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Are Gastrointestinal Symptoms Specific for Coronavirus 2019 Infection? A Prospective Case-Control Study From the United States

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The reported prevalence of gastrointestinal (GI) symptoms, including anorexia, diarrhea, nausea, vomiting, and abdominal pain, in severe acute respiratory syndrome coronavirus 2 infection has been highly variable, ranging from 5% to 61%.[1–7] Although the Centers for Disease Control and Prevention guidelines for testing for coronavirus disease 2019 (COVID-19) include vomiting and diarrhea, to our knowledge, all studies to date have been retrospective, and none have evaluated the prevalence of GI symptoms among patients who tested negative for COVID-19. In this prospective case-control study, we compared the prevalence of GI symptoms between those who tested positive and negative for COVID-19 and determined the association between GI symptoms and COVID-19 diagnosis or outcomes.

Methods

This was a prospective case-control study performed at a single tertiary care hospital in Baltimore, Maryland, after institutional review board approval. The study population included all adult patients who tested positive (case patients) or negative (control individuals) for COVID-19 by nasopharyngeal swab between March 9, 2020, and April 15, 2020. A telephone survey was conducted to obtain information including demographics, comorbid conditions, GI symptoms, respiratory symptoms, fever, gustatory symptoms, olfactory symptoms, and need for hospitalization by using a predesigned questionnaire. The primary outcome was the prevalence of GI symptoms in COVID-19–positive and –negative patients, and the secondary outcomes were to determine the utility of GI symptoms for COVID-19 screening and the association of GI symptoms with need for hospitalization. Logistic regression and univariate followed by multivariable analysis using a backward model selection approach were conducted to evaluate risk factors of COVID-19, and the area under the receiver operating characteristic (AUROC) for COVID-19 using a combination of different symptoms was determined.

Results

The demographics of 340 patients (COVID-19 positive, 101; COVID-19 negative, 239) included in the study are shown in Table 1. The COVID-19 patients were more likely to be men and have higher body mass index and were less likely to be smokers. Otherwise, comorbidities were similar in both groups.

GI symptoms were more common (74% vs 53%; $P < .001$) in patients with COVID-19 compared to COVID-19–negative patients; patients with COVID-19 were more likely to have anorexia (53% vs 26%; $P < .001$) and diarrhea (50% vs 30%; $P < .001$). Other GI symptoms such as nausea, vomiting, abdominal pain, and hematochezia were similar in both groups. Loss of smell or taste (67% vs 14%; $P < .0001$) and fever (65% vs 44%; $P < .001$) were more prevalent in COVID-19–positive patients. The median duration of symptoms before COVID-19 testing was not significantly different between COVID-19–positive and –negative patients (4 days; interquartile range, 5; $P = .549$) (Table 1). There was no significant difference in hospitalization and mean days to testing between patients with COVID-19 with or without any GI symptoms.

Multivariable analysis showed that African American patients (odds ratio [OR] 2.62; 95% confidence interval [CI], 1.38–4.99; $P = .003$) and men (OR, 3.23; 95% CI, 1.68–6.20; $P < .001$) were more likely to test positive for COVID-19. Loss of smell (OR, 8.29; 95% CI, 3.56–19.28; $P < .001$) or taste (OR, 3.41; 95% CI, 1.53–7.61; $P < .003$) and fever (OR, 2.14; 95% CI, 1.17–3.92; $P = .014$) were the symptoms most likely to be associated with COVID-19. Diarrhea and anorexia alone were not specific for COVID-19 infection on multivariable analyses. However, the specificity for COVID-19 infection was 99% if patients had symptoms of diarrhea and anorexia in addition to fever and loss of smell and taste, and the negative predictive value was 75%. The specificity (94%–95%) was only marginally lower if patients had fever with loss of smell or taste (Supplementary Table 1). The AUROC was good (0.74) for a combination of fever with loss of smell or taste; including diarrhea (0.72), anorexia (0.71) or both anorexia and diarrhea (0.71) to fever with taste or smell did not improve the AUROC (Supplementary Figure 1).

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Table 1. Demographics, Comorbidities, and Symptoms of COVID-19–Positive and COVID-19–Negative Patients

Variable	All (N = 340)	Negative (n = 239)	Positive (n = 101)	*P* value
Age, *y*, mean ± SD	46.89 ± 15.34	46.30 ± 15.57	48.32 ± 14.74	.28
Race, n (%)				.21
White	163 (48)	122 (51)	41 (41)	
African American	153 (45)	101 (42)	52 (51)	
Other	24 (7)	16 (7)	8 (8)	
Male sex, n (%)	96 (28)	55 (23)	41 (41)	<.001
BMI, kg/m^2, mean ± SD	29.87 ± 7.23	29.24 ± 7.41	31.28 ± 6.65	.03
Asthma, n (%)	71 (21)	56 (24)	15 (15)	.06
CAD, n (%)	15 (4)	10 (4)	5 (5)	.78
COPD, n (%)	17 (5)	15 (6)	2 (2)	.09
Cancer, n (%)	14 (4)	13 (6)	1 (1)	.06
DM, n (%)	41 (12)	27 (11)	14 (14)	.54
HLD, n (%)	52 (20)	33 (19)	19 (24)	.36
HTN, n (%)	99 (30)	67 (29)	32 (32)	.59
IBD, n (%)	5 (2)	3 (1)	2 (2)	.63
Immunosuppression, n (%)	18 (5)	15 (6)	3 (3)	.21
Liver disease, n (%)	13 (4)	12 (5)	1 (1)	.08
NSAID, n (%)	90 (27)	61 (26)	29 (29)	.58
OSA, n (%)	23 (7)	15 (6)	8 (8)	.61
Smoker, n (%)				.05
No	229 (72)	158 (70)	71 (75)	
Current	34 (11)	30 (13)	4 (4)	
Former	57 (18)	37 (16)	20 (21)	
Symptoms, n (%)				
Any gastrointestinal symptoms	201 (59)	126 (53)	75 (74)	<.001
Nausea	92 (27)	62 (26)	30 (30)	.48
Vomiting	43 (13)	29 (12)	14 (14)	.66
Diarrhea	123 (36)	72 (30)	51 (50)	<.001
Abdominal pain	72 (21)	46 (19)	26 (26)	.18
Loss of appetite	117 (34)	63 (26)	54 (53)	<.001
Hematochezia	7 (2)	6 (3)	1 (1)	.37
Loss of smell or taste	101 (30)	33 (14)	68 (67)	<.001
Loss of smell	81 (24)	21 (9)	60 (59)	<.001
Loss of taste	86 (25)	26 (11)	60 (59)	<.001
Any fever or respiratory symptoms	304 (89)	208 (87)	96 (95)	.03
Cough	242 (71)	167 (70)	75 (74)	.42
Fever	170 (50)	104 (44)	66 (65)	<.001
SOB	167 (49)	116 (49)	51 (50)	.74
Hospitalization, n (%)	33 (10)	18 (8)	15 (15)	.03
Median days of symptoms before getting tested (IQR)	4 (5)	4 (5)	4 (4)	.55
ICU-level care, n (%)	8 (2)	5 (2)	3 (3)	.61

BMI, Body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; IBD, inflammatory bowel disease; ICU, intensive care unit; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnea; SD, standard deviation; SOB, shortness of breath.

Discussion

To our knowledge, this is the first prospective case-control study of GI symptoms in patients with COVID-19. We found a high prevalence of GI symptoms (74%) in patients with COVID-19, with the most common GI symptoms being anorexia (53%) and diarrhea (50%). However, GI symptoms were also prevalent (53%) in COVID-19–negative patients, and multivariable analysis showed that GI symptoms were not associated with an increased likelihood of testing positive for COVID-19. This has not yet been reported in prior studies, which have been limited by a retrospective review of symptoms done in hospitalized patients. The strength of our study is the prospective design with a predesigned questionnaire and negative control group, which removes some of the inherent bias present in retrospective chart reviews.

Other studies have reported increased severity of symptoms and a longer time to diagnosis in patients with COVID-19 with GI symptoms.[2,7,8] These studies are limited by the potential bias due to a retrospective review of symptoms done primarily in hospitalized patients. Using patients who tested negative for COVID-19 as a control group in our study perhaps gives a more accurate representation of GI symptoms in patients with COVID-19. Our study of mostly outpatients with mild to moderate

symptoms did not show increased hospitalization rates or ICU care needs for patients with COVID-19 with GI symptoms. This may partly be due to an increased awareness of GI symptom prevalence in COVID-19 and, hence, increased screening.

With regard to other symptoms, the loss of smell/taste and fever were strongly associated with testing positive for COVID-19 (AUROC, 0.74; specificity, 94%–96%; negative predictive value, 77%–78%). Furthermore, patients without any symptoms of fever, loss of smell/taste, diarrhea, and anorexia had a negative predictive value of 75% (specificity, 99%) for not having COVID-19 infection. The negative predictive value is likely to improve as the prevalence of disease decreases, with increased testing making the screening of these symptoms even more important. Our study is limited to a mostly outpatient patient population and was performed at a single center. However, the study size, negatively tested control group, and prospective nature increase its generalizability.

In conclusion, GI symptoms, especially anorexia and diarrhea, are very common in COVID-19 but also common in patients who test negative. However, symptoms of anorexia and diarrhea combined with loss of smell/taste and fever are 99% specific for COVID-19 infection. Current testing guidelines should highlight the symptoms of loss of smell and taste, fever, anorexia, and diarrhea as highly specific for COVID-19 infection.

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.2020.05.036.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Methods

Study Design and Population

This was a prospective, telephone survey–based study comparing patients tested for COVID-19 at all testing points within our integrated health care system (inpatient setting, emergency department, and outpatient setting). Institutional review board approval was obtained to perform this study, and informed consent was obtained verbally. All patients who received at least 1 nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (hereafter referred to as *COVID-19 test*) were identified by an audit of the electronic medical record, and the list was refreshed every week. The institution provided access to the electronic medical records of all patients who were tested at the hospital.

All patients with either a positive or negative result were included; patients who were ordered a test but did not complete the test or for whom the test was still in process at time of data collection were excluded. Patients were called by telephone, the research study was described, and they were given the option to consent to their participation in the survey and allow the research to review their electronic medical records; if a patient declined to participate or did not answer the telephone after a maximum of 3 attempts, he or she was excluded from the study. Furthermore, patients younger than 18 years were excluded. All telephone interviews were conducted by board-certified GI or hepatology fellows by a predesigned questionnaire.

Telephone Survey

After telephone consent was obtained, the following data points were collected from each patient and recorded in a secure database: age, sex, primary zip code, employment status (currently employed, unemployed, or recently furloughed or laid off because of COVID-19), contact with any person with confirmed COVID-19, contact with any person who was ill regardless of COVID-19 testing status, number of days of any symptoms that prompted the COVID-19 test, site of test (inpatient, emergency department, our outpatient facility), and if they had any of the following symptoms or comorbidities.

Symptoms

Patients were asked if they had any of the following symptoms during their disease course, and if they affirmed having any symptom, we determined whether it was an initial symptom or occurred later in the illness course. The symptoms were divided into GI (nausea, vomiting, diarrhea, abdominal pain or discomfort, loss of appetite, blood in stools), gustatory/olfactory (loss or change in smell, loss or change in taste), respiratory (cough, shortness of breath), or fever/chills.

Comorbidities

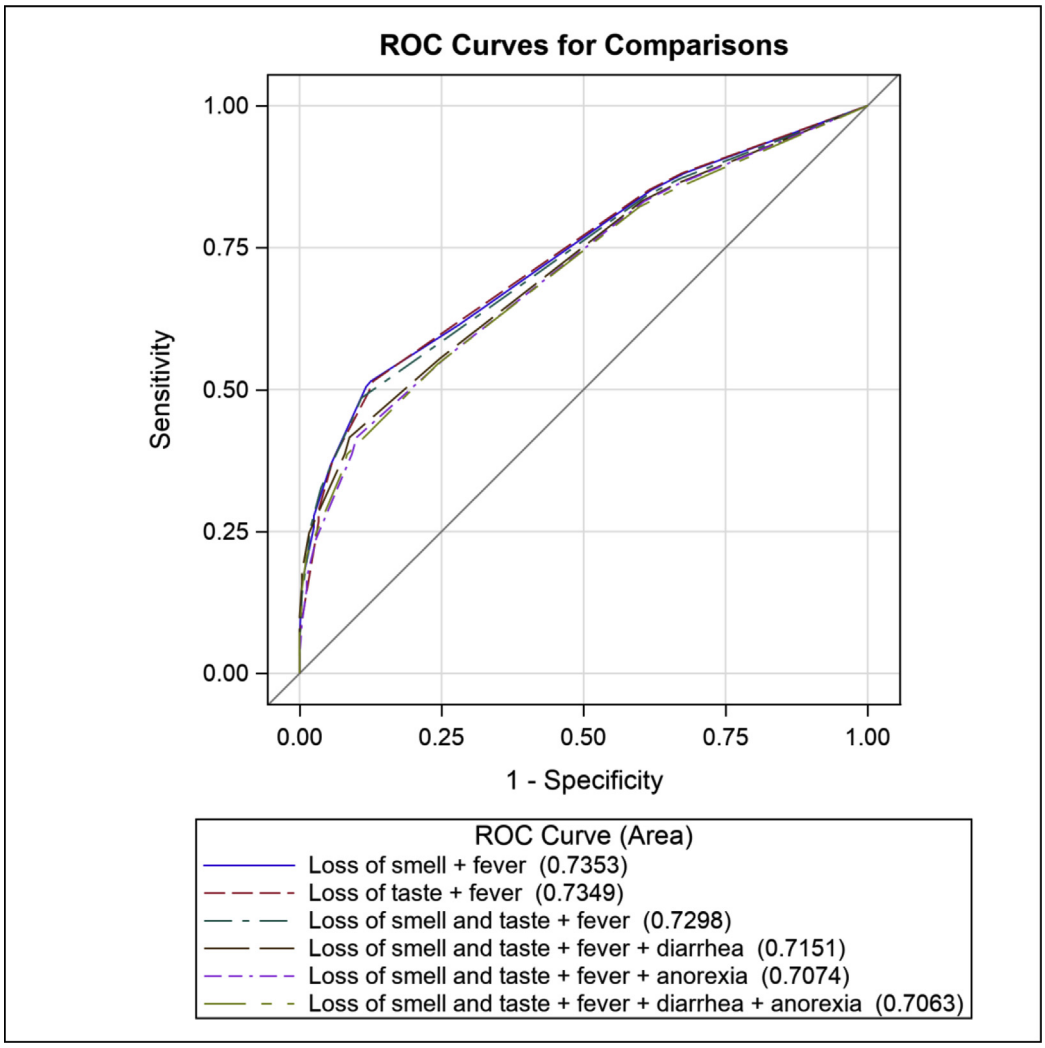
Comorbidities included heart disease (cardiomyopathy or coronary artery disease), lung disease (chronic obstructive pulmonary disease, sleep apnea, or asthma), tobacco use status (current smoker, former smoker, or never smoker), diabetes mellitus, chronic liver disease, hypertension, hyperlipidemia, inflammatory bowel disease, and active cancer diagnosis of any type. Each patient's body mass index was calculated using self-reported height and weight information. Patients were also asked if they were taking any immunosuppression medication or using nonsteroidal anti-inflammatory drugs during their illness.

Outcomes

The primary outcome was relative risk of GI symptoms in patients with confirmed-positive COVID-19 compared to confirmed COVID-19–negative control individuals. The secondary outcome was frequency of GI symptoms as initial or presenting symptoms compared between positive case patients and negative control individuals.

Statistical Analysis

Descriptive statistics of patients' characteristics are presented as means and standard deviations or median (interquartile range) for continuous variables and as frequencies for categorical variables. The differences in patients' characteristics between those who were COVID-19 positive and negative were assessed by using the chi-squared test for categorical variables and t test for continuous variables; normality was checked for all continuous variables, and the nonparametric Wilcoxon test was used when data were not normally distributed. Logistic regression was conducted to evaluate risk factors of COVID-19. We started with univariate analysis, followed by multivariable analysis using a backward model selection approach. The final model was selected by balancing goodness of fit (eg, Bayesian information criteria). The final model retained variables with a P value of .05 or less. Estimations of adjusted ORs and 95% CIs were reported. All analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).



Supplementary Figure 1. The AUROC for COVID-19 infection using a combination of different symptoms.

Supplementary Table 1. Models' Predictive Accuracy Based on Different Symptoms

Symptoms	Sensitivity	Specificity	PPV	NPV	Accuracy
Fever + loss of taste + loss of smell (n = 42)	0.33	0.96	0.79	0.77	0.77
Fever + loss of smell (n = 50)	0.37	0.95	0.74	0.78	0.77
Fever + loss of taste (n = 52)	0.38	0.94	0.73	0.78	0.77
Fever + loss of taste + loss of smell + diarrhea + anorexia (n = 24)	0.21	0.99	0.88	0.75	0.76
Fever + loss of taste + loss of smell + diarrhea (n = 29)	0.25	0.98	0.86	0.76	0.76
Fever + loss of taste + loss of smell + anorexia (n = 31)	0.24	0.97	0.77	0.75	0.75

NPV, negative predictive value; PPV, positive predictive value.