2 expression in the GI tract, we envision that such a change indicates the potential of virus mutation towards increased transmissibility, decreased virulence and multiorgan infection, as reflected in the clinics of increased R0 and infection routes. Taken together, the patients with COVID-19 showed an increased tendency to present with GI symptoms in dissemination, increasing infection risk in healthcare providers who were treating suspected patients with COVID-19 without respiratory symptoms and fever.

We further analysed the epidemiological and clinical characteristics of patients with COVID-19 with GI symptoms. We identified a significantly higher rate of >38.5°C fever and family clustering, increased complications of ARDS and a high severity tendency (rate of severe/critical type, mechanical ventilation and ICU admission) in patients with COVID-19 with GI symptoms, when compared with those without GI symptoms. We suspect that GI symptoms may cause patients with COVID-19 to be more prone to electrolyte disturbance, such as significantly decreased serum sodium levels (p=0.016), and hence they trend towards the severe/critical type of the disease. Other reasons should be considered and explored based on future data. In addition, the higher rates of familial clustering may be related to faecal shedding in shared toilets in households. Further multivariate analysis revealed sputum production from infected areas and increased LDH/glucose levels as independent risk factors for the disease. In addition, symptoms of fatigue, shortness of breath and headache were also significantly higher in patients with COVID-19 with GI symptoms, which may be caused by their higher fevers and increased electrolyte imbalance. Liver damage should be carefully monitored, as we found significantly increased AST levels and coexisting conditions of liver disease in patients with COVID-19 with GI symptoms. Since the ratio of chronic liver disease was higher in patients with COVID-19 with GI symptoms, it could lead to increased levels of ALT and AST. Although there were no significant differences in glucocorticoid and antibiotic therapy between patients with COVID-19 with and without GI symptoms, they were both lower than their counterparts in Wuhan,[4] showing our own experience in effective therapy.

The change and mutation of SARS-CoV-2 are the basis of its variation in epidemiological and clinical features. Using in-depth bioinformatics analysis of the novel identified SARS-CoV-2 sequence from Zhejiang province, we identified many m^6A methylation sites in the S1 segment of ZJ01 and S2 segment of SARS, indicating that the S proteins of the two viruses may have structural and functional differences due to m^6A methylation. The addition of chemical modifications is critical to many steps of mRNA processing and fate regulation, while the most abundant internal modification is N^6-methyladenosin.[19 20] Given the wide prevalence of m^6A modification on cellular mRNA, it is not surprising that a number of viruses contain m^6A in their RNA.[21 22] The function of m^6A methylation on viruses may be diverse with both proviral and antiviral roles.[23 24] Coronaviruses are enveloped RNA viruses containing the largest single-stranded, positive-sense RNA genome with a length between 25.5 and 32 kb.[25] In contrast to previously reported m^6A modification in viruses, methylation at the N7 position of the 5'-cap structure of coronavirus RNA is commonly identified, which facilitates viral RNA escape recognition by the host innate immune system.[26] Therefore, our findings on the novel m^6A methylation situation in SARS-CoV-2 may provide a novel mechanism for further study.

A large reservoir of SARS-like bat coronavirus has the capacity to efficiently use the human ACE2 receptor for docking, replication and entry.[27] ACE2 is predominantly expressed in human alveolar cells and intestinal epithelial cells. The binding force change is caused by the sequence mutation of SARS-CoV-2, which merits further investigation. We found that the electrostatic changes between ZJ01 and Wuhan-Hu-1 were highly concentrated in the mutation zone of S2 (the portion of S protein which promotes the fusion of the virus into host cells). Therefore, further studies exploring the underlining mechanisms for these conformations and binding force changes are urgently needed. These may help explain the increased GI symptoms in the later phase of this virus outbreak and their novel epidemiological/clinical features.

This study has several limitations . First, it is better to obtain the outcomes and more detailed therapeutic responses in a cohort study of patients with COVID-19 with GI symptoms. Second, although the risk factors for the severe/critical type of COVID-19 were identified according to patient data on admission, there is still a lack of a predictive model for disease progression. Third, cytokine storm is common in coronavirus[28] and reported in a previous SARS-CoV-2 study[5]; thus, it would be better if we could also detect cytokine changes in this study. Fourth, it will have more clinical relevance to propose an effective strategy for identifying patients with COVID-19 with GI symptoms who lack the typical symptoms such as fever and cough in the early stage. According to our experience, we should pay more attention to exposure history and family clustering during the screening process. Fifth, it would be meaningful to investigate the correlation between the viral genome and GI symptoms. Finally, since over 50% of SARS-CoV-2 was detected in the faeces according to one study,[29] the prevalence of viral RNA from faeces samples in patients with GI symptoms should be compared with those in patients without GI symptoms in the future. Moreover, because of the relatively low detection rate for virus in the stool (three of nine patients with COVID-19 positive in our hospital) and rare stool samples were re-tested for the virus in patients after their recovery in this study, it is difficult to evaluate the implications of faecal-oral transmission, so this needs further investigation.

In summary, we reported, for the first time, the largest cases of patients with COVID-19 with GI symptoms outside Wuhan and showed its novel characteristics of increased family clustering and liver injury, severe/critical tendency and higher rate of body temperature >38.5°C. Global authorities should pay more attention to patients with COVID-19 with GI and other non-classic symptoms and remain cautious in health provider protection.

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REFERENCES

1 Lu H, Stratton CW, Tang Y-W. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol* 2020;92:401–2.
2 Zhao S, Lin Q, Ran J, *et al*. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. *Int J Infect Dis* 2020;92:214–7.
3 Bogoch II, Watts A, Thomas-Bachli A, *et al*. Potential for global spread of a novel coronavirus from China. *J Travel Med* 2020;27.
4 Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
5 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.
6 Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020. doi:10.1056/NEJMoa2001316. [Epub ahead of print: 29 Jan 2020].
7 Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet* 2020;395:689–97.
8 Lu R, Zhao X, Li J, *et al*. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–74.
9 Wan Y, Shang J, Graham R, *et al*. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94. doi:10.1128/JVI.00127-20. [Epub ahead of print: 17 Mar 2020].
10 Zhao S, Zhuang Z, Ran J, *et al*. The association between domestic train transportation and novel coronavirus (2019-nCoV) outbreak in China from 2019 to 2020: a data-driven correlational report. *Travel Med Infect Dis* 2020;33:101568.
11 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.
12 Zhang H, Kang Z, Gong H, *et al*. The digestive system is a potentila route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv* 2020:927806.
13 WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. Available: https://www.who.int/internal-publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected [Accessed 30 Jan2020].
14 Guan WJ, Ni ZY, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
15 Li G, Fan Y, Lai Y, *et al*. Coronavirus infections and immune responses. *J Med Virol* 2020;92:424–32.
16 Xia J, Tong J, Liu M, *et al*. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol* 2020. doi:10.1002/jmv.25725. [Epub ahead of print: 26 Feb 2020].
17 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. doi:10.1001/jama.2020.1585. [Epub ahead of print: 07 Feb 2020].
18 Fang Dan MJ, Guan J, Wang M, *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.
19 Roundtree IA, Evans ME, Pan T, *et al*. Dynamic RNA modifications in gene expression regulation. *Cell* 2017;169:1187–200.
20 Wang X, Lu Z, Gomez A, *et al*. N6-methyladenosine-dependent regulation of messenger RNA stability. *Nature* 2014;505:117–20.
21 Kennedy EM, Bogerd HP, Kornepati AVR, *et al*. Posttranscriptional m(6)A Editing of HIV-1 mRNAs Enhances Viral Gene Expression. *Cell Host Microbe* 2016;19:675–85.
22 Gokhale NS, McIntyre ABR, McFadden MJ, *et al*. N6-Methyladenosine in Flaviviridae viral RNA genomes regulates infection. *Cell Host Microbe* 2016;20:654–65.
23 Karikó K, Buckstein M, Ni H, *et al*. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* 2005;23:165–75.
24 Courtney DG, Kennedy EM, Dumm RE, *et al*. Epitranscriptomic enhancement of influenza A virus gene expression and replication. *Cell Host Microbe* 2017;22:377–86.
25 Schäfer A, Baric RS. Epigenetic landscape during coronavirus infection. *Pathogens* 2017;6. doi:10.3390/pathogens6010008. [Epub ahead of print: 15 Feb 2017].
26 Chen Y, Guo D. Molecular mechanisms of coronavirus RNA capping and methylation. *Virol Sin* 2016;31:3–11.
27 Menachery VD, Yount BL, Debbink K, *et al*. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* 2015;21:1508–13.
28 Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017;39:529–39.
29 Pan Y, Zhang D, Yang P, *et al*. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 2020. doi:10.1016/S1473-3099(20)30113-4. [Epub ahead of print: 24 Feb 2020].

ORIGINAL RESEARCH

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

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ABSTRACT

Objective To study the GI symptoms in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients.

Design We analysed epidemiological, demographic, clinical and laboratory data of 95 cases with SARS-CoV-2 caused coronavirus disease 2019. Real-time reverse transcriptase PCR was used to detect the presence of SARS-CoV-2 in faeces and GI tissues.

Results Among the 95 patients, 58 cases exhibited GI symptoms of which 11 (11.6%) occurred on admission and 47 (49.5%) developed during hospitalisation. Diarrhoea (24.2%), anorexia (17.9%) and nausea (17.9%) were the main symptoms with five (5.3%), five (5.3%) and three (3.2%) cases occurred on the illness onset, respectively. A substantial proportion of patients developed diarrhoea during hospitalisation, potentially aggravated by various drugs including antibiotics. Faecal samples of 65 hospitalised patients were tested for the presence of SARS-CoV-2, including 42 with and 23 without GI symptoms, of which 22 (52.4%) and 9 (39.1%) were positive, respectively. Six patients with GI symptoms were subjected to endoscopy, revealing oesophageal bleeding with erosions and ulcers in one severe patient. SARS-CoV-2 RNA was detected in oesophagus, stomach, duodenum and rectum specimens for both two severe patients. In contrast, only duodenum was positive in one of the four non-severe patients.

Conclusions GI tract may be a potential transmission route and target organ of SARS-CoV-2.

Significance of this study

What is already known on this subject?

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of coronavirus disease 2019 (COVID-19) pneumonia globally.
- The most common symptoms in patients infected with SARS-CoV-2 were fever and cough.

What are the new findings?

- Infected patients may have no imaging features of COVID-19 pneumonia but only show GI symptoms.
- There was no significant difference in the clinical outcomes (remained in hospital, discharged or died) between patients with and without GI symptoms.
- The presence of SARS-CoV-2 RNA in faeces does not necessarily indicate more severe GI symptoms.
- SARS-CoV-2 RNA could be detected in the oesophagus, stomach, duodenum and rectum in severe patients.

How might it impact on clinical practice in the foreseeable future?

- The impact of SARS-CoV-2 on GI system warrants further investigation to promote early identification and timely treatment of patients.
- Understanding the varied susceptibility of individual GI system to SARS-CoV-2 will promote the personalised COVID-19 therapy.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has rapidly spread around China and other countries.[1–9] The most common symptoms of COVID-19 at the onset of illness are fever, cough, fatigue, myalgia and dyspnoea, whereas the incidence of GI symptoms is low.[1–5] Evidence indicate that human-to-human transmission has occurred in close contacts, mainly transmitted through respiratory droplets and direct contact.[7 8] Given that SARS-CoV-2 RNA has been detected in the patient's stool,[9] it is possible that SARS-CoV-2 could also be transmitted via the faecal–oral route, causing viral GI infection. In this study, to further investigate the impact of SARS-CoV-2 on GI system, we systemically characterised the GI manifestations in patients with COVID-19 in the Zhuhai outbreak.

MATERIALS AND METHODS

Study design and participants

In this retrospective, single-centre study, we reviewed the admission data including clinical records, laboratory findings and endoscopy results on 95 laboratory-confirmed cases of SARS-CoV-2 infection from 17 January to 15 February 2020, at the Fifth Affiliated Hospital of Sun Yat-sen University, which is a designated hospital for all SARS-CoV-2 infected patients in Zhuhai, China. The data cut-off for the study was 15 February 2020. The laboratory-confirmed cases included suspected and clinically diagnosed cases with pharyngeal swab

Table 1 Demographics, baseline features and clinical outcomes of 95 patients infected with SARS-CoV-2

	All patients (n=95)	Patients with GI symptoms (n=58)	Patients without GI symptoms (n=37)	P value
Age, years	45.3±18.3	48.0±17.1	41.1±19.5	0.073
Age groups				
<15	5 (5.3)	1 (1.7)	4 (10.8)	0.30
15–39	37 (38.9)	23 (39.7)	14 (37.9)	
40–49	9 (9.5)	5 (8.6)	4 (10.8)	
50–64	31 (32.6)	19 (32.8)	12 (32.4)	
≥65	13 (13.7)	10 (17.2)	3 (8.1)	
Sex				
Female	50 (52.6)	31 (53.4)	19 (51.4)	0.84
Male	45 (47.4)	27 (46.6)	18 (48.6)	
Epidemiological history				
Recently been to Wuhan or surrounding cities	76 (80.0)	45 (77.6)	31 (83.8)	0.46
Contacted with people from Wuhan	19 (20.0)	13 (22.4)	6 (16.2)	
Smoking history				
Current smoking	6 (6.3)	5 (8.6)	1 (2.7)	0.40
Drinking history				
Current drinking	9 (9.5)	6 (10.3)	3 (8.1)	1.00
Disease classification				
Non-severe	75 (78.9)	44 (75.9)	31 (83.8)	0.36
Severe	20 (21.1)	14 (24.1)	6 (16.2)	
Coexisting illness				
Hypertension	16 (16.8)	10 (17.2)	6 (16.2)	0.90
Diabetes mellitus	6 (6.3)	3 (5.2)	3 (8.1)	0.67
Cardio-cerebrovascular disease	4 (4.2)	3 (5.2)	1 (2.7)	1.00
Malignant tumour	5 (5.3)	4 (6.9)	1 (2.7)	0.65
Chronic lung disease	5 (5.3)	1 (1.7)	4 (10.8)	0.074
Chronic kidney disease	1 (1.1)	1 (1.7)	0	1.00
Viral RNA detection				
Positive faeces	31/65 (47.7)	22/42 (52.4)	9/23 (39.1)	0.31
Clinical outcome				
Remained in hospital	58 (61.1)	35 (60.3)	23 (62.2)	0.86
Discharged	37 (38.9)	23 (39.7)	14 (37.8)	
Died	0	0	0	

Data are presented as n (%), n/N (%) and N is the total number of patients with available data.
P value refers to the comparison between patients with GI symptoms and those without.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

specimens tested positive using real-time reverse transcription PCR (RT-PCR) for SARS-CoV-2.

The diagnose of COVID-19 was according to the WHO interim guidance and new coronavirus pneumonia prevention and control programme (in Chinese).[3 10] Briefly, a suspected case was defined by the epidemiological history and clinical manifestations. The epidemiological history includes travel history to Wuhan or contact with patients with COVID-19 or other person with fever or respiratory symptoms from Wuhan, within 14 days before illness onset. The clinical manifestations include fever with or without respiratory symptoms and normal or reduced white blood cell count or reduced lymphocyte count in early onset. Suspected cases were classified as clinically diagnosed cases if they have CT imaging characteristics of COVID-19 pneumonia. Symptoms of COVID-19 were classified into four grades: mild clinical symptoms without CT imaging features of pneumonia (mild); fever, respiratory symptoms and imaging features of COVID-19 pneumonia (ordinary); respiratory distress (respiratory rate ≥30 breaths/min), oxygen saturation ≤93% and arterial oxygen tension (or pressure) (PaO_2)/fractional inspired oxygen (FiO_2) ratio ≤300 mm Hg (serious), respiratory failure *requiring mechanical ventilation* and organ failure (critically). The patients were divided into non-severe (mild and ordinary) and severe (serious and critically) groups.

Gastroscopy and rectoscopy

Six patients with GI symptoms (two severe and four non-severe cases) were subjected to gastroscopy and two severe of them were subjected to proctoscopy in a negative pressure room, preventing virus from drifting to other areas. Routine stool tests for other pathogens were negative. Endoscopy staff were equipped with protective suits, goggles, N95 mask and surgical gloves to protect themselves from exposure. Endoscopic images were recorded by mobile phones, and the GI specimens were taken from the oesophagus, stomach, duodenum and rectum for viral RNA detection. One severe patient (case 1) exhibited symptoms of GI bleeding. Therefore, gastroscopy was used to localise the bleeding, and the diagnosis revealed the bleeding in the oesophagus. The other five patients (cases 2–6) exhibiting worsening digestive symptoms also underwent

Table 2 GI manifestations of 58 patients with SARS-CoV-2 infection

	All patients (n=58)	On initial presentation (n=11)	During hospitalisation (n=47)
Symptoms			
Diarrhoea	23 (24.2)	5 (5.3)	18 (18.9)
Anorexia	17 (17.9)	5 (5.3)	12 (12.6)
Nausea	17 (17.9)	3 (3.2)	14 (14.7)
Vomiting	4 (4.2)	0	4 (4.2)
Acid reflux	2 (2.1)	1 (1.1)	1 (1.1)
Epigastric discomfort	2 (2.1)	0	2 (2.1)
Upper GI haemorrhage	2 (2.1)	0	2 (2.1)
Hepatic function impairment	31 (32.6)	1 (1.1)	30 (31.6)
Total bilirubin (μmol/L; normal range 3.0–24.0)			11.4±3.6 (37.7±18.2)
Increased	22 (23.2)	0	22 (23.2)
ALT (U/L; normal range 7–40 in female, 9–50 in male)			22.5±19.2 (91.8±31.5)
Increased	5 (5.3)	1 (1.1)	4 (4.2)
AST (U/L; normal rage 13–35 in female, 15–40 in male)			17.6±5.6 (73.2±19.0)
Increased	4 (4.2)	0	4 (4.2)

Data are presented as n (%) and mean±SD on initial presentation (maximum value during hospitalisation). % is the percentage in 95 patients.
ALT, alanine aminotransferase; AST, aspartate transaminase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

endoscopy as we tried to exclude the possibility of erosions, ulcers and bleeding.

Real-time RT-PCR assay for screening of SARS-CoV-2

Pharyngeal swab specimens were collected from all suspected cases at admission. Specimens of confirmed cases, including oesophagus, stomach, duodenum, rectum and faeces, were collected during hospitalisation. RNA was extracted from different specimens using the QIAamp Viral RNA Mini Kit (Qiagen), according to the manufacturer's instructions. RT-PCR assays were performed using the novel coronavirus real-time RT-PCR Kit (Shanghai ZJ Bio-Tech Co, Ltd, Shanghai, China), targeting the open reading frame lab (ORF1ab) and nucleoprotein (N) gene regions.[4 10 11] If two targets tested positive, the case was considered to be laboratory confirmed. A cycle threshold value (Ct-value) less than 37 was treated as a positive test, while a Ct-value of 40 or more was defined as a negative test. A Ct-value of 37–40 required sample retesting. If the repeated Ct-value was less than 40 and an obvious peak was observed, the retest was considered as positive.

Table 3 Drug treatment involvement in GI symptoms developed during hospitalisation

	Antibiotic treatment	Non-antibiotic treatment	P value
Diarrhoea	17/90 (18.9)	1/90 (1.1)	0.034
Non-diarrhoea	49/90 (54.4)	23/90 (25.6)	
Anorexia	11/90 (12.2)	1/90 (1.1)	0.17
Non-anorexia	54/90 (60.0)	24/90 (26.7)	
Nausea	12/92 (13.0)	2/92 (2.2)	0.33
Non-nausea	54/92 (58.7)	24/92 (26.1)	
Vomiting	3/95 (3.2)	1/95 (1.1)	1.00
Non-vomiting	66/95 (69.5)	25/95 (26.3)	
Increased bilirubin	20/95 (21.1)	2/95 (2.1)	0.028
Normal bilirubin	49/95 (51.6)	24/95 (25.3)	
	Antiviral treatment	**Non-antiviral treatment**	**P value**
Diarrhoea	18/90 (20.0)	0	0.34
Non-diarrhoea	66/90 (73.3)	6/90 (6.7)	
Anorexia	12/90 (13.3)	0	1.00
Non-anorexia	72/90 (80.0)	6/90 (6.7)	
Nausea	14/92 (15.2)	0	0.59
Non-nausea	72/92 (78.3)	6/92 (6.5)	
Vomiting	4/95 (4.2)	0	1.00
Non-vomiting	85/95 (89.5)	6/95 (6.3)	
Increased bilirubin	22/95 (23.2)	0	0.33
Normal bilirubin	67/95 (70.5)	6/95 (6.3)	

Data are presented as n/N (%). N is the total number of patients except for those who have related GI symptoms on initial presentation.

Statistical analysis

All statistical analyses were processed with SPSS software (V.19.0). Continuous variables expressed as mean±SD were compared by unpaired ttest and categorical data presented as number (%) were compared by χ^2 test or Fisher's exact test between GI symptoms group and non-GI symptoms group. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 95 patients (50 women and 45 men) were included in this study with an average age of 45.3±18.3 years (table 1). Among them, 76 (80.0%) patients recently had been to Wuhan or surrounding cities, and the remaining 19 (20.0%) patients were in close contact with people from Wuhan. Most of the patients (78.9%) were non-severe. Additionally, 35 (36.8%) patients had coexisting illnesses, including hypertension in 16, diabetes mellitus in 6, malignant tumour in 5, chronic lung disease in 5, cardiocerebrovascular disease in 4 and chronic kidney disease in 1 patient. There was no statistically significant difference in the general demographics or clinical outcomes between patients with and without GI symptoms (table 1). For the 58 (61.1%) patients showing GI symptoms, only 11 patients (11.6%) occurred on admission, while the remaining 47 (49.5%) developed symptoms during hospitalisation (table 2). Moreover, 32.6% of the patients developed hepatic function impairment during hospitalisation with elevated bilirubin, aspartate transaminase or alanine aminotransferase (table 2). Diarrhoea (2–10 loose or watery stools a day, 24.2%), anorexia (17.9%) and nausea (17.9%) were the most frequently observed manifestations. We found that antibiotic treatment was associated with diarrhoea (p=0.034) and elevated bilirubin levels (p=0.028)

Table 4 Viral RNA detection of GI system specimens in six patients underwent endoscopy examination or biopsy

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	77	60	34	62	29	23
Sex	Male	Male	Female	Male	Male	Female
Disease severity	Severe	Severe	Non-severe	Non-severe	Non-severe	Non-severe
Viral detection						
Oesophagus	+	+	–	–	–	–
Stomach	+	+	–	–	–	–
Duodenum	+	+	+	–	–	–
Rectum	+	+	NA	NA	NA	NA
Syndromes of other organ systems	Acute respiratory distress syndrome, septic shock, multiple organ dysfunction syndrome (lung, heart and kidney).	Acute respiratory distress syndrome, respiratory failure and septic shock.	None	None	None	None
Clinical outcome	Hospitalisation	Hospitalisation	Hospitalisation	Hospitalisation	Discharged	Discharged

+, means positive; –, means negative; NA, not available.

during hospitalisation (table 3). However, antiviral treatment did not exert such effects. Importantly, 11 (11.6%) patients did not have any imaging features of COVID-19 pneumonia but only show GI symptoms (see online supplementary table S1). Among them, 3 (27.3%) occurred at diagnosis and 8 (72.7%) during hospitalisation.

We explored the associations between GI symptoms and the presence of SARs-CoV-2 in faeces for 65 hospitalised patients including 42 with and 23 without GI symptoms, of which 22 (52.4%) and 9 (39.1%) had SARS-CoV-2 positive faeces, respectively (table 1). The proportion of positive faecal cases did not show significant difference between two groups, suggesting the presence of SARS-CoV-2 RNA in faeces does not necessarily indicate more severe GI symptoms.

To further determine the causes of GI symptoms, six cases of this cohort were subjected to gastroscopy examination (table 4, online supplementary figure S1). One severe patient (case 1) exhibited symptoms of GI bleeding and the source of bleeding was localised in the oesophagus by endoscopy. There were multiple round herpetic erosions and ulcers with a diameter of 4–6 mm at a distance of 26 cm from incisors. The surface of ulcers was covered with white moss and blood clots, and some of them were fused into pieces with a small amount of bleeding (figure 1). SARS-CoV-2 RNA was detected in the oesophageal erosion and bleeding site, as well as in the stomach, duodenum and rectum tissues of case 1. Further follow-up of this patient revealed increased bilirubin and organ failure in the heart and kidney (online supplementary figure S1). The other five patients (cases 2–6) exhibiting worsening digestive symptoms also underwent endoscopy, and we did not observe any erosions, ulcers or bleeding (table 4). SARS-CoV-2 RNA could also be detected in the oesophagus, stomach, duodenum and rectum of another severe patient (case 2). In contrast, it was only detected in the duodenum of the non-severe case 3 and could not be detected in any GI specimens of the non-severe cases 4–6.

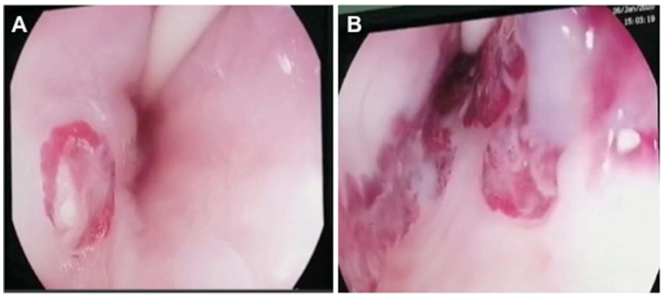

Figure 1 Gastroscopy of the oesophagus in a severe patient with SARS-CoV-2 infection. A and B were different parts of the oesophagus under the endoscopy. (A) A round ulcer (4–6 mm in size) was covered with white moss. (B) Some ulcers were fused into pieces with a small amount of bleeding.

DISCUSSION

In early reports, 2%–10% of patients with COVID-19 had GI symptoms such as diarrhoea and vomiting.[1–5] In our study, 11 (11.6%) cases presented with GI symptoms *at the onset* of illness. In contrast, 47 (49.5%) cases exhibited GI symptoms during hospitalisation, which could be aggravated by various drugs including antibiotics. Nevertheless, there was no significant difference in the clinical outcomes between patients with and without GI symptoms.

A recent study reported a patient initially presented with only GI symptoms.[12] In our study, 11 (11.6%) patients did not have any CT imaging features of COVID-19 pneumonia but only show GI symptoms with 3 (27.3%) occurred at diagnosis, indicating their higher susceptibility of GI system to SARS-CoV-2. While the presence of SARS-CoV-2 in faeces does not necessarily indicate more GI symptoms, the presence of SARS-CoV-2 in GI tissue generally indicates severe symptoms based on the fact that two severe patients have SARS-CoV-2 positive oesophagus, stomach, duodenum and rectum specimens but not the four non-severe patients. In summary, the significance of GI symptoms in clinical practice should not be underestimated. Understanding the varied susceptibility of individual GI system to SARS-CoV-2 will promote the personalised COVID-19 therapy.

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REFERENCES

1 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020;395:497–506.
2 Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* 2020;395:507–13.
3 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.
4 Zhu N, Zhang D, Wang W, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
5 Guan W-jie, Ni Z-yi, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
6 Young BE, Ong SWX, Kalimuddin S, *et al*. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020.
7 Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199–207.
8 Rothe C, Schunk M, Sothmann P, *et al*. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970–1.
9 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.
10 Ren L-L, Wang Y-M, Wu Z-Q, *et al*. Identification of a novel coronavirus causing severe pneumonia in human. *Chin Med J* 2020:1.
11 Wu F, Zhao S, Yu B, *et al*. A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579:265–9.
12 Song Y, Liu P, Shi XL, *et al*. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut* 2020;69:1143–4.