



Factors Associated with the Development of Gastrointestinal Symptoms in Patients Hospitalized with Covid-19

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Abstract

Background and Aims The most common symptoms of Covid-19 are respiratory; however, gastrointestinal symptoms are present in up to 50% of patients. We aimed to determine characteristics associated with the development of gastrointestinal symptoms in patients with Covid-19.

Methods A case–control study of adults hospitalized for Covid-19 was conducted across a geographically diverse alliance of 36 US and Canadian medical centers. Data were manually abstracted from electronic health records and analyzed using regression analyses to determine characteristics associated with any gastrointestinal symptoms and diarrhea specifically.

Results Of 1406 patients, 540 (38%) reported at least one gastrointestinal symptom and 346 (25%) reported diarrhea. Older patients (≥ 80 years) had significantly lower rates of any gastrointestinal symptoms and diarrhea (vs. patients 18–79 years, OR 0.41, $p < 0.01$ and OR 0.43 $p = 0.01$, respectively), while those with IBS (OR 7.70, $p = 0.02$ and OR 6.72, $p < 0.01$, respectively) and on immunosuppressive therapy (OR = 1.56, $p = 0.02$) had higher rates of any gastrointestinal symptom and diarrhea. Patients with constitutional symptoms exhibited significantly higher rates (OR 1.91, $p < 0.01$), while those with pulmonary disease alone had lower rates of gastrointestinal symptoms (OR 0.23, $p = 0.01$). A significant interaction between constitutional symptoms and pre-existing pulmonary conditions was observed.

Conclusions Several patient- and disease-specific characteristics associate with gastrointestinal symptoms in patients with Covid-19. Knowledge of these may provide insights into associated pathophysiologic mechanisms, and help health care professionals provide targeted attention to reduce morbidity related to Covid-19.

Keywords Covid-19 · Gastrointestinal symptoms · Characteristics

Abbreviations

ACE2	Angiotensin-converting enzyme 2
BMI	Body mass index
CI	Confidence interval
Covid-19	Coronavirus disease 2019
GLMM	Generalized linear mixed models

IBS	Irritable bowel syndrome
IQR	Interquartile range
OR	Odds ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Background & Aims

In December 2019, a new respiratory disease was discovered in Wuhan, China, and has since evolved into a global pandemic. The disease, termed coronavirus disease-19 or Covid-19, is caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, there are more than 39.8 million confirmed cases worldwide and more than 1,000,000 deaths. Since the first case was reported in the US on January 20, 2020 [1], there have been over 9.5 million confirmed cases resulting in over 230,000 deaths.

The most common symptoms of Covid-19 are fever, cough and shortness of breath, which commence on average between 2 and 14 days following exposure to the virus and which may progress to acute respiratory distress syndrome [2], requiring ventilatory support. However, various gastrointestinal symptoms including diarrhea, abdominal pain, nausea and vomiting have been reported in subsets of patients [3]. Our appreciation for and recognition of the gastrointestinal manifestations of Covid-19 has improved over the course of the pandemic. Early reports from Wuhan, China, suggested that gastrointestinal manifestations were uncommon, affecting less than 5.0% of patients with Covid-19 [4]. More recent reports suggest that gastrointestinal manifestations are far more common than initially appreciated, with an estimated prevalence of diarrhea between 5 and 18%, nausea and vomiting between 5 and 15% and abdominal pain between 3 and 5% [3]. Collectively, gastrointestinal manifestations have been reported to be highly prevalent, accompanying acute Covid-19 in up to 53% of hospitalized patients [5].

SARS-CoV-2 gains cellular entry through the angiotensin-converting enzyme 2 (ACE2) receptor [6–8]. Although respiratory manifestations of Covid-19 are exceedingly more common than gastrointestinal manifestations, ACE2 receptor expression is higher in the gastrointestinal tract than in the respiratory system [9]. To date, there is a paucity of data describing which patient- and disease-related characteristics are associated with the development of gastrointestinal symptoms in Covid-19. A better understanding of these characteristics has the potential to lead to insights regarding pathophysiologic mechanisms that underlie gastrointestinal symptoms in Covid-19.

We aimed to determine characteristics associated with the development of gastrointestinal symptoms in patients with Covid-19. We hypothesized that specific patient- and disease-related factors are associated with the development of gastrointestinal symptoms, and specifically diarrhea, in patients with Covid-19. We evaluated this hypothesis by analyzing detailed data collected in an observational cohort of 1406 subjects hospitalized for Covid-19 from

April 2020 to June 2020 within an alliance of medical centers in the US and Canada.

Methods

Study Design

We used a case–control study design in patients hospitalized for Covid-19 with and without GI symptoms. The dataset was developed by North American Alliance for the Study of Digestive Manifestations of Covid-19 (NAADMC), a network of 36 medical centers across the USA and Canada [5]. Institutional review board approval was obtained at each center prior to patient identification and data collection. The Medical University of South Carolina served as the Data Coordinating Center.

Data Source

The dataset included consecutively enrolled patients ≥ 18 years old who were hospitalized with a confirmed diagnosis of Covid-19, according to local testing standards. To avoid potential selection bias, enrollment was targeted to include the first 50–100 patients admitted with Covid-19 at each participating institution. Eligible patients were identified by the research team at each participating institution by data warehouse and electronic health record queries and by lists provided by hospital services and entities. Data were manually abstracted through review of electronic health records by study personnel under the oversight of a designated clinician-investigator at each center. These data were then directly entered into an electronic data collection form in de-identified fashion, as previously described [5]. Data quality was ensured to the greatest extent possible using a three-tiered system [5]. The presence or absence of gastrointestinal symptoms was noted. If gastrointestinal and respiratory symptoms were both present, the timing of gastrointestinal symptoms in relation to respiratory symptoms was also abstracted.

Patients

Eligible cases consisted of patients hospitalized with Covid-19 who developed gastrointestinal symptoms (1) either prior to or concurrent with the development of respiratory symptoms or (2) as the sole manifestation of their acute infection. Eligible controls consisted of patients hospitalized with Covid-19 in whom no gastrointestinal symptoms were recorded in the electronic health record as part of the presenting illness. Patients with Covid-19 who developed gastrointestinal symptoms following respiratory symptoms were excluded from this analysis because it could not be

determined whether gastrointestinal symptoms in these patients were a consequence of Covid-19 itself or of treatments administered during hospitalization. Patients were also excluded if review of the medical record did not allow for accurate determination of the relationship between the onset gastrointestinal and respiratory symptoms. Cases with gastrointestinal symptoms were further subdivided into two groups: (1) those with *any gastrointestinal symptom*, including diarrhea, abdominal pain, nausea or vomiting; and (2) those without any gastrointestinal symptoms. Patients with *any gastrointestinal symptom* were further grouped into: (1) those who developed diarrhea; and (2) those who did not develop diarrhea. Diarrhea was defined as the presence of acute diarrhea within the past 24 h as documented in the medical record.

Data Collection

Information abstracted from the database relevant to this study included demographic, clinical and medical center data at the time of hospitalization. Demographic data included age, sex, race and ethnicity. Clinical data points of interest included pre-existing comorbid conditions (including Charlson comorbidity index), body mass index (BMI), social history, home medications and type of symptoms leading to hospitalization. Medical center data included geographic location and consecutive patient hospitalization sequences.

Definitions

Gastrointestinal symptoms, respiratory symptoms (which included cough or shortness of breath), and constitutional symptoms (which included fever, myalgia or fatigue) were categorized as being present or absent.

US medical centers were grouped into one of four geographic regions, including the Northeast, Midwest, South and West, as defined by the US Census Bureau. Medical centers in Canada were included in a separate geographic group. Geographic grouping was conducted to account for differences in Covid-19 case volumes in different geographic locations early in the pandemic, which could have impacted recognition of gastrointestinal symptoms as a manifestation of Covid-19.

Consecutive patient hospitalization sequences were generated by ordering patients according to the timing of their admission relative to one another. For example, patient 1 of 50 in the sequence was the first patient hospitalized with Covid-19 at any given institution, while patient 50 of 50 was the fiftieth patient hospitalized with Covid-19 at any given institution. Hospitalization sequences within institutions were used to group patients into tertiles, with the first, second and third tertiles being the first, second and third

consecutive groups of patients hospitalized with Covid-19 among all participating institutions, respectively. This grouping was performed to evaluate for trends in the detection of gastrointestinal symptoms over time with accumulating knowledge in the literature.

Statistical Analysis

Characteristics of patients with Covid-19 who developed gastrointestinal symptoms (cases) and patients with Covid-19 who did not develop gastrointestinal symptoms (controls) were described and compared. A subgroup analysis was subsequently performed to describe and compare characteristics between patients with Covid-19 who developed diarrhea and who did not develop diarrhea. Categorical variables were expressed as counts and percentages, and continuous variables were expressed as medians and interquartile ranges. Pearson's chi-square test was used to compare categorical variables, and the Wilcoxon rank-sum test was used to compare continuous variables, between patient groups.

Generalized linear mixed models (GLMM), with logit link function, were used to evaluate association between risk factors and two binary outcomes: 1) any gastrointestinal symptom and 2) diarrhea, after adjusting for other significant risk factors and clinically meaningful parameters (age, gender, race and ethnicity, geography and tertile of hospitalization). A normally distributed random intercept was used for each center to model the correlation among patients from the same center. Clinically meaningful variables were always included in these regression models. Other variables were selected as candidate clinical markers if their adjusted *p* values were less than 0.20 in the corresponding GLMM models. After that screening step, all selected candidate clinical markers and the clinically meaningful variables were included in a stepwise selection process, where a threshold of *p* value < 0.05 was used to determine the main effects in the final parsimonious multivariable model. Interaction terms between selected main effects were also tested via the likelihood ratio test and included in the final models if the *p* values were less than 0.05.

All statistical analyses were performed using R version 3.6.1.

Results

Of 1992 patients in the registry, 1406 met eligibility criteria, of whom 540 patients (38%) reported having at least one gastrointestinal symptom and 346 patients (25%) reported having diarrhea. The mean age of patients was 60.83 ± 16.26 years; 57% were male; 44% were Black or African American; 77% were not Hispanic or Latino.

Bivariable Associations (Tables 1 and 2)

Characteristics of the study population and comparisons between groups of patients with and without any gastrointestinal symptom, and with and without diarrhea are displayed in Tables 1 and 2, respectively. Sex and race did not differ significantly between groups. Patients with any gastrointestinal symptom and diarrhea were more likely to be non-Hispanic or non-Latino than those without symptoms (82.2% vs 74.5%, $p=0.024$ and 85.0% vs 75.0%, $p<0.01$, respectively). Gastrointestinal symptoms were significantly associated with younger age ($p<0.01$); specifically, patients 70 years and older had significantly lower prevalence of gastrointestinal symptoms when compared with those <70 years age (32% vs. 41%). Patients admitted to hospitals in the Midwest had higher rates of gastrointestinal symptoms when compared with other regions. The prevalence of pulmonary (84%) and constitutional (84%) symptoms was high irrespective of the presence of gastrointestinal symptoms, and however, constitutional symptoms associated with Covid-19 were more commonly exhibited in patients who also had gastrointestinal symptoms (90.7% vs 80.0%, $p<0.001$). Although relatively uncommon in our study population, IBS was significantly more prevalent in patients with any gastrointestinal symptom and specifically with diarrhea (1.9% vs 0.2%, $p<0.01$; 2.6 vs 0.3, $p<0.001$, respectively).

Bivariable associations were mostly similar for patients who experienced diarrhea (Table 2). Patients with diarrhea had statistically significantly higher BMI (31[27,37] vs 30[25,35], $p=0.02$) and immunosuppression or chemotherapy use in the preceding 6 months when compared with those who did not have diarrhea (15.3% vs. 9.9%, $p<0.01$). It was notable that respiratory symptoms were more commonly exhibited in patients with diarrhea compared to those without diarrhea (89.3% vs 84.0%, $p=0.02$), and the prevalence of IBS in patients with diarrhea was greater than any gastrointestinal symptoms (2.6 vs. 1.9%).

Multivariable Regression Modeling

Any Gastrointestinal Symptom (Table 3)

In the adjusted model, age and IBS were independently associated with the presence of any gastrointestinal symptom. Specifically, patients aged 80 years or older had significantly lower rates of gastrointestinal symptoms compared with patients aged 18–79 years (OR 0.41, $p<0.01$). Additionally, there were 7.7-fold increased odds of gastrointestinal symptoms in patients with IBS when compared with patients without IBS ($p=0.02$). There was a trend toward higher rates of gastrointestinal symptoms in patients in the Midwest compared with patients in other regions (OR 1.66, $p=0.06$). Patients with constitutional symptoms exhibited higher rates

of gastrointestinal symptoms (OR 1.91, $p<0.01$), and however, patients with pulmonary disease exhibited significantly lower rates of gastrointestinal symptoms (OR 0.23, $p=0.01$). A significant interaction between constitutional symptoms and pre-existing pulmonary disease (e.g., chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, interstitial lung disease or pulmonary fibrosis) was found. Specifically, among patients without pre-existing pulmonary disease, constitutional symptoms were associated with higher rates of gastrointestinal symptoms (OR 1.91, $p<0.01$). Among patients with pre-existing pulmonary disease, the odds of gastrointestinal symptoms in patients with constitutional symptoms were even higher (OR 6.42, $p=0.04$).

Diarrhea (Table 4)

In the adjusted model, age, IBS, constitutional symptoms, immunocompromised state and diabetes were independently associated with diarrhea. Patients aged 80 years or older exhibited lower rates of diarrhea compared with patients aged 18–79 years (OR 0.43, $p=0.01$). Additionally, patients with IBS had higher rates of diarrhea (OR 6.72, $p<0.01$). As described above, similar associations were seen between age and IBS and any gastrointestinal symptom. Patients with constitutional symptoms (OR 2.15, $p=0.001$) and on immunosuppressive medications (OR = 1.56, $p=0.02$) exhibited higher rates of diarrhea, while patients with diabetes exhibited lower rates of diarrhea (OR 0.69, $p=0.01$). Patients in the Midwest exhibited higher rates of diarrhea than patients in other geographic regions; however, this result was not statistically significant (OR = 1.72, $p=0.09$).

Discussion

In this large and geographically diverse cohort of North American patients hospitalized with Covid-19, 38% of patients reported at least one gastrointestinal symptom and 25% reported having diarrhea prior to or at the time of hospitalization. These rates are similar to those reported in other Western studies [10, 11]. We also found that gastrointestinal symptoms are associated with several patient- and disease-related characteristics including constitutional symptoms, younger age, IBS and immunosuppressive therapy or chemotherapy. Additionally, we noted a significant interaction between pre-existing pulmonary disease and constitutional symptoms.

The prevalence of gastrointestinal symptoms, including diarrhea, nausea, vomiting and abdominal pain, in patients with Covid-19 has been reported to range between 0 and over 37%, and among these, diarrhea is most common [3, 5, 12–14]. The wide variation in the reported prevalence is likely the result of a lack of recognition of the

Table 1 Characteristics compared between groups of patients with and without any gastrointestinal symptom (diarrhea, nausea, vomiting or abdominal pain) at the time of Covid-19

Characteristics	Patients with gastrointestinal symptoms (n = 540)	Patients without gastrointestinal symptoms (n = 866)	p values
<i>Male</i>	296 (54.8)	506 (58.4)	0.20
<i>Age (years)</i>			< 0.01
18–39	59 (10.9)	100 (11.5)	
40–49	75 (13.9)	107 (12.4)	
50–59	110 (20.4)	156 (18.0)	
60–69	158 (29.3)	207 (23.9)	
70–79	91 (16.9)	163 (18.8)	
> 79	47 (8.7)	133 (15.4)	
<i>Body Mass Index (kg/m²)</i>	30 [26, 35]	30 [25, 36]	0.55
<i>Tertiles of Hospitalization</i>			0.74
1	185 (34.3)	296 (34.2)	
2	170 (31.5)	288 (33.3)	
3	185 (34.3)	282 (32.6)	
<i>Geographic Region</i>			0.04
Canada	18 (3.3)	34 (3.9)	
Midwest	210 (38.9)	267 (30.8)	
Northeast	93 (17.2)	169 (19.5)	
South	167 (30.9)	292 (33.7)	
West	52 (9.6)	104 (12.0)	
<i>Race</i>			0.77
American Indian/Alaska Native	2 (0.4)	2 (0.2)	
Asian	12 (3.1)	24 (2.8)	
Black/African American	253 (46.9)	367 (42.2)	
Multiple	3 (0.6)	5 (0.6)	
White	197 (36.5)	332 (38.3)	
Unknown	68 (12.6)	136 (15.7)	
<i>Ethnicity</i>			0.02
Hispanic or Latino	65 (12.0)	138 (15.9)	
Not Hispanic or Latino	444 (82.2)	645 (74.5)	
Unknown	31 (5.7)	83 (9.6)	
<i>Symptoms associated with Covid-19</i>			
Respiratory symptoms	466 (86.3)	733 (84.6)	0.44
Constitutional symptoms	490 (90.7)	693 (80.0)	< 0.001
<i>Charlson Comorbidity Index</i>	1 [0, 2]	1 [0, 3]	0.09
<i>Comorbid Conditions</i>			
Diabetes	204 (37.8)	323 (37.3)	0.90
Hypertension	345 (63.9)	538 (62.1)	0.54
Cardiac disease	115 (21.3)	212 (24.5)	0.19
Pulmonary disease	100 (18.5)	193 (22.3)	0.10
Active/current malignancy	28 (5.2)	69 (8.0)	0.06
Immunocompromised state	75 (13.9)	105 (12.1)	0.38
Moderate to severe kidney disease	53 (9.8)	79 (9.1)	> 0.99
Pancreaticobiliary disease	15 (2.8)	24 (2.8)	0.45
Chronic liver disease	19 (3.5)	23 (2.7)	0.74
Inflammatory bowel disease	5 (0.9)	1 (0.1)	0.07
Irritable bowel syndrome	10 (1.9)	2 (0.2)	< 0.01
<i>Smoking Status</i>			0.05
Current smoker	28 (5.2)	61 (7.0)	

Table 1 (continued)

Characteristics	Patients with gastrointestinal symptoms (n = 540)	Patients without gastrointestinal symptoms (n = 866)	p values
Ex-smoker	154 (28.5)	269 (31.1)	
Non-smoker	336 (62.2)	467 (53.9)	
Unknown	22 (4.1)	69 (8.0)	
<i>Alcohol use</i>			0.52
Never	417 (77.2)	631 (72.9)	
Prior	28 (5.2)	51 (5.9)	
Current	53 (9.8)	69 (8.0)	
Unknown	42 (7.8)	115 (13.3)	
<i>Illicit Drug Use</i>			0.06
Never	459 (85.0)	669 (77.3)	
Prior	20 (3.7)	25 (2.9)	
Current	3 (0.6)	17 (2.0)	
Unknown	58 (10.7)	155 (17.9)	
<i>Cannabis Use</i>			0.64
Never	422 (78.1)	603 (69.6)	
Prior	11 (2.0)	14 (1.6)	
Current	14 (2.6)	27 (3.1)	
Unknown	93 (17.2)	222 (25.6)	
<i>Immunosuppressive or chemotherapy in past 6 months</i>			0.45
No	469 (86.9)	756 (87.3)	
Yes	66 (12.2)	92 (10.6)	
Unknown	5 (0.9)	18 (2.1)	
<i>Angiotensin-converting enzyme (ACE) inhibitor use within the past 1 month</i>			0.24
No	446 (82.6)	678 (78.3)	
Yes	87 (16.1)	159 (18.4)	
Unknown	7 (1.3)	29 (3.3)	
<i>Angiotensin receptor blocker (ARB) use within the past 1 month</i>			0.18
No	465 (86.1)	744 (85.9)	
Yes	71 (13.1)	89 (10.3)	
Unknown	74 (0.7)	33 (3.8)	
<i>NSAID use within the past 1 month</i>			0.89
No	341 (63.1)	509 (58.8)	
Yes	139 (25.7)	213 (24.6)	
Unknown	60 (11.1)	144 (16.6)	

*Numbers represented as n(%) or median[IQR]

gastrointestinal manifestations in Covid-19 patients early in the pandemic and the retrospective nature of data acquired during the pandemic. Data elucidating the association between gastrointestinal symptoms and disease severity are conflicting. Specifically, some studies have reported worse outcomes among patients with gastrointestinal symptoms [13], while others have reported no association [5]. These differences are likely due to variability in the way gastrointestinal symptoms were analyzed and different criteria used to define disease severity.

Although numerous studies have reported on the prevalence gastrointestinal symptoms, ours is only the second

study evaluating the factors associated with the presence of these symptoms in patients with Covid-19. When compared with Redd et al., we had a larger sample size (1406 vs 318), we included patients until June 5, 2020 (vs. April 2, 2020), and our cohort was geographically diverse, including centers across the US and Canada (vs. only Massachusetts) [11]. Similar to Redd et al. [11], we noted a higher prevalence of myalgia and fatigue in patients with Covid-19 and associated gastrointestinal symptoms. Specifically, the odds of having constitutional symptoms, including fever, myalgia and fatigue, were approximately twofold greater in patients who also experienced gastrointestinal symptoms. The presence of

Table 2 Characteristics compared between groups of patients with and without diarrhea at the time of Covid-19

Characteristics	Patients with diarrhea (n = 346)	Patients without diarrhea (n = 1060)	p values
<i>Male</i>	190 (54.9)	612 (57.1)	0.39
<i>Age (years)</i>			< 0.01
18–39	35 (10.1)	124 (11.7)	
40–49	40 (11.6)	142 (13.4)	
50–59	78 (22.5)	188 (17.7)	
60–69	109 (31.5)	256 (24.2)	
70–79	57 (16.5)	197 (18.6)	
> 79	27 (7.8)	153 (14.4)	
<i>Body Mass Index (kg/m²)</i>	31 [27, 37]	30 [25, 35]	0.02
<i>Tertiles of Hospitalization</i>			0.78
1	116 (33.5)	365 (34.4)	
2	118 (34.1)	340 (32.1)	
3	112 (32.4)	355 (33.5)	
<i>Geographic Region</i>			< 0.01
Canada	8 (2.3)	44 (4.2)	
Midwest	143 (41.3)	334 (31.5)	
Northeast	60 (17.3)	202 (19.1)	
South	106 (30.6)	353 (33.3)	
West	29 (8.4)	127 (12.0)	
<i>Race</i>			0.53
American Indian/Alaska Native	0 (0.0)	4 (0.4)	
Asian	8 (2.3)	33 (3.1)	
Black/African American	167 (48.3)	453 (42.7)	
Multiple	2 (0.6)	6 (0.6)	
White	129 (37.3)	400 (37.7)	
Unknown	40 (11.6)	164 (15.5)	
<i>Ethnicity</i>			< 0.01
Hispanic or Latino	33 (9.5)	170 (16.0)	
Not Hispanic or Latino	294 (85.0)	795 (75.0)	
Unknown	19 (5.5)	95 (9.0)	
<i>Symptoms associated with Covid-19</i>			
Respiratory symptoms	309 (89.3)	890 (84.0)	0.02
Constitutional symptoms	314 (90.8)	869 (82.0)	< 0.001
<i>Charlson Comorbidity Index</i>	1 [0, 2]	1 [0, 3]	0.10
<i>Comorbid Conditions</i>			
Diabetes	115 (33.2)	412 (38.9)	0.07
Hypertension	217 (62.7)	666 (62.8)	> 0.99
Cardiac disease	76 (22.0)	251 (23.7)	0.56
Pulmonary disease	71 (20.5)	222 (20.9)	0.93
Active/current malignancy	20 (5.8)	77 (7.3)	0.41
Immunocompromised state	60 (17.3)	120 (11.3)	< 0.01
Moderate to severe kidney disease	36 (10.4)	96 (9.1)	0.52
Pancreaticobiliary disease	8 (2.3)	31 (2.9)	0.68
Chronic liver disease	19 (3.5)	23 (2.7)	0.74
Inflammatory bowel disease	3 (0.9)	3 (0.3)	0.07
Irritable bowel syndrome	9 (2.6)	3 (0.3)	< 0.001
<i>Smoking Status</i>			0.16
Current smoker	19 (5.5)	70 (6.6)	
Ex-smoker	96 (27.7)	327 (30.8)	

Table 2 (continued)

Characteristics	Patients with diarrhea (n = 346)	Patients without diarrhea (n = 1060)	p values
Non-smoker	218 (63.0)	585 (55.2)	
Unknown	13 (3.8)	78 (7.4)	
<i>Alcohol use</i>			0.52
Never	273 (78.9)	775 (73.1)	
Prior	16 (4.6)	63 (5.9)	
Current	31 (9.0)	91 (8.6)	
Unknown	26 (7.5)	131 (12.4)	
<i>Illicit Drug Use</i>			0.23
Never	293 (84.7)	835 (78.8)	
Prior	10 (2.9)	35 (3.3)	
Current	2 (0.6)	18 (1.7)	
Unknown	41 (11.8)	172 (16.2)	
<i>Cannabis Use</i>			0.81
Never	270 (78.0)	755 (71.2)	
Prior	7 (2.0)	18 (1.7)	
Current	9 (2.6)	32 (3.0)	
Unknown	60 (17.3)	255 (24.1)	
<i>Immunosuppressive or chemotherapy in past 6 months</i>			<0.01
No	289 (83.5)	936 (88.3)	
Yes	53 (15.3)	105 (9.9)	
Unknown	4 (1.2)	19 (1.8)	
<i>Angiotensin-converting enzyme (ACE) inhibitor use within the past 1 month</i>			0.11
No	290 (83.8)	834 (78.7)	
Yes	51 (14.7)	195 (18.4)	
Unknown	5 (1.4)	31 (2.9)	
<i>Angiotensin receptor blocker (ARB) use within the past 1 month</i>			0.30
No	298 (86.1)	911 (85.9)	
Yes	46 (13.3)	114 (10.8)	
Unknown	2 (0.6)	35 (3.3)	
<i>NSAID use within the past 1 month</i>			0.75
No	213 (61.6)	637 (60.1)	
Yes	92 (26.6)	260 (24.5)	
Unknown	41 (11.8)	163 (15.4)	

*Numbers represented as n(%) or median[IQR]

pre-existing pulmonary disease influenced the prevalence of constitutional symptoms—in patients without pre-existing pulmonary disease, the odds of gastrointestinal symptoms were 1.9-fold greater among patients with constitutional symptoms. In contrast, among patients with pre-existing pulmonary disease, the odds of gastrointestinal symptoms increased to 6.4-fold among patients who also had constitutional symptoms.

Although reported in fewer than 4% patients initially [4], as knowledge grew, gastrointestinal manifestations of Covid-19 were reported to be far more common. The pandemic spread across North America and affected specific geographic regions at different time points during the

Spring and Summer of 2020. Specifically, it first entered North America in Canadian provinces and the Northeast and West of the USA [15]. Subsequently, Covid-19 went on to affect the South and Midwest regions of the USA [15]. In our adjusted models, the odds of gastrointestinal symptoms were 1.7-fold higher in Covid-19 patients hospitalized in the Midwest compared to those in other regions in North America; however, these results were not statistically significant (p=0.06). We hypothesize that increased awareness with the evolution of the Covid-19 pandemic led to the higher rates of gastrointestinal symptoms in the Midwest region. Interestingly, the tertile of hospitalization did not associate with gastrointestinal symptoms—this may suggest that knowledge

Table 3 Generalized linear mixed model of characteristics of gastrointestinal symptoms (diarrhea, nausea, vomiting or abdominal pain) in patients with Covid-19

Variable	Odds ratio	95% CI	p values
Male	0.83	0.65, 1.06	0.13
<i>Age (years)</i>			
≤34	1.00		
35–54	0.77	0.46, 1.29	0.32
55–79	0.87	0.53, 1.42	0.58
≥80	0.41	0.23, 0.74	<0.01
<i>Tertile of hospitalization</i>			
1	1.00		
2	1.05	0.79, 1.41	0.73
3	1.08	0.80, 1.45	0.62
<i>Race and ethnicity</i>			
Black/African American	1.00		
Hispanic or Latino and others	0.88	0.60, 1.30	0.52
Non-Hispanic white	0.97	0.71, 1.32	0.82
<i>Region</i>			
Northeast	1.00		
Canada	1.75	0.64, 4.78	0.27
Midwest	1.66	0.98, 2.80	0.06
South	1.14	0.67, 1.95	0.63
West	1.09	0.54, 2.21	0.80
Pulmonary disease	0.23	0.07, 0.70	0.01
Constitutional symptoms	1.91	1.27, 2.88	<0.01
Irritable bowel syndrome	7.70	1.48, 40.18	0.02
Constitutional symptoms*Pulmonary disease	3.36	1.04, 10.85	0.04

acquired within individual institutions over time was not as impactful in our recognition of gastrointestinal symptoms as was knowledge gained across institutions. Alternatively, this may be due to an inability to observe changes in practice and symptom recognition over the relatively short ascertainment period in our study.

It is well-accepted that severe outcomes of Covid-19 are associated with older age [16]. However, the reason SARS-CoV-2 infections are more severe, and fatal in the aged is not known. Emerging hypotheses include changes to the immune cell repertoire, the epigenome, inflammasome activity, biological clocks, and covalent modifications of human and viral protein [17]. In our adjusted models, we found that older patients with Covid-19 were less likely to exhibit gastrointestinal symptoms. The protective effect of age against gastrointestinal symptoms may be explained by differences in the immune response and activation among older patients. Alternatively, our findings may reflect differences in the ability of SARS-CoV2 to invade enterocytes as a result of diminished ACE2 receptor expression in older as compared with younger patients [18]. Lastly, older patients and those with underlying pulmonary disease are more likely to be

Table 4 Generalized linear mixed model of characteristics of diarrhea in patients with Covid-19

Variable	Odds ratio	95% CI	p values
Male	0.90	0.69, 1.19	0.46
<i>Age (years)</i>			
≤34	1.00		
35–54	0.67	0.38, 1.19	0.17
55–79	0.98	0.56, 1.69	0.93
≥80	0.43	0.21, 0.84	0.01
<i>Tertile of hospitalization</i>			
1	1.00		
2	1.24	0.89, 1.72	0.20
3	1.05	0.75, 1.48	0.76
<i>Race and ethnicity</i>			
Black/African American	1.00		
Hispanic or Latino and others	0.73	0.46, 1.16	0.18
Non-Hispanic white	0.95	0.67, 1.35	0.78
<i>Region</i>			
Northeast	1.00		
Canada	0.96	0.27, 3.43	0.95
Midwest	1.72	0.92, 3.20	0.09
South	1.17	0.61, 2.22	0.64
West	1.11	0.47, 2.60	0.82
Diabetes	0.69	0.51, 0.92	0.01
Immunocompromised status	1.56	1.06, 2.30	0.02
Constitutional symptoms	2.15	1.65, 27.3	<0.01
Irritable bowel syndrome	6.72	1.37, 3.38	<0.01

hospitalized. Therefore, the association we found between and lack of gastrointestinal symptoms and older age may be related to inclusion of only hospitalized patients in this study and may not persist in patients who are seen and treated in the outpatient setting.

In our study, IBS was associated with a 6–sevenfold increased odds of exhibiting gastrointestinal manifestations. Despite this association, the overall prevalence of IBS in our cohort was exceedingly low at <1% (12 of 1406 patients). The prevalence of IBS varies considerably by country [19, 20]; however, in North America, the prevalence of IBS ranges between approximately 6.5–16% [21], which is considerably higher than the prevalence reported in our study. Because IBS is likely to be under-reported in the medical record [22, 23], the low prevalence of IBS in our study is likely an underestimation of the true prevalence. Despite the overall low prevalence of IBS, our finding of the strong association between IBS and gastrointestinal manifestations is rooted in logical supposition. There is growing evidence to support that in IBS, the epithelial barrier, gut microbiota, food antigens and bile acids elicit abnormal responses in key regulators of sensorimotor function [21]. It is this alteration in sensorimotor function that may predispose patients

with IBS toward developing gastrointestinal symptoms in response to the presence of SARS-CoV-2 in the gastrointestinal tract. Alternatively, the higher prevalence of gastrointestinal symptoms may simply reflect increased symptom reporting in patients with IBS [24].

Immunosuppression can result from underlying systemic disease, such as cancer or immunodeficiency syndromes, or may be secondary to organ transplantation or use of an immunosuppressive therapy or chemotherapy. Immunosuppressed patients with cancer have more severe presentations [25] and higher mortality [26] rates from Covid-19 than the general population. However, the effects of immunosuppressive therapy in modulating the inflammatory response to Covid-19 are not well understood, and whether these medications are harmful or protective against severe disease is still being explored [27]. We noted gastrointestinal manifestations to be more common among patients who were on immunosuppressive therapy or chemotherapy within the preceding 6 months. This could be related to adverse reactions of the immunosuppressive or chemotherapeutic agent patients received in the weeks preceding Covid-19 or the fact that immunosuppressive therapy predisposes patients to manifest more systemic symptoms in response to infection.

Our study has several strengths, including the large and geographically diverse sample, systematic approach to patient selection, detailed patient-level data, and multi-layered and rigorous strategy to ensure the veracity of collected data. Moreover, the analyses employed were rigorous and include controlling for geographic region and tertile of hospitalization, which are critically important in contextualizing results from a pandemic in which knowledge and experience evolved differently within and across individual North American institutions over time. We evaluated symptoms at or prior to the time of admission—therefore, a progressive decline in mortality from Covid-19 due to therapeutic advances will not affect our observations.

Despite the strengths of this study, our findings should be interpreted in the context of several limitations, some of which are inherent to observational research on Covid-19. As highlighted above, symptom attribution and ascertainment were influenced by several factors related to conducting research during a pandemic, including retrospective data collection and reliance on medical record review rather than direct patient interviews. These limitations may have led to misclassification of cases and controls; however, data quality was ensured to the greatest possible extent using rigorous chart review procedures at each participating institution. An additional limitation is that our study focused on data collected early in the pandemic from April 2020 to June 2020 when the gastrointestinal manifestations of Covid-19 were still being elucidated. We attempted to control for knowledge gained from accumulating experience and the literature by specifically adjusting for geographic region and tertiles

of hospitalization in our analyses—however, unmeasured confounders may still have been present. Additionally, only hospitalized patients were included in this study, and therefore, our findings cannot be extrapolated to outpatients with Covid-19.

In conclusion, several patient- and disease-specific characteristics are associated with the development of gastrointestinal symptoms among patients with Covid-19, including older age, constitutional symptoms, pre-existing IBS and immunosuppressive therapy prior to hospitalization. This gained understanding can help identify at-risk groups early in the disease course and potentially reduce morbidity. Prospective studies in both outpatients and inpatients aimed to assess gastrointestinal symptoms from the time of onset of Covid-19 until its resolution is needed to obtain additional insights and further improve our care of patients with Covid-19.

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