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ORIGINAL ARTICLE

Prevalence of Gastrointestinal Symptoms in COVID-19 Patients; Result From Tertiary Care Hospital in Pakistan

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Abstract

Background/Aim: The most commonly reported COVID-19 symptoms are high-grade fever, cough and body aches with atypical symptoms ie vomiting, diarrhoea and abdominal discomfort. The primary purpose of this research was to ascertain the frequency of gastrointestinal problems experienced by patients due to COVID-19. Goal was to determine whether or not there was a correlation between the severity of COVID-19 disease and the presence of gastrointestinal symptoms in studied individuals.
Methods: The study was conducted at the Gastroenterology Department, PEMH Rawalpindi, Pakistan from January 2022 to January 2023. Confirmed inpatient cases of COVID-19 disease were recruited, referred to Pak Emirates Military Hospital Rawalpindi, Pakistan. Real-time polymerase chain reaction (RT-PCR) verified the presence of COVID-19 in the patients of this research study.
Results: There were 345 patients (335 men and 10 women), with 116 patients exhibiting gastrointestinal symptoms and only 27 patients presented with severe disease. Diarrhoea and anorexia were the most frequently reported digestive symptoms with a frequency of 44 (12.8 %) and 34 (9.9 %), respectively. Clinical outcomes and disease severity were not significantly different between patients with and without digestive issues.
Conclusion: The course of a COVID-19 infection seems to include gastrointestinal symptoms, which include, but are not limited to vomiting, diarrhoea, anorexia, etc. Numerous gastrointestinal symptoms are linked to COVID-19 infection even in the absence of respiratory symptoms. As a result, COVID-19 infection should be taken into account for individuals who primarily present with gastrointestinal symptoms. The establishment of personalised COVID-19 therapies will be aided by an understanding of the varying susceptibility of the individual gastrointestinal system to SARS-CoV-2.

Key words: COVID-19; Signs and symptoms, digestive; Anorexia; Diarrhoea; SARS-CoV-2.

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Introduction

Early in the month of March 2020, the WHO declared Coronavirus Disease 2019 (COVID-19) a global pandemic.[1] An outbreak of pneumonia with no known cause was the spark that set off this worldwide epidemic in Wuhan, China. The coronavirus 2 that causes COVID-19 is responsible for a severe form of respiratory illness (SARS-CoV-2). COVID-19 is the seventh coronavirus identified

as a human infecting coronavirus. It has been reported that previously two coronaviruses named ie Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome infected humans and the target were older people but with more fatal outcomes.[1] As mentioned, the overall death rate was significantly higher in people over the age of 50 years and those with other comorbidities. The most commonly reported COVID-19 symptoms are high-grade fever, cough and body aches with atypical symptoms ie vomiting, diarrhoea and abdominal discomfort. Patients with gastrointestinal (GI) symptoms may continue viral shedding even after their recovery. Even though, the significant frequency of COVID-19 patients who presented with GI symptoms like diarrhoea, anorexia, nausea/vomiting, screening for GI symptoms remains critical.[2]

It has been confirmed that the coronavirus has the potency to multiply rapidly in the human gut. Due to the limited research understanding, the association between digestive abnormalities and COVID-19 implications are still unknown and needs more insights to explore. Even, we were not able to explore the mechanism of GI manifestations of previously reported coronaviruses. However, COVID-19 has elucidated the potential mechanism of COVID-19-related GI symptoms.

SARS-CoV-2 is the causative agent of COVID-19; nevertheless, the clinical presentation of SARS-CoV-2 symptoms varies substantially from organism to organism. SARS-CoV-2 primarily affects the respiratory system, presenting symptoms ranging from influenza to acute respiratory distress syndrome.[3] Angiotensin-converting enzyme 2 (ACE-2) is largely expressed in the epithelial layer of the gut mucosa, while extra-pulmonary involvement has been demonstrated consistently since the outbreak's onset.[4] The increased expression of ACE-2 within the digestive tract may account for COVID-19's GI symptoms. Several investigations have shown the presence of SARS-CoV-2 in the GI tract. In gastric, duodenal and rectal glandular epithelial cells, SARS-CoV-2 nucleocapsid proteins were detected.[5]

Viral RNA was also detected in oesophageal, gastric and duodenal biopsies from patients infected with COVID-19 demonstrating that it exists in gut tissues and is suspected to have some link with the severity of the disease. Studies have indicated that patients with GI symptoms have increased viral replication and viral levels. Anorexia, diarrhoea, nausea, vomiting and body ache or abdominal discomfort are frequently occurring digestive symptoms associated with COVID-19 and they are typically acute and mild in nature. According to some studies, the most prevalent digestive complications were anorexia and diarrhoea, while nausea and vomiting were more common in others.[5, 6]

The rationale of this study was to determine the prevalence of GI issues that were encountered by patients who had COVID-19 and to rule out whether or not there is an association between the severity of COVID-19 disease and the presence of GI symptoms.

Methods

The study was conducted by Gastroenterology Department of Pak Emirates Military Hospital Rawalpindi, Pakistan (PEMH) after taking approval from Ethical Committee (IRB no A/28/138/) in January 2022. It was a prospective study, included only one/single-centre and conducted from January 2022 to January 2023.

Laboratory-confirmed cases of COVID-19 disease were investigated. The laboratory confirmed cases included patients who had been clinically diagnosed of having COVID-19 after a positive nasopharyngeal swab test using real-time reverse transcription polymerase chain reaction (RT-PCR) and findings on computed tomography (CT) scan. The age range of our study participants was with age ≥ 15 - 80 years. At the time of initial evaluation and hospital admission, respondents were divided into 2 categories ie with or without digestive symptoms. Respondents were monitored for vital signs (pulse rate, respiratory rate, temperature and peripheral O_2 saturation) and demographic features with presenting symptoms at the time of admission. Laboratory information was extracted from medical records.

Respondents with chronic health issues were not included in this study. Nevertheless, patients with negative nasopharyngeal swab test using RT-PCR were also excluded from this study.

SPSS Version 19.0 was used to perform statistical analysis. Categorical data were reported as numbers and percentages, on the other hand,

continuous data were given as mean ± standard deviation (SD). The Student's t-test was used to compare normally distributed variables between groups and the Mann-Whitney U-test to analyse non-parametric variables. Using the Chi-square test, proportions were compared between groups. P-values were only considered statistically significant if they were less than 0.05 in all statistical analyses.

Results

The 345 study participants had a mean age of 41.24 ± 4.7 years, consisting of 335 males and 10 females. In addition, 27 (7.8 %) had the severe type of COVID-19 out of total study participants. Total of 241 (69.9 %) patients were recruited who were less than 50 years of age whereas, 102 (29.6 %) of them were older than 50 years. The frequency of digestive symptoms was 116 (33.6 %) in COVID-19 patients, on the other hand 229 (66.4 %) were admitted without any digestive symptoms. As far as disease severity is concerned, 27 (7.8 %) were admitted with severe condition whereas 318 (92.2 %) were relatively stable. Considering COVID-19 associated GI manifestations, diarrhoea with a frequency of 44 (12.8 %) was the leading symptom along with anorexia 29 (8.4 %). Nausea and vomiting were the third most frequent digestive symptoms with a frequency 29 (8.4 %). Ageusia and dyspepsia were reported but with low frequency ie 11 (3.2 %) and 8 (2.3 %), respectively (Table 1).

Table 1: Demographic and clinical symptoms in COVID-19 patients (n = 345)

Characteristics	N	%
Gender		
Male	335	97.1
Female	10	2.9
Age (years)		
< 50 years	241	69.9
≥ 50 Years	102	29.6
Gastrointestinal (GI) symptoms		
With GI symptoms	116	33.6
Without GI symptoms	229	66.4
Severity of disease		
Severe	27	7.8
Non-severe	318	92.2
GI manifestations		
Diarrhoea	44	12.8
Anorexia	34	9.9
Nausea	29	8.4
Vomiting	29	8.4
Ageusia	11	3.2
Dyspepsia	8	2.3

Patients were screened for baseline markers and statistical significance was determined using the Mann-Whitney U test at the 0.05 level of significance (Table 2). Laboratory data depicted that almost all parameters were in the normal range except alkaline phosphatase (ALP). Neutrophil count was slightly in the upper range ie 61.3 (13.6 %).

Table 2: Laboratory parameters of study participants

Parameters	Mean ± SD	p-value*
Haemoglobin (g/dL)	14.39 ± 7.44	< 0.001
WBC (x 10^{12}/L)	7.73 ± 6.11	< 0.001
Platelet count (x10^9/L)	224.30 ± 5.04	< 0.001
Neutrophil (%)	61.37 ± 13.69	0.277
Lymphocyte (%)	30.09 ± 12.65	0.340
Bilirubin (µmol/L)	8.96 ± 5.18	< 0.001
ALT (U/L)	34.06 ± 24.82	< 0.001
ALP (U/L)	235.86 ± 153.98	< 0.001
Albumin (g/L)	39.81 ± 7.93	0.013

*WBC: total white blood cell count; ALT: alanine aminotransferase; ALP: alkaline phosphatase; * Mann-Whitney U test; SD: standard deviation;*

The independent t-test was used in order to check the association of clinical markers with GI complications in COVID-19 patients. No significant differences were found in clinical parameters between patients with and without GI complaints. White blood cell count, as well as kidney and liver damage markers (serum albumin, bilirubin, alanine aminotransferase (ALT) and alkaline phosphatase (ALP)), did not change significantly between COVID-19 patients with GI symptoms and those without them (Table 3).

Table 3: Clinical characteristics of COVID-19 patients with and without gastrointestinal (GI) complications

Parameters	With GI symptoms	Without GI symptoms	p-value*
Haemoglobin (g/dL)	15.17 ± 12.57	13.99 ± 1.74	0.108
WBC (x 10^{12}/L)	7.70 ± 4.14	7.76 ± 6.94	0.636
Platelet count (x10^9/L)	216.32 ± 91.52	228.59 ± 97.04	0.948
Neutrophil (%)	62.00 ± 5.03	61.08 ± 13.01	0.098
Lymphocyte (%)	29.68 ± 13.51	30.29 ± 12.24	0.285
Bilirubin (µmol/L)	9.03 ± 5.06	8.92 ± 5.26	0.973
ALT (U/L)	31.51 ± 25.25	35.59 ± 24.53	0.431
ALP (U/L)	218.13 ± 112.66	246.48 ± 173.70	0.298
Albumin (g/L)	38.93 ± 6.19	40.34 ± 8.82	0.379

*WBC: total white blood cell count; ALT: alanine aminotransferase; ALP: alkaline phosphatase; * Independent t-test;*

Chi-square test was used to compare the difference in severity of disease in between patients with and without digestive symptoms. When comparing COVID-19 patients with and without GI symptoms, no significant difference in disease severity was found (p = 0.249).

Discussion

Presented study reported an increase in the prevalence of GI manifestations among COVID-19 patients compelling healthcare professionals to consider digestive symptoms in coronavirus-infected patients. Findings indicate a higher rate of GI complications (33.6 %) than previous Iranian and Chinese studies.[7-11] A number of studies reported diarrhoea, loss of appetite (anorexia) and nausea were more frequent manifestations, which is consistent with presented findings.[12] Whereas, some studies found that anorexia with nausea and vomiting were more prevalent digestive symptoms in COVID-19 patients.[10, 13] In analysed study group, diarrhoea was the most common GI complication with a frequency of 44 (12.8 %) as compere to other symptoms. SARS-CoV-2 can induce direct or indirect damage to the digestive tract through the inflammatory response. Infection with SARS-CoV-2 may result in an "inflammatory storm," in which over-activated cytokines, inflammatory storms and immunological dysregulation induce inflammatory damage to the bowel, leading in diarrhoea. The presence of SARS-CoV-2 RNA in stool samples from COVID-19 patients suggests that SARS-CoV-2 may directly impact the intestinal mucosa, causing digestive symptoms such as diarrhoea.[14]

ACE-2 is highly expressed in the glandular cells, lining the digestive tract (the stomach, duodenum and colon). ACE-2 receptor binding affinity dictates SARS-CoV-2 infectivity, large levels of these receptors signal that the virus may infect and spread in the GI tract can be found. Intestinal inflammation and diarrhoea can be caused by a lack of amino acids or peptides; ACE-2 mutants showed decreased expression of antimicrobial peptides and resulted in altered gut microbial makeup.[15, 16]

Anorexia or loss of appetite is the most prevalent GI manifestation associated with SARS-CoV-2 infection. According to the results of this study, anorexia accounted for 32 (9.3 %) of COVID-19 patients, making it the second most prevalent GI symptom. A pooled data from a meta-analysis of 60 different research studies found that around 26.8 % of the COVID-19 patients presented with diarrhoea but there were discrepancies in data among different research studies.[15] With a pooled prevalence of 12.5 %, diarrhoea was the second most frequent GI symptom among COVID-19 patients. The prevalence of diarrhoea in COVID-19 patients was found to be 10.4 %, which was based on a pooled review of clinical studies.[17] However, recent data from the United States indicated higher rates up to 33.7 %.[18] Nevertheless, diarrhoea with mild severity was also indicated in some research studies, whereas another study in China linked COVID-19 to a severe form of diarrhoea ie acute haemorrhagic colitis.[12]

According to US data, 10.3 % to 26.4 % of COVID-19 patients experience nausea or vomiting.[18, 19] In presented study, the prevalence of nausea and vomiting were 31 (9.0 %) and 29 (8.4 %), respectively. Dysgeusia has also been documented among COVID-19 patients, typically alongside anosmia. The incidence of COVID-19-related GI symptoms was found to be considerable, although the incidence was lower in the majority of trials. However, disease severity was connected with a higher incidence of nausea. Patients who exhibited multiple digestive symptoms like diarrhoea, vomiting/nausea are expected to present with fever more often compared to patients with a single symptom. Intriguingly, dysgeusia and anosmia were independently associated with nausea and anorexia in patients with digestive symptoms.[18] While less common than other GI symptoms, abdominal discomfort was common among patients who had severe COVID-19 illness.

Initial findings indicated that GI problems were linked with disease severity and prognosis. In one study, it was discovered that patients with nausea/vomiting and diarrhoea had more severe disease outcomes when compared to patients without GI problems.[20] A meta-analysis revealed that patients with digestive symptoms had higher rates of severe disease than those without digestive symptoms.[7] Nevertheless, there are some studies present which have not found a correlation between GI symptoms and poorer outcomes.[6, 18] Possible explanations for these discrepancies include differences in reporting data, diverse study cohorts and different strains of virus. Moreover, viral clearance appears to be significantly slower in patients reported with GI complications than presented with respiratory symptoms only.[21]

Intriguingly, patients with COVID-19 and digestive symptoms appear to have a longer duration of illness than patients without digestive symptoms.[22] Regarding disease severity and GI problems in this study population, no statistically significant differences were discovered.

Presented study has some limitations. It is a single-centre-based study with limited reliability and generalisability. To determine whether there is a correlation between GI symptoms and COVID-19 disease, it is necessary to recruit female respondents to supplement the data collected from men. Digestive signs and disease onset might be caused by several reasons, such as ethnic/geographic disparities and concomitant comorbidities. It is vital to be aware of the variety of GI manifestations associated with COVID-19 so that possible causes can be considered before they lead to any severe outcome. Healthcare professionals should consider such patients who present with GI complications along with fever as it may result in poor patient outcomes. Aside from a history of liver disease, there were no other risk factors identified that facilitate digestive symptoms in COVID-19 patients and thus making it difficult to predict who may develop these symptoms.

In the early stages of the pandemic, probably, mild GI abnormalities were not noted (and hence underestimated). Extending the evidence base and providing better answers to the various concerns at hand will be facilitated by well-conducted research from several hospitals or centres. More data being provided from several countries should lead to a more complete and thorough profile of certain elements.

Conclusion

COVID-19 is not merely a respiratory sickness. The virus can also impact the digestive system. It is essential to identify the numerous manifestations in different organ system, as these symptoms may aid in community-based dissemination. In clinical settings, GI problems are not to be taken lightly. Understanding the variable vulnerability of the individual GI system to SARS-CoV-2 will aid in the development of personalised COVID-19 treatments.

Ethics

The study was approved by Ethical Committee of the Pak Emirates Military Hospital Rawalpindi, Pakistan (PEMH), decision No: IRB no A/28/138, dated 15 January 2022.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. Vespa E, Pugliese N, Colapietro F, Aghemo A. Stay (GI) Healthy: COVID-19 and Gastrointestinal Manifestations. Tech Innov Gastrointest Endosc. 2021;23(2):179-89. doi: 10.1016/j.tige.2021.01.006.
2. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: What we know. Int J Infect Dis. 2020 May;94:44-48. doi: 10.1016/j.ijid.2020.03.004.
3. Yang Y, Xiao Z, Ye K, He X, Sun B, Qin Z, et al. SARS-CoV-2: characteristics and current advances in research. Virol J. 2020;17(1):117. doi: 10.1186/s12985-020-01369-z.
4. Wark PAB, Pathinayake PS, Kaiko G, Nichol K, Ali A, Chen L, et al. ACE2 expression is elevated in airway epithelial cells from older and male healthy individuals but reduced in asthma. Respirology. 2021;26(5):442-51. doi: 10.1111/resp.14003.
5. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158(6):1831-3 e3. doi: 10.1053/j.gastro.2020.02.055.
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 Jun;69(6):997-1001. doi: 10.1136/gutjnl-2020-321013.
7. Hajifathalian K, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, et al. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. Gastroenterology. 2020;159(3):1137-40 e2. doi: 10.1053/j.gastro.2020.05.010.
8. Montazeri M, Maghbouli N, Jamali R, Sharifi A, Pazoki M, Salimzadeh A, et al. Clinical characteristics of COVID-19 patients with gastrointestinal symptoms. Arch Iran Med. 2021;24(2):131-8. doi: 10.34172/aim.2021.21.
9. Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut. 2020;69(6):973-4. doi: 10.1136/gutjnl-2020-321195.
10. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18(7):1636-7. doi: 10.1016/j.cgh.2020.03.043.
11. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-93. doi: 10.1016/j.jinf.2020.02.016.
12. 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;115(5):766-73. doi: 10.14309/ajg.0000000000000620.
13. 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;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
14. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763. doi: 10.1016/j.ebiom.2020.102763.
15. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of sars-cov-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020;159(1):81-95. doi: 10.1053/j.gastro.2020.03.065.
16. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012;487(7408):477-81. doi: 10.1038/nature11228.
17. 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. doi: 10.1016/j.cgh.2020.04.001.
18. 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. 2020;159(2):765-7 e2. doi: 10.1053/j.gastro.2020.04.045.
19. Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: early experience from California. Gastroenterology. 2020;159(2):775-7. doi: 10.1053/j.gastro.2020.04.008.
20. 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. doi: 10.1136/gutjnl-2020-320926.
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;115(6):916-23. doi: 10.14309/ajg.0000000000000664.
22. Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, et al. Gastrointestinal symptoms and coronavirus disease 2019: a case-control study from the United States. Gastroenterology. 2020 Jul;159(1):373-375.e2. doi: 10.1053/j.gastro.2020.04.017.