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ORIGINAL RESEARCH—CLINICAL

Gastrointestinal Manifestations of Coronavirus Disease 2019 Across the United States: A Multicenter Cohort Study

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BACKGROUND AND AIMS: Gastrointestinal (GI) symptoms occur among patients diagnosed with coronavirus disease 2019 (COVID-19), and there is clear evidence that SARS-CoV-2, the causative pathogen, infects the GI tract. In this large, multicenter cohort study, we evaluated variations in gastrointestinal and hepatic manifestations of COVID-19 throughout the United States (US). **METHODS:** Patients hospitalized with a positive COVID-19 test prior to October 2020 were identified at 7 US academic centers. Demographics, presenting symptoms, laboratory data, and hospitalization outcomes were abstracted. Descriptive and regression analyses were used to evaluate GI manifestations and their potential predictors. **RESULTS:** Among 2031 hospitalized patients with COVID-19, GI symptoms were present in 18.9%; diarrhea was the most common (15.2%), followed by nausea and/or vomiting (12.6%) and abdominal pain (6.0%). GI symptoms were less common in the Western cohort (16.0%) than the Northeastern (25.6%) and Midwestern (26.7%) cohorts. Compared to nonintensive care unit (ICU) patients, ICU patients had a higher prevalence of abnormal aspartate aminotransferase (58.1% vs 37.3%; $P < .01$), alanine aminotransferase (37.5% vs 29.3%; $P = .01$), and total bilirubin (12.7% vs 9.0%; $P < .01$). ICU patients also had a higher mortality rate (22.7% vs 4.7%; $P < .01$). Chronic liver disease was associated with the development of GI symptoms. Abnormal aspartate aminotransferase or alanine aminotransferase was associated with an increased risk of ICU admission. **CONCLUSION:** We present the largest multicenter cohort of patients with COVID-19 across the United States. GI manifestations were common among patients hospitalized with COVID-19, although there was significant variability in prevalence and predictors across the United States.

Keywords: Coronavirus Disease 2019; COVID-19; SARS-CoV-2; Gastrointestinal

Introduction

The World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020.[1] Since that declaration, it has led to millions of lost lives and unprecedented global socioeconomic disruption.[2] Although COVID-19 is primarily a virus involving the respiratory tract, studies have revealed a high prevalence of gastrointestinal (GI) symptoms among patients diagnosed with COVID-19. SARS-CoV-2 replicates in the intestinal epithelium and viral RNA particles are commonly shed in stool of infected patients which sometimes persists for months after initial infection.[3–8] Reported GI and hepatic manifestations include abdominal pain, diarrhea, nausea, and elevated aminotransferases. Identifying these

Abbreviations used in this paper: **ALT, alanine aminotransferase; aOR, adjusted odds ratio; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; GI, gastrointestinal; ICU, intensive care unit; OR, odds ratio; SD, standard deviation; UCLA, University of California Los Angeles.**

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manifestations is vital as GI symptoms may present earlier or in the absence of respiratory symptoms in patients with COVID-19.[9] The incidence of GI symptoms suggested by the literature ranges from 9% to 33%, with a higher prevalence noted in Western populations.[10,11] Some studies found that certain GI and hepatic manifestations are associated with severe illness, while others did not find an association.[10–12] Most of the data thus far exploring GI and hepatic manifestations of COVID-19 have consisted of single-center studies or meta-analyses.[10,13] We thus present a multicenter retrospective study evaluating GI and hepatobiliary manifestations and related outcomes in hospitalized patients with COVID-19 across several academic centers throughout the United States.

Methods

Study Population

Adults hospitalized with a positive COVID-19 test prior to October 2020 were identified at 7 large academic centers across the United States: University of California Los Angeles (UCLA), UCLA-Olive View Medical Center, University of California Irvine, Oregon Health and Science University, Washington University, Tufts University, and St. Elizabeth's Medical Center. Data on patient demographics, medical and social history, presenting symptoms, laboratory data, imaging data, procedural data, treatment information, and hospitalization outcomes were abstracted from the electronic medical records. We included all hospitalized adults diagnosed with COVID-19 regardless of the indication for admission. As our study was focused on GI manifestations of COVID-19 in hospitalized patients, patients who were not admitted to the hospital were excluded.

During the COVID-19 pandemic, several institutions established *ad hoc* committees to control access to clinical data from patients with COVID-19. Data were de-identified and a limited subset of clinical variables was made available to clinical investigators. Four institutions not listed above were prohibited from sharing de-identified data externally and were thus unable to participate in this multicenter cohort study. Data variables that were commonly available across all participating sites were identified prior to creation of a standardized database template for use in local instances of REDCap.

Each participating institution received approval from their respective institutional review board and COVID-19 data access committees, as determined by local institution policy, prior to initiation of data abstraction.

Study Variables and Outcomes

Demographic variables included age, sex, race, body mass index (BMI), comorbidities, substance use, and COVID-19 exposure. Laboratory data included transaminases, total bilirubin, and lipase. Clinical outcomes included the development of GI symptoms, admission to the intensive care unit (ICU), and death.

Statistical Analyses

Patients were stratified into regions (West, Midwest, or Northeast) depending on hospital location. Chi-squared test or Fisher exact test was used to compare categorical data and the Student t test or analysis of variance was used to evaluate continuous data, where appropriate. Univariable and multivariable logistic regression were used to evaluate the association between different factors and clinical outcomes (GI symptoms, ICU admission, and death) in the overall population. All analyses were performed using Python 3.8 with SciPy and statsmodels packages.

Results

Demographic Data

A total of 2031 patients hospitalized with a positive COVID-19 test were identified (Table 1). Most patients were male (57.4%) and Caucasian (39.0%). The mean age was 57.8 years (standard deviation [SD] 19.0) and the BMI was 29.9 kg/m^2 (SD 8.2). Patients in the Western cohort were significantly younger on average (56.4 years; SD 19.3). Over a third (36.5%) of patients had cardiovascular comorbidities and 20.1% had chronic GI or liver disease. A third (32.7%) of patients endorsed a history of smoking, while 22.2% endorsed alcohol use. Over a third (39.9%) of patients had a known COVID-19 exposure.

GI Manifestations

GI symptoms were present in 18.9% of the overall cohort; diarrhea was the most common (15.2%), followed by nausea and/or vomiting (12.6%) and abdominal pain (6.0%) (Table 2). The overall laboratory means were: lipase 57.4 U/L (SD 84.1), serum aspartate aminotransferase (AST) 60.3 U/L (SD 123.3), serum alanine aminotransferase (ALT) 45.5 U/L (SD 66.8), and total bilirubin 0.9 mg/dL (SD 2.5). Geographically, GI symptoms were significantly less common in the Western cohort (16.0%) than the Northeastern (25.6%) and Midwestern (26.7%) cohorts ($P < .01$). GI complications (GI hemorrhage and pancreatitis) were also less common in the Western cohort (2.7%, 0.4%) than the Northeastern (7.6%, 1.7%) and Midwestern (3.6%, 1.8%) cohorts. The Midwestern cohort had a higher prevalence of moderately elevated serum AST (22.8% vs 8.0% in Western and 10.7% in Northeastern cohorts). Compared with the Northeastern and Midwestern cohorts, the Western cohort had a higher prevalence of mildly elevated ALT (20.9% and 21.0% vs 28.0%) and total bilirubin (6.7% and 7.0% vs 10.6%). In subgroup analyses, race was not associated with GI or hepatic manifestations, although there were substantial missing data on race (Table A1). Hispanic ethnicity was associated with an abnormal ALT level in univariable but not multivariable models (Table A2). There was otherwise no significant association between Hispanic ethnicity and other GI or hepatic manifestations.

Table 1. Baseline Patient Characteristics

Characteristic	All sites (n = 2031)	West (n = 1435)	Midwest (n = 120)	Northeast (n = 476)	*P*
Age, mean years (SD)	57.8 (19.0)	56.4 (19.3)	63.0 (17.0)	61.0 (18.0)	<.01
Sex (%)					.92
Male	1153 (57.4)	807 (57.1)	70 (58.3)	276 (58.0)	
Female	856 (42.6)	606 (42.9)	50 (41.7)	200 (42.0)	
Race (%)					
White	793 (39.0)	545 (38.0)	9 (7.5)	239 (50.2)	<.01
Black	172 (8.5)	72 (5.0)	16 (13.3)	84 (17.6)	
Asian/Pacific Islander	165 (8.1)	100 (7.0)	1 (0.8)	64 (13.4)	
Other	300 (14.8)	234 (16.3)	0 (0)	66 (13.9)	
Unknown	601 (29.6)	484 (33.7)	94 (78.3)	23 (4.8)	
Hispanic ethnicity (%)	435 (21.4)	350 (24.4)	9 (7.5)	76 (16.0)	<.01
BMI, mean kg/m^2 (SD)	29.9 (8.2)	30.2 (8.2)	31.0 (9.9)	28.9 (7.7)	.01
Chronic comorbidities (%)					
Gastrointestinal disease	180 (11.7)	129 (13.6)	10 (8.3)	41 (8.6)	.01
Liver disease	130 (8.4)	120 (12.7)	2 (1.7)	8 (1.7)	<.01
Cardiovascular disease	742 (36.5)	571 (39.8)	51 (42.5)	120 (25.2)	<.01
Cerebrovascular disease	203 (10.0)	165 (11.5)	15 (12.5)	23 (4.8)	<.01
Lung disease	335 (16.5)	267 (18.7)	22 (18.3)	46 (9.7)	<.01
Diabetes	659 (32.5)	540 (37.8)	49 (40.8)	70 (14.7)	<.01
Kidney disease	362 (17.9)	285 (19.9)	26 (21.7)	51 (10.7)	<.01
Cancer	214 (11.9)	164 (13.3)	16 (13.3)	34 (7.1)	<.01
HIV/AIDS	13 (0.8)	8 (0.8)	5 (4.2)	0 (0)	<.01
Organ transplant recipient	88 (5.8)	68 (7.4)	3 (2.5)	17 (3.6)	<.01
Smoking (%)					<.01
Never	964 (67.2)	641 (71.4)	56 (47.4)	267 (63.9)	
Former	349 (24.3)	212 (23.6)	50 (42.4)	87 (20.8)	
Current	121 (8.4)	45 (5.0)	12 (10.2)	64 (15.3)	
Alcohol use (%)	280 (22.2)	168 (22.7)	28 (23.7)	84 (20.7)	.68
Drug use (%)	57 (2.8)	29 (2.0)	28 (23.3)	0 (0)	<.01
Recent travel (%)					<.01
No	1033 (85.9)	604 (81.4)	101 (84.9)	328 (96.2)	
Yes	74 (6.2)	59 (8.0)	2 (1.7)	13 (3.8)	
Unknown	95 (7.9)	79 (10.6)	16 (13.4)	0 (0)	
Known COVID-19 exposure (%)	480 (39.9)	306 (41.4)	43 (36.1)	131 (38.0)	.38

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; SD, standard deviation.

ICU vs Non-ICU Patients

There were 770 patients (37.9%) admitted to the ICU (Table 3). ICU admissions were more likely to be female (64.7% vs 52.9%; $P < .01$) and older (59.7 ± 17.9 vs 56.7 ± 19.6; $P < .01$). The most common presenting symptom was dyspnea in both ICU patients (61.1%) and non-ICU patients (46.6%). The prevalence of patients reporting GI symptoms was similar between ICU and non-ICU patients (18.0% vs 19.4%; $P = .48$). More patients suffered a GI hemorrhage in the ICU (8.9% vs 1.6%; $P < .01$). Compared with non-ICU patients, ICU patients had a higher prevalence of abnormal AST (58.1% vs 37.3%; $P < .01$), ALT (37.5% vs 29.3%; $P = .01$), and total bilirubin (12.7% vs 9.0%; $P < .01$). There was not a significant difference in prevalence of elevated lipase between the 2 groups (29.1% vs 25.0%; $P = .09$). ICU patients had a significantly higher mortality rate (22.7% vs 4.7%; $P < .01$). The overall mortality rate was 11.2%. The mortality rate in patients with GI symptoms was 8.4%, compared to 11.7% in patients without GI symptoms. In subgroup analyses, BMI was associated with an abnormal ALT level in non-ICU patients in univariable but not multivariable models (Table A3). There was otherwise no significant association between BMI and GI or hepatic manifestations in the ICU and non-ICU populations.

Predictors of Gastrointestinal Manifestations and Clinical Outcomes

In multivariable analyses, older age (adjusted odds ratio [aOR] = 0.68 (0.56–0.82)), female sex (aOR = 0.68 (0.48–0.95)), and abnormal bilirubin (aOR = 0.48 (0.31–0.76)) were associated with a reduced risk of GI symptoms (Table 4). Chronic liver disease was associated with developing GI symptoms. Female sex and abnormal AST or ALT were associated with an increased risk of ICU admission, while abnormal bilirubin was associated with a reduced risk of ICU admission. Older age (aOR = 2.23 (1.59–3.14)) and ICU admission (aOR = 11.20 (6.16–20.35))

Table 2. Gastrointestinal and Hepatic Manifestations in Patients With COVID-19

Characteristic	All sites (n = 2031)	West (n = 1435)	Midwest (n = 120)	Northeast (n = 476)	*P*
Gastrointestinal symptoms (%)					
Overall	384 (18.9)	230 (16.0)	32 (26.7)	122 (25.6)	<.01
Nausea/vomiting	196 (12.6)	126 (13.2)	15 (12.5)	55 (11.6)	.67
Abdominal pain	92 (6.0)	49 (5.2)	4 (3.3)	39 (8.2)	.03
Diarrhea	235 (15.2)	138 (14.5)	21 (17.5)	76 (16.0)	.59
Gastrointestinal complications (%)					
Hemorrhage	56 (4.5)	19 (2.7)	4 (3.6)	33 (7.6)	<.01
Pancreatitis	12 (1.0)	3 (0.4)	2 (1.8)	7 (1.7)	.09
Laboratory findings on admission					
Lipase, mean (SD)[a]	57.4 (84.1)	52.9 (48.3)	114.8 (249.9)	52.7 (52.3)	.01
Normal lipase (%)[a]	137 (68.8)	46 (70.8)	10 (58.8)	81 (69.2)	.54
Mildly elevated lipase (%)[a]	54 (27.1)	17 (26.2)	5 (29.4)	32 (27.4)	
Moderately elevated lipase (%)[a]	8 (4.0)	2 (3.1)	2 (11.8)	4 (3.4)	
AST, mean (SD)	60.3 (123.3)	53.3 (64.7)	89.7 (151.7)	63.2 (172.6)	.01
Normal AST (%)	650 (53.9)	374 (56.7)	44 (38.6)	232 (53.8)	<.01
Mildly elevated AST (%)[b]	430 (35.7)	233 (35.3)	44 (38.6)	153 (35.5)	
Moderately elevated AST (%)[b]	125 (10.4)	53 (8.0)	26 (22.8)	46 (10.7)	
ALT, mean (SD)	45.5 (66.8)	46.0 (59.8)	56.1 (125.9)	41.9 (53.0)	.12
Normal ALT	816 (67.3)	434 (64.9)	76 (66.7)	306 (71.2)	.03
Mildly elevated ALT (%)[b]	301 (24.8)	187 (28.0)	24 (21.0)	90 (20.9)	
Moderately elevated ALT (%)[b]	96 (7.9)	48 (7.2)	14 (12.3)	34 (7.9)	
Total bilirubin, mean (SD)	0.9 (2.5)	1.1 (3.3)	0.6 (0.5)	0.7 (1.0)	.04
Normal bilirubin (%)	1059 (89.4)	560 (87.6)	105 (92.1)	394 (91.4)	.20
Mildly elevated bilirubin (%)[c]	105 (8.9)	68 (10.6)	8 (7.0)	29 (6.7)	
Moderately elevated bilirubin (%)[c]	20 (1.7)	11 (1.7)	1 (0.9)	8 (1.8)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; SD, standard deviation.
Moderately elevated lipase was defined as a serum lipase >180 U/L (3 times the upper limit of normal).
[a]Serum lipase was not routinely tested among hospitalized patients. When collected, mildly elevated lipase was defined as a serum lipase between 60 and 180 U/L.
[b]Mildly elevated AST or ALT was defined as a serum AST or ALT between 40 and 100 U/L. Moderately elevated AST or ALT was defined as a serum AST or ALT >100 U/L.
[c]Mildly elevated bilirubin was defined as a serum total bilirubin between 1.2 and 3 mg/dL. Moderately elevated bilirubin was defined as a serum total bilirubin >3 mg/dL.

were associated with a higher likelihood of death. GI symptoms and chronic liver disease were not independently associated with death.

Discussion

In this nationwide multicenter cohort study, we found that GI symptoms were present in 19% of our patient population. Geographic variation was evident with a decreased prevalence of GI symptoms and GI complications in the Western cohort. There was also variance in liver function tests by region, but mortality was not significantly different across the country. In regards to disease severity, GI symptoms did not differ between ICU and non-ICU patients. However, frequencies of elevated ALT, AST, and total bilirubin levels were significantly different between the 2 cohorts. Female sex and abnormal AST or ALT were predictors for ICU admission, while ICU admission and age were predictors of mortality.

Similar to our study, the prevalence of GI symptoms was found to be 17.6% in a meta-analysis of 4243 patients with COVID-19 across 6 countries.[4] However, the literature is variable with regards to the presence of GI symptoms and disease severity. Certain studies have suggested a positive correlation between GI symptoms on presentation and risk of severe disease and complications from COVID-19.[4,14,15] However, these findings were not duplicated in several other studies, though possibly given the smaller number of patients studied.[16,17] In our large US cohort, the relatively similar frequency of GI symptoms in ICU and non-ICU patients in our cohort suggests that GI symptoms in COVID-19 may not be associated with disease severity. Notably, 2 US single-center studies along with the meta-analysis by Shehab et al. also found no statistical correlation between GI symptoms and disease severity.[10–12]

Unlike the variability seen in different studies regarding the presence of GI symptoms and disease severity, several prior studies have consistently shown an association between elevated aminotransferases and disease severity or ICU admission for COVID-19.[10,12,18,19] Similarly, abnormal liver function tests were more prominent in our ICU cohort; however, it is not entirely clear if this is secondary to direct

Table 3. Characteristics and Outcomes of Patients With COVID-19 Requiring and Not Requiring Admission to Intensive Care Unit

Characteristic	Admitted to ICU (n = 770)	Not admitted to ICU (n = 1261)	*P*
Demographics			
Age, mean years (SD)	59.7 (17.9)	56.7 (19.6)	<.01
Female (%)	498 (64.7)	655 (52.9)	<.01
BMI, mean kg/m^2 (SD)	30.1 (8.3)	29.7 (8.2)	.45
Current smoker (%)	43 (7.9)	78 (8.8)	.26
General signs and symptoms on hospital admission			
Temperature, mean C (SD)	37.4 (1.0)	37.3 (1.3)	<.01
Fever (%)	275 (44.5)	400 (43.2)	.66
Cough (%)	289 (40.2)	524 (44.6)	.06
Dyspnea (%)	450 (61.1)	548 (46.6)	<.01
Gastrointestinal symptoms (%)			
Overall	139 (18.0)	245 (19.4)	.48
Nausea/vomiting	63 (10.2)	133 (14.3)	.02
Abdominal pain	30 (4.9)	62 (6.7)	.16
Diarrhea	88 (14.2)	147 (15.8)	.43
Gastrointestinal complications (%)			
Hemorrhage	44 (8.9)	12 (1.6)	<.01
Pancreatitis	9 (1.8)	3 (0.4)	.03
Laboratory findings on hospital admission			
Lipase, mean (SD)[a]	69.7 (113.1)	47.6 (48.5)	.04
Normal lipase (%)[a]	53 (60.9)	84 (75.0)	.09
Mildly elevated lipase (%)[a]	29 (33.3)	25 (22.3)	
Moderately elevated lipase (%)[a]	5 (5.7)	3 (2.7)	
AST, mean (SD)	76.8 (176.4)	48.3 (58.2)	<.01
Normal AST (%)	212 (41.9)	438 (62.7)	<.01
Mildly elevated AST (%)[b]	215 (42.5)	215 (30.8)	
Moderately elevated AST (%)[b]	79 (15.6)	46 (6.6)	
ALT, mean (SD)	53.1 (90.0)	40.1 (42.2)	<.01
Normal ALT	317 (62.5)	499 (70.7)	.01
Mildly elevated ALT (%)[b]	143 (28.2)	158 (22.4)	
Moderately elevated ALT (%)[b]	47 (9.3)	49 (6.9)	
Total bilirubin, mean (SD)	1.0 (3.0)	0.8 (2.1)	.07
Normal bilirubin (%)	441 (87.3)	618 (91.0)	<.01
Mildly elevated bilirubin (%)[c]	49 (9.7)	56 (8.2)	
Moderately elevated bilirubin (%)[c]	15 (3.0)	5 (0.7)	
Disposition (%)			<.01
Discharged alive	488 (65.2)	1030 (83.9)	
Still hospitalized	30 (4.0)	45 (3.7)	
Transferred to another facility	49 (6.6)	79 (6.4)	
Death	170 (22.7)	58 (4.7)	
Palliative discharge	11 (1.5)	8 (0.6)	
Unknown	0 (0)	7 (0.6)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SD, standard deviation.
Moderately elevated lipase was defined as a serum lipase >180 U/L (3 times the upper limit of normal).
[a]Serum lipase was not routinely tested among hospitalized patients. When collected, mildly elevated lipase was defined as a serum lipase between 60 and 180 U/L.
[b]Mildly elevated AST or ALT was defined as a serum AST or ALT between 40 and 100 U/L. Moderately elevated AST or ALT was defined as a serum AST or ALT >100 U/L.
[c]Mildly elevated bilirubin was defined as a serum total bilirubin between 1.2 and 3 mg/dL. Moderately elevated bilirubin was defined as a serum total bilirubin >3 mg/dL.

effects of COVID-19 on the liver or a byproduct of systemic illness. Further research into how COVID-19 correlates with liver injury is warranted to further understand disease pathophysiology. Understanding this concept may help with management of patients with persistent liver function test abnormalities after resolution of infection.

The reasons for GI manifestations being overall less common in the Western cohort when compared with the Midwestern and Northeastern cohorts are unclear. One could postulate that different strains of COVID-19 predominated in these different regions of the United States, although successive viral strains have tended to spread throughout the

Table 4. Predictors of Gastrointestinal Manifestations and Clinical Outcomes

	OR (95% CI)	*P*	aOR (95% CI)	*P*
Gastrointestinal symptoms[a]				
Age, 20-y increments	0.84 (0.75–0.94)	<.01	0.68 (0.56–0.82)	<.01
Female	0.80 (0.64–1.00)	.05	0.68 (0.48–0.95)	.02
Chronic gastrointestinal disease	1.12 (0.78–1.59)	.55	1.10 (0.63–1.94)	.73
Chronic liver disease	0.97 (0.64–1.48)	.90	2.50 (1.02–6.11)	.04
Abnormal AST or ALT	0.61 (0.48–0.77)	<.01	0.73 (0.52–1.02)	.07
Abnormal bilirubin	0.51 (0.40–0.64)	<.01	0.48 (0.31–0.76)	<.01
ICU admission	0.91 (0.72–1.15)	.44	0.84 (0.60–1.18)	.33
ICU admission[b]				
Age, 20-y increments	1.18 (1.08–1.29)	<.01	1.18 (0.97–1.43)	.09
Female	1.63 (1.36–1.96)	<.01	2.05 (1.47–2.87)	<.01
Chronic gastrointestinal disease	0.74 (0.53–1.03)	.07	1.18 (0.68–2.02)	.56
Chronic liver disease	0.75 (0.51–1.09)	.13	0.65 (0.25–1.74)	.39
Abnormal AST or ALT	1.31 (1.07–1.60)	<.01	1.98 (1.42–2.77)	<.01
Abnormal bilirubin	0.72 (0.60–0.86)	<.01	0.46 (0.30–0.70)	<.01
Gastrointestinal symptoms	0.91 (0.72–1.15)	.44	0.84 (0.60–1.18)	.33
Death[b]				
Age, 20-y increments	2.01 (1.72–2.36)	<.01	2.23 (1.59–3.14)	<.01
Female	1.21 (0.91–1.60)	.19	1.52 (0.88–2.64)	.13
Chronic gastrointestinal disease	1.36 (0.88–2.11)	.16	1.92 (0.92–3.99)	.08
Chronic liver disease	0.44 (0.21–0.92)	.03	0.69 (0.16–3.01)	.62
Abnormal AST or ALT	1.12 (0.82–1.52)	.47	0.87 (0.51–1.46)	.59
Abnormal bilirubin	0.72 (0.55–0.96)	.02	1.37 (0.73–2.56)	.33
Gastrointestinal symptoms	0.78 (0.54–1.14)	.20	0.78 (0.44–1.38)	.40
ICU admission	5.88 (4.29–8.04)	<.01	11.20 (6.16–20.35)	<.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
[a]Multivariable models adjusted for age, sex, race, BMI, chronic comorbidities, smoking, alcohol use, drug use, and region. Not all predictors are reported in Table.
[b]Multivariable models adjusted for age, sex, race, BMI, chronic comorbidities, smoking, alcohol use, drug use, region, gastrointestinal symptoms, abnormal serum transaminases, and abnormal bilirubin. Not all covariates are reported in Table.

country over time. Another possibility involves interactions between diverse gut microbiota and viral illness. Regional variation in the composition of the gut microbiome has been described within and between countries globally.[20,21] However, the mechanisms of gut microbial-COVID virus interactions remain unknown. In addition, there was variation in ethnic makeup among the geographic cohorts with a higher proportion of African-American patients in the Midwestern and Northeast cohorts than in the Western cohort. Although there are several studies observing differences in microbiome makeup across ethnicities, exploratory analyses did not show an association between race and GI manifestations in our study population.[22,23]

There are some limitations to our study. Our data represented early outcomes of COVID-19, as our patients were all admitted prior to October 2020. This would not have factored in the impact of treatments that developed later and could have resulted in overestimated mortality and ICU outcomes. Adequate geographic variation may not have been achieved given that the majority of patients in the study were from the Western cohort, with fewer institutions representing the Midwest and Northeast. Given the rapid spread of COVID-19 and subsequent development of variants since the time of data abstraction, the geographic variability suggested by our data may be less evident now. Furthermore, differences in hospital admission criteria and electronic documentation of symptoms may have contributed to bias in the data. This could have affected standardization of our inclusion and exclusion criteria. Additionally, laboratory data were gathered at the time of admission, which may not have represented peak disease severity, undermining the impact of COVID-19 on liver function and the immune system.

Although GI manifestations were common among patients hospitalized with COVID-19, there was significant variability in prevalence across the United States and between ICU and non-ICU patients in our cohort of patients. This variability could be attributed to differing viral strains and severity of illness. Additional investigation into these trends could identify strategies to mitigate GI complications of COVID-19 infection through an improved understanding of pathophysiology and better tailored treatments. Further studies are needed to clarify the degree of hepatobiliary dysfunction that stems from direct injury from COVID-19 compared to the indirect effect of ICU-related multi-organ dysfunction. Such insight would help guide future management to reduce the risk of and mitigate hepatic injury in these patients. Overall, we present the largest known multicenter cohort of patients throughout the United States with COVID-19. This data can serve as a foundational resource for studies evaluating the evolution of the COVID-19 pandemic, including research into

the delta and omicron variants, long-term postinfection sequelae, and COVID-19 antibodies.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.07.002.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Due to institutional restrictions, data, analytics, and study materials will not be made available to other researchers.