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Gastrointestinal symptoms predict the outcomes from COVID-19 infection

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Abstract

Coronavirus disease 2019 (COVID-19) has taken hundreds of thousands of lives globally. Besides respiratory tract, the virus can affect the gastrointestinal (GI) tract. Data regarding the significance of GI symptoms in the COVID-19 course is limited. In this largest U.S. study to-date, we reviewed electronic encounters of 1003 consecutive patients who were tested positive for the virus between March 12th and April 3rd, 2020. Initial GI symptoms were present in up to 22.4% of patients and were associated with worse outcomes after adjustment for demographics, comorbidities and other clinical symptoms. COVID-19 with GI involvement may define a more severe phenotype.

INTRODUCTION

As of May first, 2020, over 3 million confirmed cases of coronavirus disease 2019 (COVID-19) and hundreds of thousands of deaths have been reported globally.[1] The entry of SARS-CoV-2 virus into cells is mediated via Angiotensin-converting enzyme 2 (ACE2) receptor.[2, 3] This entry is facilitated by the host's transmembrane protease serine 2 (TMPRSS2) membrane protease,[4] a determinant step of tissue tropism of the virus.[5] Besides the respiratory epithelium which is a typical site for the virus entry, the gastrointestinal (GI) tract expresses high levels of both ACE2 and TMPRSS2,[6] and thus is another viral target organ of COVID-19.[7]

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Whereas COVID-19 commonly manifests respiratory symptoms, up to 10%–50% of COVID-19 patients have been reported to present GI symptoms in China.[3, 8] In a U.S. study of 318 COVID-19 patients, GI symptoms were commonly reported [9], however, data regarding the significance of GI symptoms in the COVID-19 course is limited.[9]

Herein, we aimed to determine if the presence of GI symptoms at presentation of COVID-19 in adult patients can be predictive of the disease outcomes.

METHODS

In this large retrospective cohort study, approved by the local Institutional Review at Rush University Medical Center, Chicago, we identified all patients (age ≥ 18 years) who were tested positive for SARS-Cov-2 by polymerase-chain reaction nasopharyngeal swab between March 12th and April 3rd, 2020 (n=1003). Electronic encounters of all the patients were reviewed by trained researchers to record demographics (age, sex, body mass index (BMI), diabetes, hypertension, asthma), presenting COVID-19 symptoms, laboratory data and clinical outcomes (including hospital admission, acute respiratory distress syndrome (ARDS) intensive care unit admission (ICU), and intubation). As part of a pre-designed screening template, all patients were screened for constitutional symptoms (fever, loss of appetite, body aches), respiratory symptoms (cough, shortness of breath (SOB), smell loss, chest tightness) and GI symptoms (diarrhea, nausea/vomiting, abdominal pain), prior to the patient receiving treatment for COVID-19.

Baseline characteristics are presented as mean (SD), medians (quartiles), and percentages. The differences, according to the presence of initial GI symptoms, were analyzed with the chi-square test, Student's t-test, or Kruskal-Wallis rank-sum test as appropriate. Logistic regression models were used to examine the associations of initial GI symptoms and clinical outcomes of the COVID-19 infection, after adjustment for age, sex, race, and co-morbidities (e.g., diabetes, hypertension, and/or obesity).

RESULTS and DISCUSSION

Out of 1003 patients with positive COVID-19 test results, complete data was available in 921 (91.8%) patients who were included in this study. Among the 921 cases, 329 (46.0%) were male, the mean (± SD) of age was 47.87±16.4 years and the mean (±SD) of BMI was 30.7±7.27 kg/m^2.

Overall, 206/921 (22.4%) of patients reported at least one GI symptom at the onset of their infection with diarrhea being the most common complaint 144/206 (69.9%).

Patients with GI symptoms were older (52.4±17.1 vs 47.6±16.0; $p<0.001$) and had higher BMI (33.1±8.2 vs 31.5±7.4; $p < 0.009$). Compared to patients without GI symptom, those with GI symptoms at presentation had a higher prevalence of diabetes and hypertension and were more African-American (Table 2).[2, 3, 9]

While patients with initial GI symptoms showed lower mean hemoglobin, calcium, albumin, and higher creatinine and AST, most of the observed statistical laboratory differences did not appear to be of clinical significance (Table 2).

In addition to the number of abnormal laboratory values, patients presenting with GI symptoms showed higher admission rates to the hospital, ICU, and higher intubation rates (Table 2).

After correction for demographics, comorbidities and all other symptoms, the presence of GI symptoms remained significantly associated with the need for hospital admission (odds ratio, and 95% CI=4.4 (3.03–6.45), p<0.001), ARDS (2.76 (1.68–4.52), p<0.001), ICU admission (2.53 (1.63–3.91), p=0.001), and intubation (2.43 (1.46–4.02), p=0.001) (Table 2). The interaction term between GI symptoms and age, sex, and race, in separate logistic regression models were assessed, and all were non-significant (p-value > 0.3).

A separate analysis on the association of more specific GI symptoms with the COVID-19 outcomes indicated that patients with the initial symptoms of diarrhea or abdominal pain (n=162) had higher hospital admission (5.08 (3.44–7.56), p<0.001), ARDS (2.63 (1.56–4.38), p<0.001), ICU admission (2.47 (1.57–3.87), p<0.001), and intubation (2.20 (1.28–3.72), p=0.004). Similarly, diarrhea alone was associated with unfavorable outcomes: hospital admission (5.08 (3.38–7.71), p<0.001), ARDS (2.02 (1.15–3.45), p=0.012), ICU admission (2.13 (1.32–3.40), p=0.002), and intubation (1.74 (0.97–3.03), p=0.054).

Analyzing the predictive value of GI symptoms based on the frequency of initial GI symptoms (1: only one GI symptom and 2: two or three GI symptoms) revealed a step wise increased likelihood of worsened outcome when compared to those without GI symptoms (0) (Table 2). It is possible that increased number of GI symptoms led to the clinical decision for hospitalization. However, the increased risk of COVID-19 respiratory complications (i.e, ARDS, and intubation) in those presenting with GI symptoms are indicative of a more severe disease associated with the GI involvement.

In this large single center study, GI symptoms in COVID-19 patients were present in up to 22.4% of patients and were associated with worse outcomes after adjustment for demographics, comorbidities, and all other clinical symptoms. These results expand on a recently reported smaller series from china where 74 patients with GI manifestation of COVID-19 from China had higher complications.[3]

Association of GI symptoms with age, higher BMI, African-American race, and hypertension is noteworthy as these factors are shown to predict worse course of COVID-19 infections.[10] However, our analysis, adjusted for all these factors, indicates that GI symptoms are independently linked to poor outcomes. Therefore, presence of GI symptoms in such patients may place them at a markedly higher risk for a worsened disease course from COVID-19. Translation of these results to clinical practice may involve additional focus on screening for GI symptoms to help better risk stratify COVID-19 positive patients.

Mechanisms that could explain how GI involvement may impact the phenotype and prognosis of COVID-19 is unclear. [11–13] Recently, human enterocytes were shown to be

readily infected by SARS-CoV-2. High viral replication in the enterocytes and exposure to viral nucleic acids activated multiple inflammatory response elements including board spectrum of cytokines and interferon stimulating genes in the enterocytes.[7, 14]

Our study is limited by the retrospective data collection. To ensure that we captured the reported symptoms at the time of diagnosis, all available initial encounters for patients were carefully reviewed. We are aware that a number of patients may develop symptoms later or during admission. However, we excluded any GI symptoms occurring after admission as delayed symptoms could be due to factors other than COVID-19 (i.e., in-hospital treatments or associated infections).

In conclusion, in this largest U.S. study to-date on the significance of gastrointestinal symptoms in COVID-19 infection, GI symptoms were independently predictive of worse outcomes. Further studies are needed to determine if COVID-19 with GI involvement causes an enhanced inflammatory profile that may lead to a more severe phenotype.

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Table 1:

Gastrointestinal symptoms in COVID-19 patients at initial presentation. Data presented as n (%).

GI symptoms	N (%)
Initial GI symptoms	206/921 (22.4%)
In those with GI symptoms	
Diarrhea	144/206 (69.9%)
Nausea/vomiting	127/206 (61.7%)
Abdominal pain	52/206 (25.2%)
Only one GI symptom	113/206 (49.5%)
Two GI symptoms	69/206 (33.4%)
All three GI symptoms	24/206 (11.6%)
GI symptoms according to race	
Black/African American	124/206 (60.2%)
White/Caucasian	33/206 (16.0%)
Latino/Hispanic	11/206 (5.3%)
Others /Unknown	38/206 (18.4%)

Table 2:

Characteristics and outcomes of COVID-19 patients in association with gastrointestinal symptoms. Data presented as n (%), mean (SD) and median [interquartile].

Characteristics/Symptoms (N=921)	Without Initial GI symptoms (N=715)	With GI symptoms (N=206)	P-Value
Age (Years)	47.63 (16.01)	52.36 (17.08)	<0.001
Sex (Males)	329 (46.0%)	80 (38.8%)	0.08
Race (African American)	369 (51.7%)	124 (60.2%)	0.038
BMI (kg/m^2)	31.50 (7.42)	33.06 (8.19)	0.009
Diabetes	161 (22.5%)	77 (37.4%)	<0.001
Hypertension	260 (36.4%)	122 (59.2%)	<0.001
Fever	549 (76.8%)	178 (86.4%)	0.004
Body aches	360 (50.3%)	128 (62.1%)	0.004
Cough	637 (89.1%)	190 (92.2%)	0.24
Shortness of breath	411 (57.6%)	143 (69.4%)	0.003
Loss of appetite	129 (18.0%)	105 (51.0%)	<0.001
Constitutional symptoms	610 (85.3%)	195 (94.7%)	0.001
Respiratory symptoms	660 (92.3%)	195 (94.7%)	0.32
Lab Values $^{£}$			
Highest WBC × 10^3/mm^3	7.38 [5.38, 10.85]	7.52 [5.84, 11.45]	0.31
Hemoglobin g/dL	11.68 (2.30)	11.02 (2.46)	0.006
Lowest Platelet Count × 10^3/mm^3	203.09 (83.31)	191.66 (86.04)	0.19
Neutrophils × 10^3/mm^3	4.57 [2.95, 8.11]	4.90 [3.52, 9.19]	0.11
Lymphocytes 10^3/ mm^3	1.37 (2.24)	1.01 (0.55)	0.05
Eosinophils × 10^3/ mm^3	0.06 [0.01, 0.18]	0.08 [0.01, 0.19]	0.47
Calcium mg/dL	8.42 (0.76)	8.18 (0.67)	0.002
Albumin mg/dL	2.89 (0.85)	2.68 (0.80)	0.02
Creatinine mg/dL	1.06 [0.80, 1.55]	1.27 [0.90, 2.69]	0.001
AST units/L	40.00 [24.00, 99.50]	50.50 [31.0,108.5]	0.03
ALT units/L	35.00 [20.00, 77.75]	43.00 [24.0,94.75]	0.06
Bilirubin mg/dL	1.03 (2.03)	1.31 (2.57)	0.24
Outcomes *			
Hospital admission	169 (23.6%)	125 (60.7%)	<0.001
Odds Ratio (95% CI)	4.4 (3.03, 6.45)		<0.001
ICU admission	72 (10.1%)	53 (25.7%)	<0.001
Odds Ratio (95% CI)	2.53 (1.63, 3.91)		<0.001
ARDS	50 (7.0%)	41 (19.9%)	<0.001
Odds Ratio (95% CI)	2.76 (1.68, 4.52)		<0.001
Intubated	48 (6.7%)	37 (18.0%)	<0.001

Characteristics/Symptoms (N=921)	Without Initial GI symptoms (N=715)	With GI symptoms (N=206)	P-Value
Odds Ratio (95% CI)	2.43 (1.46, 4.02)		0.001
GI symptom frequency and outcomes¥	**Number (%) of Subjects according to GI symptom frequency**	**Number (%) of Events**	**OR (95% CI), P value**
Hospital admission			
	0: 715 (77.6)	169 (23.6)	1 (reference)
	1: 113 (12.3)	55 (48.7)	3.05 (1.94–4.79), <0.001
	2: 93 (10.1)	70 (75.3)	9.69 (5.72–17.00), <0.001
ARDS			
	0: 715 (77.6)	50 (7.0)	1 (reference)
	1: 113 (12.3)	21 (18.6)	3.06 (1.63 – 5.64), <0.001
	2: 93 (10.1)	20 (21.5)	3.32 (1.75–6.15), <0.001
ICU admission			
	0: 715 (77.6)	72 (10.1)	1 (reference)
	1: 113 (12.3)	26 (23.0)	2.62 (1.50–4.50), 0.001
	2: 93 (10.1)	27 (29.0)	3.24 (1.85–5.57), <0.001
Intubated			
	0: 715 (77.6)	48 (6.7)	1 (reference)
	1: 113 (12.3)	21 (18.6)	3.13 (1.66–5.78), <0.001
	2: 93 (10.1)	16 (17.2)	2.48 (1.25–4.72), 0.007

£: Laboratory findings were available in 378–405/921 (41–44%) of cases; values are presented as mean (standard deviation) and median [interquartile] for normally and not-normally distributed values, respectively.

*: Odds Ratio is calculated in patients with GI symptoms compared to those without GI symptoms after adjustment for age, sex, race, and co-morbidities (e.g., diabetes, hypertension, and/or obesity)

¥: Gastrointestinal symptom frequency was calculate based on the number of initial GI symptoms (0: No GI symptoms, 1: only one GI symptom and 2: two or three GI symptoms).