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Are Gastrointestinal Symptoms Specific for COVID-19 Infection?

A Prospective Case-Control Study from the United States

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INTRODUCTION

The reported prevalence of gastrointestinal (GI) symptoms, including anorexia, diarrhea, nausea, vomiting, and abdominal pain, in SARS-2-CoV infection has been highly variable ranging from 5-61%.[1-7] Although the Centers for Disease Control (CDC) guidelines for testing for COVID-19 include vomiting and diarrhea, all studies to date have been retrospective and none have evaluated the prevalence of GI symptoms among patients 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 the approval of Institutional Review Board. The study population included all adult patients who were tested positive (cases) or negative (controls) 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, respiratory, fever, gustatory, olfactory symptoms, and need for hospitalization 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 and need for hospitalization. Logistic regression, univariate followed by multivariable analysis using a backward model selection approach, was 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, negative 239) included in the study are shown in table 1. The COVID-19 patients were more likely to be men, have higher BMI, and less likely to be smokers. Otherwise, comorbidities were similar in both groups.

GI symptoms were more common (74% vs. 53%, p< 0.001) in COVID-19 patients compared COVID-19 negative patients; COVID-19 patients were more likely to have anorexia (53% vs 26%, p<0.001) and diarrhea (50% vs 30%, p<0.001). 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<0.0001) and fever (65% vs. 44%, p<0.001) 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 [IQR, 5]), p=0.549) (Table 1). There was no significant difference in hospitalization and mean days to testing between COVID-19 patients with or without any GI symptoms.

Multivariable analysis showed that African-Americans (OR 2.62, 95% CI 1.38-4.99; p=0.003) and men (OR 3.23, 95% CI 1.68-6.20; p<0.001) were more likely to test positive for COVID-19. Loss of smell (OR 8.29, 95% CI 3.56-19.28; p<0.001) or taste (OR 3.41, 95% CI 1.53-7.61; p<0.003) and fever (OR 2.14, 95% CI 1.17-3.92; p=0.014) 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, 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 table1). The area under the receiver operating characteristic (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 AUROC (supplementary figure 1).

DISCUSSION

To our knowledge, this is the first prospective case-control study of GI symptoms in COVID-19 patients. We found a high prevalence of GI symptoms (74%) in COVID-19 patients, 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 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 COVID-19 patients 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 tested negative for COVID-19 as a control group in our study perhaps gives a more accurate representation of GI symptoms in COVID-19 patients. Our study of mostly outpatients with mild to moderate symptoms did not show increased hospitalization rate or ICU care needs for COVID-19 patients with GI symptoms. This may partly be due to an increased awareness of GI symptom prevalence in COVID-19 and hence increased screening.

With regards 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%, NPV 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, the 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 is 99% specific for COVID-19 infection. Current testing guidelines should highlight the symptoms of loss of smell, taste, fever, anorexia, and diarrhea as highly specific for COVID-19 infection.

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Table 1: Demographics, comorbidities and symptoms of COVID-19 positive and negative patients

Variable	Groups	All (N=340)	Negative (N=239)	Positive (N=101)	p-value
Age (Mean ± SD)		46.89 ± 15.34	46.30 ± 15.57	48.32 ± 14.74	0.28
Race					0.21
	Caucasian	163 (48%)	122 (51%)	41 (41%)	
	African American	153 (45%)	101 (42%)	52 (51%)	
	Other	24 (7%)	16 (7%)	8 (8%)	
Sex (Men)		96 (28%)	55 (23%)	41 (41%)	<.001
BMI (Mean ± SD)		29.87 ± 7.23	29.24 ± 7.41	31.28 ± 6.65	0.03
Asthma		71 (21%)	56 (24%)	15 (15%)	0.06
CAD		15 (4%)	10 (4%)	5 (5%)	0.78
COPD		17 (5%)	15 (6%)	2 (2%)	0.09
Cancer		14 (4%)	13 (6%)	1 (1%)	0.06
DM		41 (12%)	27 (11%)	14 (14%)	0.54
HLD		52 (20%)	33 (19%)	19 (24%)	0.36
HTN		99 (30%)	67 (29%)	32 (32%)	0.59
IBD		5 (2%)	3 (1%)	2 (2%)	0.63
Immunosuppression		18 (5%)	15 (6%)	3 (3%)	0.21
Liver disease		13 (4%)	12 (5%)	1 (1%)	0.08
NSAID		90 (27%)	61 (26%)	29 (29%)	0.58
OSA		23 (7%)	15 (6%)	8 (8%)	0.61
Smoker					0.05
	No	229 (72%)	158 (70%)	71 (75%)	
	Current	34 (11%)	30 (13%)	4 (4%)	
	Former	57 (18%)	37 (16%)	20 (21%)	
SYMPTOMS					
Any Gastrointestinal Symptoms		201 (59%)	126 (53%)	75 (74%)	<.001
Nausea		92 (27%)	62 (26%)	30 (30%)	0.48
Vomiting		43 (13%)	29 (12%)	14 (14%)	0.66
Diarrhea		123 (36%)	72 (30%)	51 (50%)	<.001
Abdominal pain		72 (21%)	46 (19%)	26 (26%)	0.18

Anorexia	117 (34%)	63 (26%)	54 (53%)	<.001
Hematochezia	7 (2%)	6 (3%)	1 (1%)	0.37
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%)	0.03
Cough	242 (71%)	167 (70%)	75 (74%)	0.42
Fever	170 (50%)	104 (44%)	66 (65%)	<.001
SOB	167 (49%)	116 (49%)	51 (50%)	0.74
Hospitalization	33 (10%)	18 (8%)	15 (15%)	0.03
Median days of symptoms before getting tested (IQR)	4 (5)	4 (5)	4 (4)	0.55
ICU level of care	8 (2%)	5 (2%)	3 (3%)	0.61

Abbreviations: 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, NSAID: Non-steroidal anti-inflammatory drugs, OSA: Obstructive sleep apnea, SOB: Shortness of breath.

GASTRO-D-20-01329 - SUPPLEMENTARY FILE

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 healthcare system (inpatient setting, emergency room, 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 one nasopharyngeal swab for SARS-CoV-2 (hereafter referred to as 'COVID-19 test') were identified by an audit of the electronic medical record (EMR), and the list was refreshed every week. Institution provided access to the EMR 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 if the test was still in process at time of data collection, were excluded. Patients were called by telephone and 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 patient declined to participate or they did not answer the telephone after a maximum of three attempts, they were excluded from the study. Further, patients under the age of 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 due to 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 room, 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 gastrointestinal (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**:* Heart disease (cardiomyopathy or CAD), lung disease (chronic obstructive pulmonary disease[COPD], sleep apnea [OSA], or asthma), tobacco use status (current smoker, former smoker, or never smoker), diabetes mellitus (DM), chronic liver disease, hypertension (HTN), hyperlipidemia (HLD), inflammatory bowel disease (IBD), active cancer diagnosis of any type. Patient's body mass index was calculated using self-reported height and weight information. Patients were also asked if they were on any immunosuppression medication or use non-steroidal anti-inflammatory drugs (NSAIDs) during their illness.

***Outcomes**:* Primary outcome was relative risk of gastrointestinal symptoms in confirmed positive COVID-19 cases as compared to confirmed negative COVID-19 controls. Secondary outcome was frequency of gastrointestinal symptoms as initial or presenting symptom, compared between positive cases and negative controls.

***Statistical analysis**:* Descriptive statistics patients' characteristics are presented as means and standard deviations (SDs) or median (IQR) for continuous variables, and frequencies for categorical variables. The differences in patients' characteristics between Covid-19 positive and negative were assessed by using Chi-square test for categorical variables, and T test for

continuous variables; normality was checked for all the continuous variables, and nonparametric Wilcoxon test was used when data were not normally distributed. Logistic regression was conducted to evaluate risk factors on 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 (e.g., Bayesian information criteria). The final model retained variables with a p-value 0.05 or less. Estimations of adjusted odds ratios and 95% CI were reported. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

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

PPV – positive predictive value; NPV – negative predictive value

SUPPLEMENTARY FIGURE 1: The area under the receiver operating characteristic (AUROC) for COVID-19 infection using a combination of different symptoms