ORIGINAL ARTICLE

Prevalence of *Clostridioides difficile* and Other Gastrointestinal Pathogens in Patients with COVID-19

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Abstract

Background Gastrointestinal symptoms are common in patients with COVID-19, but prevalence of co-infection with enteric pathogens is unknown.

Aims This study assessed the prevalence of enteric infections among hospitalized patients with COVID-19.

Methods We evaluated 4973 hospitalized patients ≥ 18 years of age tested for COVID-19 from March 11 through April 28, 2020, at two academic hospitals. The primary exposure was a positive COVID-19 test. The primary outcome was detection of a gastrointestinal pathogen by PCR stool testing.

Results Among 4973 hospitalized individuals, 311 were tested for gastrointestinal infections (204 COVID-19 positive, 107 COVID-19 negative). Patients with COVID-19 were less likely to test positive compared to patients without COVID-19 (10% vs 22%, $p < 0.01$). This trend was driven by lower rates of non-*C.difficile* infections (11% vs 22% in COVID-19 positive vs. negative, respectively, $p = 0.04$), but not *C. difficile* infection (5.1% vs. 8.2%, $p = 0.33$). On multivariable analysis, infection with COVID-19 remained significantly associated with lower odds of concurrent GI infection (aOR 0.49, 95% CI 0.24–0.97), again driven by reduced non-*C.difficile* infection. Testing for both *C.difficile* and non-*C.difficile* enteric infection decreased dramatically during the pandemic.

Conclusions Pathogens aside from *C.difficile* do not appear to be a significant contributor to diarrhea in COVID-19 positive patients.

Keywords COVID-19 · SARS-CoV-2 · *Clostridioides difficile* · Enteric infection · Diarrhea

Abbreviations

C. difficile	Clostridioides difficile
GI	Gastrointestinal
COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

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Introduction

The 2019 coronavirus disease (COVID-19) has become a global pandemic with cases spreading rapidly throughout the world. While fever and cough are the most common symptoms associated with this disease, gastrointestinal manifestations have also been noted in 32 to 61% of individuals [1–8]. Diarrhea, in particular, has been reported in 4 to 34% of individuals in cohorts from China and 12 to 34% in cohorts from the USA [2–8].

A likely mechanism for the prevalence of gastrointestinal symptoms in patients with COVID-19 is the presence of Angiotensin Converting Enzyme 2 (ACE2) receptors on gut epithelial cells, a well-described target for viral binding and entry [9, 10]. Nonetheless, it is also possible that intestinal inflammation due to COVID-19 could predispose individuals to co-infection with other gastrointestinal pathogens. Thus far, only one prior study from Wuhan, China, evaluated whether co-infection with enteric pathogens plays a prominent role in this presentation, finding no evidence of enteric pathogens by stool culture in 74 patients with COVID-19 and gastrointestinal symptoms [8].

Highly sensitive and specific stool polymerase chain reaction-based assays have improved the ability to diagnose gastrointestinal infections, including those caused by *Clostridioides difficile* (*C. difficile*), and are routinely used at our institution [11, 12]. Such infections, particularly *C.difficile*, can cause a significant burden to infected individuals thus making recognition and treatment key [13, 14]. This retrospective cohort study aimed to evaluate the prevalence of co-infection with gastrointestinal pathogens among admitted patients with and without COVID-19 infection. In addition, we aimed to compare institution-wide patterns in gastrointestinal infection testing and rates of positive cases before and after the start of the COVID-19 pandemic in New York City.

Methods

Study Design

This retrospective study evaluated 4973 hospitalized patients ≥ 18 years of age who underwent testing for COVID-19 from March 11, 2020, (when institution-based testing began) through April 28, 2020, at two affiliated academic medical centers (Columbia University Irving Medical Center and Allen Hospital). The primary exposure of interest was a positive COVID-19 test, defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab specimens testing for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The primary outcome of interest was the detection of a gastrointestinal (GI) pathogen (*C. difficile* and non-*C. difficile*) during the index hospitalization by PCR test of the stool. Data regarding duration of GI symptoms with COVID-19 is limited, but one study from China found that COVID-19 positive patients with GI symptoms alone had on average 16 days from initial symptom onset to hospital admission and 31 days from symptom onset to viral clearance [15]. Therefore, stool tests performed either 2 weeks before or at any time after SARS-CoV-2 testing were included in order to capture an adequate time period during which patients may have had symptoms related to COVID-19. The institutional laboratory policy during this period was that only unformed stools would be tested for enteric pathogens (i.e., implying that all tested patients did indeed have diarrhea). It was at the discretion of the provider caring for the patient whether to order a *C.difficile* PCR stool test, a gastrointestinal pathogen PCR panel stool test, or both tests. Secondary variables of interest were age, sex, body mass index (BMI), and race/ethnicity. Stool studies performed from February 1, 2020 to April 17, 2020 were used to determine trends in testing patterns before and during the pandemic.

Gastrointestinal Pathogen PCR Panel Stool Test

Gastrointestinal pathogens were identified using the FilmArray gastrointestinal pathogen PCR panel (GI PCR; BioFire Diagnostics, Salt Lake City, UT). This assay allows for simultaneous detection and identification of nucleic acids from multiple bacteria, viruses, and parasites directly from spontaneously voided stool samples. The assay identifies 20 pathogens including Adenovirus, Astrovirus, *Campylobacter*, *Cryptosporidium*, *Cyclospora*, *Entamoeba histolytica*, Enteroaggregative *E. coli*, Enteropathogenic *E. coli*, Enterotoxigenic *E. coli*, *Giardia*, Norovirus, *Plesiomonas shigelloides*, Rotavirus, *Salmonella* species, Sapovirus, Shigalike toxin-producing *E. coli* STX/ST2, Shigella/Enteroinvasive *E. coli*, *Vibrio cholerae*, *Vibrio* species, and *Yersinia enterocolitica*.

Clostridioides difficile Testing

C.difficile PCR testing was done via PCR for the toxin B gene (Xpert C. difficile, Cepheid, Sunnyvale, CA). At our institution, this test is ordered separately from and/or in addition to the GI PCR test panel at the discretion of the ordering provider. There is an institutional electronic "hard stop" that prohibits stool PCR testing in patients who have received laxatives within the previous 24 h.

Statistical Analysis

Continuous variables were expressed as medians or interquartile ranges, with Wilcoxon rank-sum test used to assess differences in distributions between the groups. Categorical variables were summarized as counts and percentages, with Chi-square or Fisher's exact tests used for comparison. A multivariable model was built to examine whether COVID-19 was independently associated with gastrointestinal infection after adjusting for all included variables. A modified Charlson comorbidity index was utilized, which incorporated weighted values of all components of the index (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus, chronic kidney disease, hemiplegia, leukemia, lymphoma, solid tumor, liver disease, and AIDS) but excluded age since it was included separately in our multivariable model. An alpha of 0.05 was considered statistically significant. Statistical calculations were performed in STATA 16 (Stata Corp, College Station, TX). This study was approved by the Institutional Review Board of Columbia University Medical Center.

Results

We identified 4973 individuals requiring inpatient admission who were tested for COVID-19 between March 11, 2020 and April 28, 2020 at two affiliated academic centers in New York City. 2870 (58%) were COVID-19 positive and 2103 (42%) tested negative. Among these individuals, 311 were also tested for gastrointestinal infections in either the 2 weeks prior or at any time after their SARS-CoV-2 PCR, including 204 COVID-19 positive and 107 COVID-19 negative patients. 261 patients were tested for *C. difficile* infection and 195 patients were tested for non-*C. difficile* infection, with 145 patients being tested for both.

Of the 311 patients with stool studies, there was no difference in age or sex between COVID-19 positive and negative individuals (see Table 1). Significantly more non-Hispanic whites were tested in the COVID-19 negative group (31%, compared to 16% in positive patients), while more Hispanics were tested among the COVID-19 positive cohort (35%, compared to 30% in negatives; see Table 1). More of the COVID-19 positive patients were also overweight or obese with a BMI ≥ 25 (69% vs. 48%, $p < 0.01$). There was a significantly higher proportion of COVID-19 negative patients with a modified Charlson comorbidity index ≥ 2 than COVID-19 positive patients (68% vs. 34% respectively, $p < 0.01$).

COVID-19 positive patients had a significantly longer median length of stay than COVID negative patients (14.6

vs. 7.7, respectively, $p < 0.01$) and were more likely to be tested for *C. difficile* later during hospitalization (73% tested > 72 h after admission, compared to 52% in COVID-19 negative patients; $p < 0.01$; see Table 1). However, there was minimal difference in the timing of testing for non-*C. difficile* enteric pathogens, comparing those with versus those without COVID-19 ($p = 0.06$, Table 1). Among all 4,973 patients, COVID-19 positive patients were tested more often for *C. difficile* compared to COVID-19 negative patients, but there was no significant difference in rates of testing for other GI pathogens (Supplementary Table 1).

COVID-19 positive patients were less likely to have any GI infection overall compared to COVID-19 negative patients (10% vs 22%, $p < 0.01$, Table 2). This trend persisted when evaluating only non-*C. difficile* infection (11% vs 22%, $p = 0.04$). However, no significant difference was seen between the two groups in testing positive for *C. difficile* infection. Of the non-*C. difficile* pathogens, enteropathogenic *E. coli* and enteroaggregative *E. coli* were the most common, found in 2.7% and 2.9% of patients with a GI PCR test, respectively. Seven patients had multiple GI pathogens detected on the GI PCR panel, including five patients with two pathogens detected and two patients with three pathogens detected. Of these, four were COVID-19 positive and three were negative. One additional patient had *C. difficile* infection as well as a second pathogen detected on the GI PCR panel. There were no significant differences in the rates or types of gastrointestinal pathogens detected in individuals with severe COVID-19 (resulting in intubation and/or death) and those with a milder course of COVID-19 (Supplementary Tables 2 and 3).

Of individuals with stool studies during the study period, those with COVID-19 were less likely to have a GI infection on univariable analysis (69% vs 47%, $p < 0.01$, Table 3). On multivariable analysis, infection with COVID-19 remained significantly associated with lower odds of GI infection in tested patients after adjusting for age, sex, BMI, and race/ethnicity (aOR 0.49, 95% CI 0.24–0.97, $p = 0.04$, Table 4).

We also evaluated the trend in GI PCR and *C. difficile* testing before and after the beginning of the COVID-19 pandemic. COVID-19 testing became widely available at our institution on March 11, 2020. As shown in Fig. 1, as of March 14, testing for both *C. difficile* and non-*C. difficile* enteric infection decreased dramatically, with the lowest volume of testing observed at the end of March. In April, *C. difficile* testing increased, approaching pre-pandemic rates, whereas GI PCR testing rates remained lower than pre-pandemic rates.

Table 1 Characteristics of COVID-19 + and COVID-19 – patients with stool studies

Variables	All $n=311$	COVID+ n (%) $n=204$	COVID- n (%) $n=107$	p Value
Age, years				
Mean (SD)	62.5 (16.5)	62.9 (15.6)	61.7 (19.3)	0.57
Median (IQR)	64.7 (53.2–74.6)	63.9 (53.6–73.2)	65.9 (50.3–75.5)	0.98
Distribution n (%)				
18–39	36 (12)	20 (10)	16 (15)	0.25
40–59	75 (24)	51 (25)	24 (22)	
60–74	125 (40)	88 (43)	37 (35)	
75+	75 (24)	45 (22)	30 (28)	
Male Sex n (%)	187 (60)	125 (61)	62 (58)	0.57
Race/ethnicity n (%)				
Non-Hispanic White	66 (21)	33 (16)	33 (31)	0.01
Hispanic	103 (33)	71 (35)	32 (30)	
Black	80 (26)	51 (25)	29 (27)	
Asian	5 (2)	4 (2)	1 (1)	
Other	57 (18)	45 (22)	12 (11)	
BMI n (%)				
<25	95 (30)	50 (25)	45 (42)	<0.01
25–30	90 (30)	67 (33)	23 (22)	
>30	102 (33)	74 (36)	28 (26)	
Unknown	24 (7)	13 (6)	11 (10)	
Modified Charlson comorbidity				
Score				
0	90 (29)	68 (33)	22 (21)	<0.01
1	59 (19)	47(23)	12 (11)	
2+	162 (52)	89 (34)	73 (68)	
Time of stool studies relative to SARS-CoV-2 test				
C. difficile ($n=261$)				
2 weeks before	13 (5)	7 (4)	6 (7)	0.51
30 days after	239 (92)	157 (92)	82 (91)	
>30 days after	9 (3)	7 (4)	2 (2)	
Other GI pathogens ($n=195$)				
2 weeks before	15 (8)	5 (4)	10 (13)	0.03
30 days after	180 (92)	112 (96)	68 (87)	
>30 days after	0 (0)	-	-	
Time of stool studies relative to Admission				
C. difficile				
Before admission	7 (3)	3 (2)	4 (5)	<0.01
Within 72 h of admission	82 (31)	45 (25)	37 (43)	
>72 h post-admission	172 (66)	128 (73)	44 (52)	
Other GI pathogens				
Before admission	7 (4)	2 (2)	5 (6)	0.06
Within 72 h of admission	94 (48)	52 (44)	42 (54)	
>72 h post-admission	94 (48)	63 (54)	31 (40)	
Length of stay[†]—Median (IQR)	12.5 (6.2–25.1)	14.6 (8.3–26.3)	7.7 (4.7–17.1)	<0.01

[†]Patients still currently admitted were censored at the conclusion of the study on 4/28/20

Table 2 GI pathogen detection rates in COVID-19 + and COVID-19—patients with stool studies

Variables	All	COVID+ *n* (%)	COVID- *n* (%)	P value
Any GI pathogen, n = 311				
Positive	45 (14.5)	21 (10.3)	24 (22.4)	< 0.01*
Negative	266 (85.5)	183 (89.7)	83 (77.6)	
C. difficile, n = 261				
Positive	16 (6.1)	9 (5.1)	7 (8.2)	0.33
Negative	245 (93.9)	167 (94.9)	78 (91.8)	
Other GI pathogens, n = 195				
Positive	30 (15.4)	13 (11.1)	17 (21.8)	0.04*
Negative	165 (84.6)	104 (88.9)	61 (78.2)	
Other GI pathogens, n = 195				
Adenovirus	0 (0)	0 (0)	0 (0)	
Astrovirus	0 (0)	0 (0)	0 (0)	
Campylobacter	2 (0.6)	1 (0.5)	1 (0.9)	
Cryptosporidium	1 (0.3)	1 (0.5)	0 (0)	
Cyclospora	0 (0)	0 (0)	0 (0)	
Entameoba histolytica	0 (0)	0 (0)	0 (0)	
Enteroaggregative *E. coli*	8 (2.7)	4 (2.0)	4 (3.7)	
Enteropathogenic *E. coli*	9 (2.9)	5 (2.5)	4 (3.7)	
Enterotoxigenic *E. coli*	0 (0)	0 (0)	0 (0)	
Giardia	1 (0.3)	1 (0.5)	0 (0)	
Norovirus	4 (1.3)	1 (0.5)	3 (2.8)	
Plesiomonas shigelloides	0 (0)	0 (0)	0 (0)	
Rotavirus	4 (1.3)	1 (0.5)	3 (2.8)	
Salmonella species	2 (0.6)	2 (1.0)	0 (0)	
Sapovirus	2 (0.6)	0 (0)	2 (1.9)	
Shigalike toxin-producing *E. coli* STX/ST2	2 (0.6)	1 (0.5)	1 (0.9)	
Shigella/enteroinvasive E. coli	2 (0.6)	0 (0)	2 (1.9)	
Vibrio cholerae	0 (0)	0 (0)	0 (0)	
Vibrio species	0 (0)	0 (0)	0 (0)	
Yersinia enterocolitica	0 (0)	0 (0)	0 (0)	

Discussion

In this retrospective study of hospitalized patients tested for COVID-19, we found that patients with COVID-19 were less likely to test positive for co-infection with typical gastrointestinal pathogens compared to those without COVID-19. This difference was driven by non-*C. difficile* pathogens. *C. difficile* infection rates were similar among COVID-19 positive and negative patients, although patients with COVID-19 had longer median hospital stays and were diagnosed with *C. difficile* later during the course of hospitalization.

Despite the high prevalence of gastrointestinal symptoms described in COVID-19 patients [3–8], a relatively small percentage of patients overall were tested during the study period. Overall, rates of *C. difficile* testing were relatively unchanged by the COVID-19 pandemic whereas rates of testing for other GI pathogens were less than half normal.

Our study suggests that *C. difficile* should remain in the differential for patients presenting with diarrhea regardless of COVID-19 status, especially later in their admission, given that patients with COVID-19 had *C. difficile* infections at the same rates as those without COVID-19. Other gastrointestinal pathogens may be less likely in patients with COVID-19, though this may have been affected by decreased rates of testing.

To our knowledge, this is the first study to report the prevalence of co-infection with enteric pathogens using PCR-based stool assays in patients under evaluation for COVID-19. Disruption of normal mucosal defenses by one enteric infection is recognized as a risk factor for other infections, and prior studies have found that up to 26% of patients undergoing stool pathogen testing have multiple pathogens detected [16]. Only 0.9% of the overall study population were positive for an enteric infection,

Table 3 Univariable predictors of GI pathogen detection in patients with stool studies

Variables	All tested $n=311$	GI pathogen detected $n=45$	No GI pathogen detected $n=266$	p Value
COVID-19 infection	204 (66)	21 (47)	183 (69)	<0.01
Age, years mean (SD)	62.0 (16.5)	65.5 (14.8)	62.0 (16.8)	0.91
Male sex n (%)	187 (60)	29 (64)	158 (59)	0.52
Race/ethnicity n (%)				
Non-Hispanic white	66 (21)	13 (20)	53 (20)	0.25
Hispanic	103 (33)	17 (37)	86 (32)	
Black	80 (26)	10 (22)	70 (26)	
Other	62 (20)	5 (11)	57 (21)	
BMI n (%)				
<25 kg/m2	95 (30)	17 (38)	78 (29)	0.08
25–30 kg/m2	90 (29)	14 (31)	76 (29)	
>30 kg/m2	102 (33)	8 (18)	94 (35)	
Unknown	24 (8)	6 (13)	18 (7)	
Modified Charlson comorbidity score				
0 points	90 (28.9)	8 (17.8)	82 (30.8)	0.09
1 point	59 (19.0)	7 (15.6)	52 (19.6)	
2+ points	162 (52.1)	30 (66.6)	132 (49.6)	

Table 4 Multivariable model of predictors of GI pathogen detection in tested patients ($n=311$)

Variables	Odds ratio	Confidence interval	p Value
COVID-19 infection	0.49	0.24–0.97	0.04
Age (per additional year)	1.01	0.99–1.03	0.38
Male sex	1.31	0.66–2.62	0.44
Race/ethnicity			
Non-Hispanic white	Reference	–	
Hispanic	0.98	0.43–2.27	0.97
Black	0.7	0.28–1.77	0.45
Other	0.42	0.13–1.31	0.14
BMI			
<25 kg/m2	Reference	–	
25–30 kg/m2	1.1	0.48–2.51	0.81
>30 kg/m2	0.5	0.20–1.34	0.18
Unknown	1.44	0.48–4.38	0.51
Modified Charlson comorbidity score			
0 points	Reference	–	
1 point	1.65	0.54–5.00	0.38
2+ points	2.04	0.85–4.89	0.11

although the prevalence of infections among those who were actually tested for enteric pathogens was much higher, at 14.5%. The majority of gastrointestinal symptoms in COVID-19 patients may be attributable to the virus itself. This is in line with the findings of the study by Jin, et al. where 0 of 74 COVID-19 patients in China with gastrointestinal symptoms had positive stool cultures [8]. Aside from *C. difficile*, the most commonly identified enteric infections were *E. coli* species, which would be expected given these are relatively common pathogens. Although a similar number of COVID-19 positive and COVID-19 negative patients had multiple pathogens detected on GI PCR, this was observed in a small number of patients making it difficult to draw definitive conclusions regarding risks of co-infection in these populations.

Patients with COVID-19 likely have low rates of non- *C. difficile* enteric infections because SARS-CoV-2 itself is the cause of diarrhea on presentation; however, over time these patients become more similar to other hospitalized patients and have a similar rate of *C. difficile* infections compared to patients without COVID-19. This is particularly notable given that the standard of care for COVID-19 positive patients includes heightened contact precautions and hand hygiene. Furthermore, while COVID-19 positive patients had fewer comorbidities than COVID-19 negative patients, the similar rates of *C. difficile* infections in these groups speak to the power of prolonged hospitalization as a risk factor for this infection.

We also found that testing for enteric infections decreased at our institution since the onset of the COVID-19 pandemic. There are several possible explanations for this. First, during the COVID-19 pandemic, patients may be less likely to seek care for symptoms that may otherwise prompt presentation to a hospital, such as diarrhea. Second, some providers evaluating patients with diarrhea may attribute these symptoms to COVID-19 and therefore defer testing for enteric

Fig. 1 Trends in stool testing and results over time during COVID-19 pandemic (2/1/2020–4/11/2020) for **a** C. difficile testing and **b** gastrointestinal PCR testing
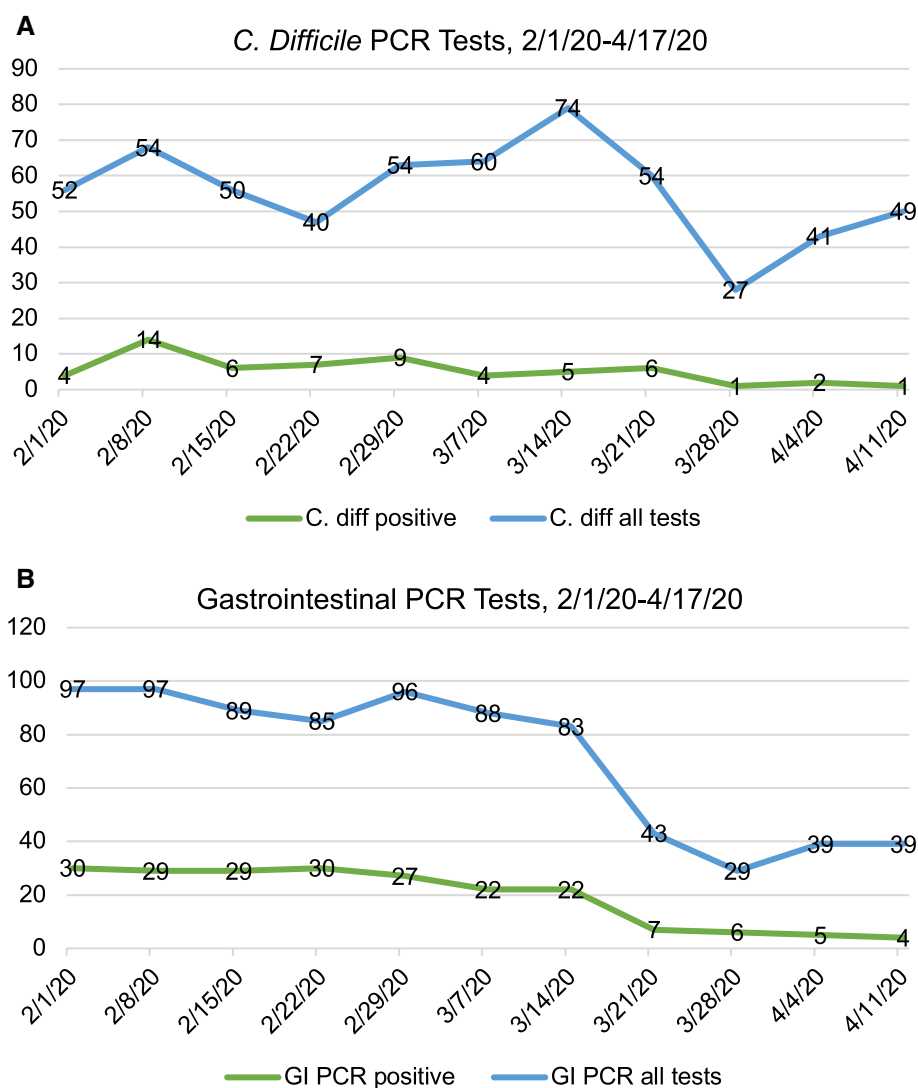
pathogens (although testing rates were significantly higher in COVID-19 positive than negative patients). It is also possible that, due to concerns over fecal shedding [17], providers may have been discouraged from ordering stool tests to limit nursing contact with stool specimens during collection. Not surprisingly, the rate of C. difficile testing, which nadired on March 28, seemed to subsequently be increasing. This is expected based on the number of critically ill patients and number of patients requiring broad spectrum antibiotics and longer hospital length of stay as the COVID-19 pandemic continued.

There are limitations to this study inherent to its retrospective and observational nature. These associations do not establish causality, and there may be an inherent bias in the types of patients that providers chose to test with stool studies in the setting of the pandemic. While this study was performed in high-volume centers, the testing

practice may be subject to institutional biases limiting generalizability. The ordering of the tests was done at the discretion of the physician caring for the patient. For some patients, only one of the two stool tests were available. There may have been differences in the approach to the workup of diarrhea given physicians were redeployed from different specialties and different institutions. Some may not have been aware of the availability of GI PCR testing options. Since the tests are collected in distinct containers, it is possible some may not have been run due to improper collection. Furthermore, both tests may not have been appropriate depending on the clinical scenario. We included all available results to maximize the available data. This study highlights the need for ongoing awareness among clinicians regarding the correct diagnosis of GI infections, particularly C. difficile, in these populations.

Despite the large study size, a relatively small absolute number of patients (311, 6.3%) underwent stool tests.

Prior reports from our institution demonstrated that 18% of individuals tested for COVID-19 presented with diarrhea, and 35% presented with gastrointestinal symptoms including nausea and vomiting [3]. Given that stool testing decreased institutionally as diarrhea become known as a COVID-19-related symptom, the actual prevalence of enteric infection among patients may have been underestimated in our study. In addition, a positive result on a gastrointestinal PCR test could represent chronic shedding or potential false positive, in addition to actual infectious gastroenteritis.

Conclusions

In conclusion, we identified that COVID-19 positive patients were less likely to test positive for enteric infections than COVID-19 negative patients overall; however, the frequency of *C. difficile*, in particular, was not significantly different between the two groups. Given the high prevalence of GI symptoms in COVID-19 patients, there may be decreased utility in using extensive gastrointestinal pathogen panels, as pathogens aside from *C. difficile* rarely contribute to diarrhea in COVID-19 positive patients. Our results suggest the need for ongoing vigilance regarding *C. difficile* infection in these populations. Furthermore, the possible long-term impact of COVID-19 on gastrointestinal problems as well as risk for future infections requires further study.

Compliance with Ethical Standards

Conflict of interest They authors declare that they have no conflict of interest.

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