Gastrointestinal Symptoms and Coronavirus Disease 2019: A Case-Control Study From the United States

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Coronavirus disease 2019 (COVID-19) is a pandemic characterized by a high fatality rate.[1] The incidence of COVID-19 has risen dramatically in the United States since March 2020, with the highest number of cases in the country present in New York City.[2] As health care systems rise to the challenge of unprecedented demands, there is an urgent need to characterize the spectrum of clinical presentations of this disease to allow early identification, isolation, and triage of affected patients.

Although fever, cough, and shortness of breath are among the most common presenting symptoms, gastrointestinal symptoms are increasingly recognized among patients with COVID-19.[3–7] This case-control study aimed to describe gastrointestinal symptomatology—including diarrhea and nausea/vomiting—in US patients with COVID-19 compared to patients presenting under similar circumstances who tested negative for COVID-19. The secondary aims were to characterize the associations of gastrointestinal symptoms with total illness duration and early clinical outcomes.

Methods

This was a retrospective case-control study. Adults ≥18 years of age were considered for the study if they underwent nasopharyngeal swab testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 10, 2020, and March 21, 2020, at outpatient settings, including clinics or the emergency departments, of New York-Presbyterian-Columbia or the medical center's affiliates in New York. Indications for testing during this period were respiratory symptoms (cough, fever, shortness of breath) with intent to hospitalize or the same symptoms in essential personnel. Patients were excluded if insufficient data were available in the electronic medical record or if testing was performed during a preexisting inpatient admission. This study was approved by the Columbia University Irving Medical Center institutional review board.

Manual chart review of randomly selected patients was performed by 3 investigators (YRN, MP, DEF) blinded to SARS-CoV-2 test result. The primary exposure was presence of gastrointestinal symptoms, including diarrhea or nausea/

vomiting, documented anywhere in the intake history. Illness duration, based on the time between earliest onset of any symptom as documented in the intake history and testing for COVID-19, was classified categorically as <1 week or ≥1 week. The primary outcome was the SARS-CoV-2 polymerase chain reaction test result, referred to as COVID-19 positive or negative. Early clinical outcomes assessed were need for hospitalization, intensive care unit (ICU) admission (including need for mechanical ventilation), and in-hospital death.

Results

A total of 278 COVID-19–positive patients and 238 COVID-19–negative patients were included in the analysis. Duration of follow-up after testing was 5 to 18 days (median, 8 days). Baseline characteristics and early clinical outcomes of COVID-19–positive and –negative patients are shown in Supplementary Table 1.

Patients with gastrointestinal symptoms, defined as diarrhea or nausea/vomiting, at the time of testing were significantly more likely to test positive for COVID-19 than to test negative (61% vs 39%; $P = .04$), whereas patients without gastrointestinal symptoms were equally likely to test positive or negative (Table 1). In a multivariable model including all variables associated with a positive COVID-19 test result, the presence of gastrointestinal symptoms was associated with a 70% increased risk of testing positive (adjusted odds ratio, 1.7; 95% confidence interval, 1.1– 2.5). Increasing body mass index was also associated with increasing odds of a positive COVID-19 test result.

Among the 278 COVID-19–positive patients, 97 (35%) had gastrointestinal symptoms, and 181 (65%) did not. Age, sex, race, ethnicity, body mass index, care setting of testing, and regional location of testing did not differ significantly based on the presence or absence of symptoms. Most patients had an illness duration by time of testing of less than 1 week, but patients with gastrointestinal symptoms were more likely to have an illness duration of ≥1 week compared to those without symptoms (33% vs 22%,

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Table 1. Rate of Positive or Negative COVID-19 Testing Based on Presence or Absence of Gastrointestinal Symptoms

Symptoms	COVID-19 positive (N = 278)	COVID-19 negative (N = 238)	P value
Any gastrointestinal symptoms			**.04**
Present (n = 160)	97 (61)	63 (39)	
Absent (n = 356)	181 (51)	175 (49)	
Diarrhea[a]			.14
Present (n = 92)	56 (61)	36 (39)	
Absent (n = 424)	222 (52)	202 (48)	
Nausea/vomiting[a]			.36
Present (n = 109)	63 (58)	46 (42)	
Absent (n = 407)	215 (53)	192 (47)	

NOTE. Row percentages are shown. Bold type: $P < .05$.
[a]Frequency of symptom, with or without the other gastrointestinal symptoms; 51 patients had diarrhea only and 68 patients had nausea/vomiting only.

respectively; $P = .048$). For patients with diarrhea or nausea/vomiting as individual symptoms, there were similar but nonsignificant trends.

Among patients with COVID-19, in patients with gastrointestinal symptoms compared to those without symptoms, there was a nonsignificant trend toward lower rates of ICU admission, and a significantly lower rate of death (0.0% with gastrointestinal symptoms vs 5.0% without; $P = .03$) during short-term follow-up (Supplementary Table 2).

Discussion

This case-control study aimed to characterize the relationship between gastrointestinal symptoms and COVID-19 in a US patient population using data from a major health care network in New York City, the current epicenter of the COVID-19 pandemic. We found a statistically significant association between presence of gastrointestinal symptoms—defined as diarrhea and nausea/vomiting—at presentation and positive COVID-19 test result among those presenting for testing. Gastrointestinal symptoms were associated with a 70% relative increased risk of testing positive.

Among COVID-19–positive patients, the presence of gastrointestinal symptoms was associated with longer illness duration, a trend toward lower ICU admission rate, and lower mortality during short-term follow-up. These combined findings may suggest that gastrointestinal symptoms are associated with a more indolent form of COVID-19, although conclusions at this time are preliminary.

Our study has limitations. The short follow-up time was accepted because of the urgent need for information that may guide clinical decision making. Future studies should incorporate longer follow-up periods and also larger patient populations. Because this was a retrospective study, identification of gastrointestinal symptoms was dependent on accurate clinical documentation. There is almost certainly some degree of misclassification of symptoms, although—because the COVID-19 test result was unknown at the time of documentation—such misclassification would likely be nondifferential and would therefore bias results toward the null.

To our knowledge, this is the first study evaluating the association of gastrointestinal symptoms with COVID-19 test result and the first to describe gastrointestinal symptoms in a large US cohort of patients with COVID-19. Among patients meeting criteria for COVID-19 testing, those with gastrointestinal symptoms were 70% more likely to test positive. Among patients with COVID-19, the presence of gastrointestinal symptoms was associated with longer illness duration and lower rate of death during short-term follow-up. Our findings suggest that among patients meeting criteria for testing, the presence of gastrointestinal symptoms is predictive of COVID-19 positivity. Among patients with COVID-19, these symptoms may portend a slower and less severe disease course. Future studies should seek to confirm these results in other populations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.04.017.

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Conflicts of interest
The authors disclose no conflicts.

BRIEF COMMUNICATIONS

Supplementary Methods

Flow of Patients Into the Study

320 COVID-19 positive and 320 COVID-19 were randomly selected for manual chart review. Of these, 42 COVID-19 positive patients were excluded (22 due to insufficient data available, and 20 due to testing during a pre-existing inpatient admission), and 82 COVID-19 negative patients were excluded (28 due to insufficient data available, and 54 due to testing during a pre-existing inpatient admission), to produce the final study populations of 278 positive patients and 238 negative patients.

Statistical Analyses

Chi-squared or Fisher's exact tests were used to compare categorical variables. A multivariable model was built to examine the relationship between gastrointestinal symptoms and COVID-19 after adjusting for other factors. The final, reduced model was produced through stepwise subtraction of variables, retaining those with an independent relationship with test result or which changed the β coefficient for gastrointestinal symptoms by $>=10\%$. An alpha of 0.05 was considered statistically significant and all testing was two-sided. Statistical calculations were performed using STATA version 16 (College Station, TX).

Supplementary Table 1. Clinical Characteristics of Patients Who Tested Positive Compared to Patients Who Tested Negative for COVID-19

Characteristics	COVID-19 positive (n = 278)	COVID-19 negative (n = 238)	P value
Age, *y*, n (%)			.73
18–30	31 (11)	31 (13)	
31–50	69 (25)	51 (21)	
51–70	103 (37)	86 (36)	
>70	75 (27)	70 (29)	
Sex, n (%)			.13
Male	145 (52)	108 (45)	
Female	133 (48)	130 (55)	
Race, n (%)			.29
White	84 (30)	88 (37)	
Black	77 (28)	68 (29)	
Asian	4 (1.4)	3 (1.3)	
Other or unknown	113 (41)	79 (33)	
Ethnicity, n (%)			.14
Hispanic	107 (39)	72 (30)	
Non-Hispanic	114 (41)	114 (48)	
Other or unknown	57 (21)	52 (22)	
Body mass index, *kg/m²*, n (%)			<.01
<25.0 (normal or underweight)	25 (9.0)	53 (22)	
25.0–29.9 (overweight)	43 (16)	41 (17)	
≥30.0 (obese)	47 (17)	44 (19)	
Not recorded	163 (59)	100 (42)	
Care setting of testing, n (%)			.90
Outpatient clinic	23 (8.0)	19 (8.0)	
Emergency department	255 (92)	219 (92)	
Regional location of testing, n (%)			<.01
Manhattan, New York City	201 (72)	201 (85)	
Brooklyn, New York City	52 (19)	27 (11)	
Westchester County, New York	25 (9.0)	10 (4.2)	
Clinical outcomes, n (%)[a]			.05
Hospital admission	207 (74)	171 (72)	
ICU admission	44 (16)	20 (8.4)	
Death	9 (3.2)	3 (1.3)	

NOTE. Column percentages are shown.
[a]Duration of follow-up time ranged from 5 to 18 days.

Supplementary Table 2. Early Clinical Outcomes of Patients With COVID-19 (N = 278), Based on Presence or Absence of Gastrointestinal Symptoms at Time of Test

Symptoms	Hospital admission	ICU admission	Death
Any gastrointestinal symptoms			
Present (n = 97)	76 (78)	14 (14)	0 (0.0)[b]
Absent (n = 181)	131 (72)	30 (17)	9 (5.0)[b]
Diarrhea[a]			
Present (n = 56)	42 (75)	11 (20)	0 (0.0)
Absent (n = 222)	165 (74)	33 (15)	9 (4.2)
Nausea/vomiting[a]			
Present (n = 63)	51 (81)	8 (13)	0 (0.0)
Absent (n = 215)	156 (73)	36 (17)	9 (4.2)

NOTE. Row percentages are shown. All P values were >.20 except where noted.
[a]Frequency of symptoms, with or without the other gastrointestinal symptoms.
[b]P value = .03 for comparison of rate of death among patients with present vs absent gastrointestinal symptoms.