Gastrointestinal symptoms in patients hospitalized with COVID-19
Prevalence and outcomes

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Abstract

To characterize outcomes in patients hospitalized with coronavirus disease 2019 (COVID-19) who present with gastrointestinal (GI) symptoms.

Clinical outcomes in patients with COVID-19 associated with GI symptoms have been inconsistent in the literature.

The study design is a retrospective analysis of patients, age 18 years or older, admitted to the hospital after testing positive for COVID-19. Clinical outcomes included intensive care unit requirements, rates of discharges to home, rates of discharges to outside facilities, and mortality.

Seven hundred fifty patients met the inclusion criteria. Three hundred seventy three (49.7%) patients presented with at least one GI symptom and 377 (50.3%) patients presented with solely non-GI symptoms. Patients who presented with at least one GI symptom had significantly lower ICU requirements (17.4% vs 20.2%), higher rates of discharges home (77.2% vs 67.4%), lower rates of discharges to other facilities (16.4% vs 22.8%), and decreased mortality (6.4% vs 9.8%) compared with patients with non-GI symptoms. However, patients who presented with solely GI symptoms had significantly higher ICU requirements (23.8% vs 17.0%), lower rates of discharges home (52.4% vs 78.7%), higher rates of discharges to facilities (28.6% vs 15.6%), and higher mortality (19.0% vs 5.7%) compared with those with mixed GI and non-GI symptoms.

Although patients with COVID-19 requiring hospitalization with GI symptoms did better than those without GI symptoms, those with isolated GI symptoms without extra-GI symptoms had worse clinical outcomes. COVID-19 should be considered in patients who present with new onset or worsening diarrhea, nausea, vomiting, and abdominal pain even without pulmonary symptoms.

Abbreviations: CCI = Charlson Comorbidity Index, COVID-19 = coronavirus 2019, CT chest = computed tomography chest, CTAP = computed tomography abdomen and pelvis, CXR = chest X-ray, GI = gastrointestinal, ICU = intensive care unit, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: coronavirus disease 2019, coronavirus, gastrointestinal symptoms

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initial symptoms of COVID-19 at the start of the pandemic were mainly characterized by respiratory manifestations but are now found to be heterogenous and can involve gastrointestinal (GI) symptoms.[1] Outcomes of patients with COVID-19 presenting with GI symptoms have been discrepant: some studies suggest better outcomes in patients with COVID-19 who present with GI symptoms while other studies suggest a poorer prognosis.[2–7] Clinical outcomes associated with GI symptoms described in these studies have largely been with concomitant extra-GI symptoms. It is possible that concurrent non-GI symptoms were confounders, which could explain the heterogeneity of outcomes in patients presenting with GI symptoms.

Infection of the GI tract by SARS-CoV-2 has been described and is thought to occur from viral entry via the ACE2 protein

receptor found in multiple organs including the small intestine.[8] The most common GI symptoms documented in patients with COVID-19 are abdominal pain, diarrhea, nausea, and vomiting.[9–11] Of these 4 symptoms, diarrhea, nausea, and vomiting have been more prevalent than abdominal pain.[12] Diarrhea is thought to occur in COVID-19 due to alteration of intestinal permeability from intestinal inflammation, resulting in enterocyte malabsorption.[13] Nausea and vomiting have been theorized to occur from aberrant viral activation of the nucleus tractus solitarus via the vagal afferent nerve and the area postrema efferent pathways with downstream effects that trigger nausea and vomiting.[14] The GI tract may also serve as a source for transmission of SARS-CoV-2 as viral RNA has been detected in stool.[15] Therefore, investigating the presenting GI symptoms and the implications of infection of the GI tract associated with COVID-19 is important for identification of COVID-19 infected patients to help mitigate the spread of the disease.

The goal of our study is to characterize outcomes in patients with COVID-19 who present with GI symptoms and compare these outcomes to those who do not present with GI symptoms. In addition, we also looked at outcomes of patients presenting solely with GI symptoms without non-GI symptoms. This will allow for better understanding of the prognosis for patients with COVID-19 who present with GI symptoms.

2. Methods

We retrospectively analyzed patients, ages 18 years or older, hospitalized with COVID-19 from March 2020 to June 2020 in our urban, academic, safety-net hospital. After Institutional Review Board (protocol #: 27297) approval by Temple University, medical records were obtained through the electronic medical record system at our institution. Only patients who tested positive for COVID-19 via nasopharyngeal swab and were hospitalized were included in this study. Patients who were deemed presumptive positive for COVID-19 but did not test positive by nasopharyngeal swab were excluded from this study.

Symptoms were stratified into GI, general, pulmonary, and head & neck symptoms. GI symptoms included abdominal pain, diarrhea, nausea, and vomiting. General symptoms included anorexia, fatigue, and fever. Pulmonary symptoms included cough and dyspnea. Head & neck symptoms included anosmia and dysgeusia. A patient's symptoms at presentation were obtained from the history and physical documented by the healthcare professional on admission. Patients were stratified based on whether they presented with solely GI (Only-GI) symptoms, only non-GI (Non-GI) symptoms, or a combination of GI and non-GI (Mixed-Sxs) symptoms. Laboratory values and imaging studies were obtained on admission to the hospital.

Results from chest X-rays (CXR) were stratified into no significant finding, patchy infiltrates, multifocal pneumonia, single consolidation, or other. Computed tomography chest (CT chest) results were stratified by our institution's categorizing system into category 1, 2, or 3. Category 1 includes findings consistent with multifocal pneumonia including viral/atypical pneumonia. Category 2 includes indeterminate presence of multifocal pneumonia including viral/atypical pneumonia. Category 3 includes no findings of pneumonia. Abdominal X-rays and CT abdomen and pelvis (CTAP) were stratified into no significant findings and significant findings. Significant findings in abdominal X-rays included small bowel obstruction and colonic distention. Significant findings on CTAP included

adrenal nodule, ascites, cholelithiasis, cirrhosis, colitis, dilation, diverticulosis, gastritis, hernia, ileus, liver lesion, pancreatitis, pyelonephritis, renal abscess, renal mass, and small bowel obstruction.

Clinical outcomes included intensive care unit requirements, rate of discharges home, rate of discharges to outside facilities, and mortality rates. Results are expressed as percentage of patients, mean values with standard deviation, and odds ratios with 95% confidence interval. Statistical significance was determined by a P-value $\leq .05$. Two-tailed Student t test was used to compare means from 2 different samples. Chi-square analysis was used to compare categorical variables. Multiple logistic regression analysis was used to compare outcomes between cohorts. Clinical significance on regression analysis was determined by confidence intervals that did not include 1.0. All statistical analyses were obtained using Graphpad Prism v 9.0.1 – 9.1.2.

3. Results

3.1. All patients

Seven hundred fifty patients met the inclusion criteria for this study: adult patients hospitalized for COVID-19, as documented by nasopharyngeal swab for SARS-CoV-2 RNA. General characteristics of the patients including age, race, gender, Charlson Comorbidity Index (CCI), median income as determined by the patient's zip code, and insurance are shown in Table 1.

Presenting symptoms are shown in Table 2. Presenting symptoms of all patients included 517 (68.9%) patients with cough, 453 (60.4%) patients with dyspnea, 415 (55.3%) patients with fever, 253 (33.7%) patients with fatigue, 219 (29.2%) patients with diarrhea, 196 (26.1%) patients with nausea, 187 (24.9%) patients with anorexia, 123 (16.4%) patients with vomiting, 106 (14.1%) patients with abdominal pain, 60 (8.0%) patients with dysgeusia, and 50 (6.7%) patients with anosmia. Results of admission laboratory values and imaging studies are shown in Table 3.

The average length of stay for the entire cohort was 8.6 ± 8.9 days. Medications for treatment included chloroquine, steroids, anakinra, tocilizumab, etoposide, intravenous immunoglobulin (IVIG), remdesivir, sarilumab, gimsilumab, ceftriaxone, azithromycin, cefepime, piperacillin-tazobactam, and vancomycin. Treatments received are summarized in Table 4.

One hundred forty one (18.8%) patients required care in the intensive care unit. Five hundred forty two (72.3%) patients were discharged home, 147 (19.6%) patients were discharged to an external facility including skilled nursing facilities, long-term acute care facilities, or hospice, and 61 (8.1%) patients died. Outcomes are summarized in Table 5. The primary cause of death of the 61 patients who died was acute hypoxic respiratory failure in 36 (59.0%) patients, multi-organ dysfunction in 12 (19.7%) patients, sepsis in 4 (6.6%) patients, cardiac arrest in 5 (8.2%) patients, renal failure in 2 (3.3%) patients, and unknown in 1 (1.6%) patient. Primary causes of death are summarized in Table 6.

3.2. Any GI symptom and Non-GI symptoms

Three hundred seventy three (49.7%) patients presented with at least one GI symptom (GI-Sxs cohort) and 377 (50.3%) patients

Table 1

General characteristics, Charlson Comorbidity Index (CCI), median income, and insurance of all patients, only-GI compared with mixed Sxs, and GI-Sxs compared with Non-GI.

		Total	Only-GI	Mixed-Sxs	Sig.	GI-Sxs	Non-GI	Sig.
Number of patients		750	21	352		373	377	
Age		58.2 ± 15.2	63.4 ± 10.4	56.4 ± 14.6	$P < .05$	56.8 ± 14.4	59.5 ± 15.9	$P < .05$
Race	Black	382 (50.9%)	12 (57.1%)	183 (52.0%)	ns	195 (52.3%)	187 (49.6%)	ns
	Asian	7 (0.9%)	0 (0.0%)	4 (1.1%)		4 (1.1%)	3 (0.8%)	
	White	55 (7.3%)	3 (14.3%)	18 (5.1%)		21 (5.6%)	34 (9.0%)	
	Hispanic	226 (30.1%)	4 (19.0%)	107 (30.4%)		111 (29.8%)	115 (30.5%)	
	Other	80 (10.7%)	2 (9.5%)	40 (11.4%)		42 (11.3%)	38 (10.1%)	
Gender	Male	401 (53.5%)	12 (57.1%)	177 (50.3%)	ns	189 (50.7%)	212 (56.2%)	ns
	Female	349 (46.5%)	9 (42.9%)	175 (49.7%)		184 (49.3%)	165 (43.8%)	
CCI		3.8 ± 3.2	5.0 ± 2.8	3.5 ± 3.0	$P < .05$	3.6 ± 3.0	4.0 ± 3.3	ns
Median income		33,266	39,146	31,258	$P < .05$	31,701	34,813	$P < .05$
Insurance	Commercial	185 (24.7%)	3 (14.3%)	93 (26.4%)	ns	96 (25.7%)	89 (23.6%)	ns
	Medicare	508 (67.7%)	18 (85.7%)	230 (65.3%)		248 (66.5%)	260 (69.0%)	
	Medicaid	52 (6.9%)	0 (0.0%)	26 (7.4%)		26 (7.0%)	26 (6.9%)	
	None	5 (0.7%)	0 (0.0%)	3 (0.9%)		3 (0.8%)	2 (0.5%)	

presented with no GI (Non-GI cohort) symptoms. General characteristics for both cohorts are shown in Table 1.

Presenting symptoms are shown in Table 2. Presenting symptoms in the GI-Sxs cohort included 274 (73.5%) patients with cough, 233 (62.5%) patients with dyspnea, 226 (60.6%) patients with fever, 219 (58.7%) patients with diarrhea, 196 (52.5%) patients with nausea, 132 (35.4%) patients with anorexia, 130 (34.9%) patients with fatigue, 123 (33.0%) patients with vomiting, 106 (28.4%) patients with abdominal pain, 37 (9.9%) patients with dysgeusia, and 29 (7.8%) patients with anosmia.

Presenting symptoms in the Non-GI cohort included 243 (64.5%) patients with cough, 220 (58.4%) patients with dyspnea, 189 (50.1%) patients with fever, 123 (32.6%) patients with fatigue, 55 (14.6%) patients with anorexia, 23 (6.1%) patients with dysgeusia, and 21 (5.6%) patients with anosmia.

General symptoms of anorexia (GI-Sxs: 35.4% vs Non-GI: 14.6%), fatigue (GI-Sxs: 34.9% vs Non-GI: 32.6%), and fever (GI-Sxs: 60.6% vs Non-GI: 50.1%), were found to be statistically different between the 2 cohorts on chi-square analysis ($P < .0001$).

Results of admission laboratory values and imaging studies are shown in Table 3. Treatments received are summarized in Table 4. Outcomes are summarized in Table 5. Average length of stay for the GI-Sxs cohort and the Non-GI cohort were 8.6 ± 8.8 days and 8.6 ± 9.0 days, respectively. In the GI-Sxs cohort, 65 (17.4%) patients required ICU level of care, 288 (77.2%) patients were discharged home, 61 (16.4%) patients were discharged to a facility, and 24 (6.4%) patients died. In the Non-GI cohort, 76 (20.2%) patients required ICU level of care, 254 (67.4%) patients were discharged home, 86 (22.8%) patients were discharged to a facility, and 38 (9.8%) patients died. Patient outcomes were significantly different between the 2 cohorts on chi-square analysis ($P = .02$).

After controlling for CCI on multiple logistic regression, the GI-Sxs cohort compared with the Non-GI cohort had an odds ratio (OR) 0.83 (95% CI: 0.57–1.20; $P = .29$) for ICU requirement, an OR 1.6 (95% CI: 1.1–2.2; $P < .0001$) for discharge home, an OR 0.70 (95% CI: 0.48–1.0; $P < .0001$) for discharge to facility, and an OR 0.71 (95% CI: 0.40–1.2; $P < .0001$) for mortality.

Table 2

Symptoms at presentation to the hospital in all patients, Only-GI compared with Mixed-Sxs, and GI-Sxs compared with Non-GI.

			Total	Only-GI	Mixed-Sxs	Sig.	GI-Sxs	Non-GI	Sig.
Symptoms at presentation	GI symptoms	Abdominal pain	106 (14.1%)	11 (52.4%)	95 (27.0%)	ns	106 (28.4%)		
		Diarrhea	219 (29.2%)	7 (33.3%)	212 (60.2%)		219 (58.7%)		
		Nausea	196 (26.1%)	12 (57.1%)	184 (52.3%)		196 (52.5%)		
		Vomiting	123 (16.4%)	8 (38.1%)	115 (32.7%)		123 (33.0%)		
	General symptoms	Anorexia	187 (24.9%)		132 (37.5%)		132 (35.4%)	55 (14.6%)	$P < .0001$
		Fatigue	253 (33.7%)		130 (36.9%)		130 (34.9%)	123 (32.6%)	
		Fever	415 (55.3%)		226 (64.2%)		226 (60.6%)	189 (50.1%)	
	Pulmonary symptoms	Cough	517 (68.9%)		274 (77.8%)		274 (73.5%)	243 (64.5%)	ns
		Dyspnea	453 (60.4%)		233 (66.2%)		233 (62.5%)	220 (58.4%)	
	Head and neck symptoms	Anosmia	50 (6.7%)		29 (8.2%)		29 (7.8%)	21 (5.6%)	ns
		Dysgeusia	60 (8.0%)		37 (10.5%)		37 (9.9%)	23 (6.1%)	

Symptoms were stratified into GI symptoms (abdominal pain, diarrhea, nausea, and vomiting), general symptoms (anorexia, fatigue, fever, and cough), pulmonary symptoms (cough and dyspnea), and head and neck symptoms (anosmia and dysgeusia).

Table 3

Data on admission to the hospital of all patients, Only-GI compared with Mixed-Sxs, and GI-Sxs compared with Non-GI.

		Total	Only-GI	Mixed-Sxs	Sig.	GI-Sxs	Non-GI	Sig.
Laboratory values	AST, U/L	50.2±70.0	73.8±131.3	51.4±65.6	ns	52.6±70.5	47.8±69.5	ns
	ALT, U/L	41.4±35.2	31.1±25.1	43.4±35.3	ns	42.8±35.0	40.0±35.4	ns
	ALK, U/L	86.5±62.2	83.1±26.5	86.2±75.8	ns	86.0±74.0	87.1±47.6	ns
	T. Bili, mg/dL	0.67±0.6	0.75±1.2	0.67±0.6	ns	0.68±0.6	0.66±0.5	ns
Imaging	CXR	743 (99.1%)	20 (95.2%)	351 (99.7%)	P<.01	371 (99.5%)	372 (98.7%)	ns
	CT chest	719 (95.9%)	20 (95.2%)	342 (97.2%)		362 (97.1%)	357 (94.7%)	
	Abd X-ray	47 (6.3%)	3 (14.3%)	18 (5.1%)		21 (5.6%)	26 (6.9%)	
	CT AP	96 (12.8%)	9 (42.9%)	48 (13.6%)		57 (15.3%)	39 (10.3%)	
CXR	No significant finding	176 (23.7%)	4 (20.0%)	93 (26.5%)	ns	97 (26.1%)	79 (21.2%)	P<.05
	Patchy infiltrates	248 (33.4%)	8 (40.0%)	121 (34.5%)		129 (34.8%)	119 (32.0%)	
	Multifocal pneumonia	179 (24.1%)	3 (15.0%)	78 (22.2%)		81 (21.8%)	98 (26.3%)	
	Single consolidation	46 (6.2%)	0 (0.0%)	28 (8.0%)		28 (7.5%)	18 (4.8%)	
	Other	94 (12.7%)	5 (25.0%)	31 (8.8%)		36 (9.7%)	58 (15.6%)	
CT chest	Category 1	599 (83.3%)	18 (90.0%)	292 (85.4%)	ns	310 (85.6%)	289 (81.0%)	ns
	Category 2	76 (10.6%)	1 (5.0%)	32 (9.4%)		33 (9.1%)	43 (12.0%)	
	Category 3	44 (6.1%)	1 (5.0%)	18 (5.3%)		19 (5.2%)	25 (7.0%)	
Abd X-ray	No significant finding	42 (89.4%)	2 (66.7%)	16 (88.9%)	ns	18 (85.7%)	24 (92.3%)	ns
	Significant finding*	5 (10.6%)	1 (33.3%)	2 (11.1%)		3 (14.3%)	2 (7.7%)	
CTAP	No significant finding	57 (59.4%)	5 (55.6%)	30 (62.5%)	ns	35 (61.4%)	22 (56.4%)	ns
	Significant finding**	39 (40.6%)	4 (44.4%)	18 (37.5%)		22 (38.6%)	17 (43.6%)	

Data includes laboratory values (ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALK = alkaline phosphatase, T. Bili = total Bilirubin).

* Significant findings in abdominal X-rays include small bowel obstruction and colonic distention.

** Significant findings on CT abdomen and pelvis includes adrenal nodule, ascites, cholelithiasis, cirrhosis, colitis, dilation, diverticulosis, gastritis, hernia, ileus, liver lesion, pancreatitis, pyelonephritis, renal abscess, renal mass, and small bowel obstruction.

The primary cause of death in the GI-Sxs cohort included 11 (45.8%) deaths from acute hypoxic respiratory failure, 10 (41.7%) from multi-organ dysfunction, 2 (8.3%) from sepsis, and 1 (4.2%) from cardiac arrest. The primary cause of death in the Non-GI cohort included 26 (70.3%) deaths from acute hypoxic respiratory failure, 2 (5.4%) from multi-organ dysfunction, 2 (5.4%) from sepsis, 4 (10.8%) from cardiac arrest, 2 (5.4%) from renal failure, and 1 (2.7%) from an unknown cause. Primary cause of death was significantly different between the 2 groups on chi-square analysis ($P=.02$). Primary causes of death in both the GI-Sxs and Non-GI cohorts are summarized in Table 6.

3.3. Only GI symptoms and mixed symptoms

Twenty one (2.8%) patients were in the Only-GI cohort and presented with only GI symptoms. Three hundred fifty two (46.9%) patients were in the Mixed-Sxs cohort and presented with concomitant GI and Non-GI symptoms. General characteristics of both cohorts are shown in Table 1.

Presenting symptoms are summarized in Table 2. Presenting symptoms for the Only-GI cohort included 12 (57.1%) patients with nausea, 11 (52.4%) patients with abdominal pain, 8 (38.1%) patients with vomiting, and 7 (33.3%) patients with diarrhea. Presenting symptoms for the Mixed-Sxs cohort included 274 (77.8%) patients with cough, 233 (66.2%)

Table 4

Treatments for all patients, Only-GI compared with Mixed-Sxs, and GI-Sxs compared with Non-GI.

		Total	Only-GI	Mixed-Sxs	Sig.	GI-Sxs	Non-GI	Sig.
Treatment	Chloroquine	26 (3.5%)	1 (4.8%)	14 (4.0%)	ns	15 (4.0%)	11 (2.9%)	ns
	Steroids	679 (90.5%)	15 (71.4%)	332 (94.3%)		347 (93.0%)	332 (88.1%)	
	Anakinra	88 (11.7%)	4 (19.0%)	43 (12.2%)		47 (12.6%)	40 (10.6%)	
	Tocilizumab	98 (13.1%)	3 (14.3%)	44 (12.5%)		47 (12.6%)	51 (13.5%)	
	Etoposide	9 (1.2%)	0 (0.0%)	3 (0.9%)		3 (0.8%)	6 (1.6%)	
	IVIG	113 (15.1%)	5 (23.8%)	51 (14.5%)		56 (15.0%)	57 (15.1%)	
	Remdesivir	150 (20.0%)	6 (28.6%)	80 (22.7%)		86 (23.1%)	64 (17.0%)	
	Sarilumab	144 (19.2%)	2 (9.5%)	65 (18.5%)		67 (18.0%)	77 (20.4%)	
	Gimsilumab	27 (3.6%)	0 (0.0%)	19 (5.4%)		19 (5.1%)	8 (2.1%)	
	Ceftriaxone	618 (82.4%)	16 (76.2%)	307 (87.2%)		323 (86.6%)	295 (78.2%)	
	Azithromycin	655 (87.3%)	15 (71.4%)	316 (89.8%)		331 (88.7%)	324 (85.9%)	
	Cefepime	106 (14.1%)	6 (28.6%)	41 (11.6%)		47 (12.6%)	59 (15.6%)	
	Piperacillin-Tazobactam	84 (11.2%)	4 (19.0%)	66 (18.8%)		70 (18.8%)	48 (12.7%)	
	Vancomycin	144 (19.2%)	6 (28.6%)	55 (15.6%)		61 (16.4%)	83 (22.0%)	

Table 5

Patient outcomes in all patients, Only-GI compared with mixed Sxs, and GI-Sxs compared with Non-GI.

		Total	Only-GI	Mixed Sxs	Sig.	GI Sxs	Non-GI	Sig.
Patient outcome	Discharged to home	542 (72.3%)	11 (52.4%)	277 (78.7%)	$P<.05$	288 (77.2%)	254 (67.4%)	$P<.05$
	Discharged to facility	147 (19.6%)	6 (28.6%)	55 (15.6%)		61 (16.4%)	86 (22.8%)	
	Deceased	61 (8.1%)	4 (19.0%)	20 (5.7%)		24 (6.4%)	37 (9.8%)	
	ICU	141 (18.8%)	5 (23.8%)	60 (17.0%)		65 (17.4%)	76 (20.2%)	
Multiple logistic regression analysis	Discharged to home		OR: 0.38			OR: 1.56		
			(95% CI: 0.15–0.99)			(95% CI: 1.10–2.20)		
	Discharged to facility		OR: 1.78			OR: 0.71		
			(95% CI: 0.60–4.69)			(95% CI: 0.48–1.03)		
	Deceased		OR: 1.68			OR: 0.83		
			(95% CI: 0.53–4.57)			(95% CI: 0.57–1.20)		
	ICU		OR: 2.99			OR: 0.71		
			(95% CI: 0.73–10.21)			(95% CI: 0.40–1.22)		

Patient outcomes were stratified into discharged to home, discharged to facility, deceased, and requirement of intensive care unit (ICU) level of care. Multiple logistic regression after controlling for age and comorbidities via the CCI are shown for these same clinical outcomes.

Table 6

Primary cause of death included acute hypoxic respiratory failure, multi-organ dysfunction, sepsis, cardiac arrest, renal failure, and unknown.

		Total	Only-GI	Mixed Sxs	Sig.	GI Sxs	Non-GI	Sig.
Primary cause of death	Acute hypoxic respiratory failure	36 (59.0%)	3 (75.0%)	8 (40.0%)	ns	11 (45.8%)	26 (70.3%)	$P<.05$
	Multi-organ dysfunction	12 (19.7%)	1 (25.0%)	9 (45.0%)		10 (41.7%)	2 (5.4%)	
	Sepsis	4 (6.6%)	0 (0.0%)	2 (10.0%)		2 (8.3%)	2 (5.4%)	
	Cardiac arrest	5 (8.2%)	0 (0.0%)	1 (5.0%)		1 (4.2%)	4 (10.8%)	
	Renal failure	2 (3.3%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	2 (5.4%)	
	Unknown	1 (1.6%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (2.7%)	

patients with dyspnea, 226 (64.2%) patients with fever, 212 (60.2%) patients with diarrhea, 184 (52.3%) patients with nausea, 132 (37.5%) patients with anorexia, 130 (36.9%) patients with fatigue, 115 (32.7%) patients with vomiting, 94 (27.0%) patients with abdominal pain, 37 (10.5%) patients with dysgeusia, and 29 (8.2%) patients with anosmia. There were no significant differences between presenting GI symptoms between the two cohorts on chi-square analysis.

Admission laboratory data and imaging studies are shown in Table 3. On admission, 20 (95.2%) patients of the Only-GI cohort received a CXR, 20 (95.2%) patients received a CT chest, 3 (14.3%) received an abdominal X-ray, and 9 (42.9%) patients received a CTAP. In the Mixed-Sxs cohort, 351 (99.7%) patients received a CXR, 342 (97.2%) patients received a CT chest, 18 (5.1%) received an abdominal X-ray, and 48 (13.6%) patients received a CTAP. There was a statistically significant difference in imaging modalities obtained between the 2 cohorts on chi-square analysis ($P<.01$). Treatments received are summarized in Table 4.

The average length of stay in the Only-GI and the Mixed-Sxs cohorts were 8.4 ± 6.0 days and 8.6 ± 9.0 days, respectively. Outcomes are summarized in Table 5. In the Only-GI cohort, 5 (23.8%) patients required ICU level of care, 11 (52.4%) patients were discharged to home, 6 (28.6%) patients were discharged to another facility, and 4 (19.0%) patients died. In the Mixed-Sxs cohort, 60 (17.0%) patients required ICU level of care, 277 (78.7%) patients were discharged to home, 55 (15.6%) patients were discharged to facility, and 20 (5.7%) patients died. Patient

outcomes were significantly different between both cohorts ($P<.05$). After controlling for CCI on multiple logistic regression, the Only-GI cohort compared with the Mixed Sxs cohort had an OR 1.7 (95% CI: 0.53–4.6; $P<.05$) for ICU requirement, an OR 0.38 (95% CI: 0.15–0.99; $P<.0001$) for discharges home, an OR 1.8 (95% CI: 0.60–4.7; $P<.001$) for discharges to a facility, and an OR 3.0 (95% CI: 0.73–10.2; $P<.0001$) for mortality.

The primary cause of death in the Only-GI cohort included 3 (75%) patients from acute hypoxic respiratory failure and 1 (25.0%) patient from multi-organ dysfunction. Primary cause of death in the Mixed-Sxs cohort included 8 (40.0%) patients from acute hypoxic respiratory failure, 9 (45.0%) patients from multi-organ dysfunction, 2 (10.0%) patients from sepsis, and 1 (5.0%) patient from cardiac arrest. There were no significant differences in the primary cause of death between both cohorts. Primary causes of death in both the Only-GI and Mixed-Sxs cohorts are summarized in Table 6.

4. Discussion

At our institution, half of the patients hospitalized for COVID-19 presented with at least one GI symptom in the form of abdominal pain, diarrhea, nausea, and vomiting. These patients who presented with GI symptoms had lower requirements of ICU level of care, higher rates of discharges to home, less rates of discharges to other facilities, and less mortality compared with those who did not present with any GI symptoms.

The outcomes of patients with COVID-19 presenting with GI symptoms have varied. The positive association between GI symptoms at presentation and better outcomes in patients with COVID-19 compared with those who only presented with non-GI symptoms has been described in the literature.[2–5,7] It is possible that infection of the GI system may portend a less severe phenotype of the disease than infection of other organ systems, particularly the respiratory system. One study found that the main cause of death in patients with COVID-19 were related to respiratory disease.[16] Another study found via autopsy that sepsis caused by purulent lung infection was the most frequent cause of death found in patients with COVID-19.[17] Most patients in our study died primarily from acute hypoxic respiratory failure. Other studies, however, suggest that there are actually worse outcomes in those with COVID-19 who present with GI symptoms.[6,18,19] This discrepancy in outcomes associated with GI symptoms is unclear, and one of the reasons that we performed this study. Notably, GI symptoms in these studies did not stratify those who presented solely with GI symptoms and those with concomitant non-GI symptoms. Therefore, it is possible that non-GI symptoms may have been a confounding factor resulting in mixed positive and negative outcomes associated with GI symptoms in these studies. In our study, patients who presented with GI symptoms had lower requirements of ICU level of care, higher rates of discharges to home, less rates of discharges to other facilities, and less mortality compared with those who did not present with any GI symptoms. After controlling for co-morbidities, the rate of discharges home was found to be clinically significant for the cohort with GI symptoms compared with the cohort without GI symptoms on multiple logistic regression analysis with an OR 1.6 (95% CI: 1.1–2.2).

We further stratified patients to those who presented solely with GI symptoms (Only-GI) and those who presented with concomitant GI and non-GI symptoms (Mixed-Sxs). The patients who presented solely with GI symptoms, although uncommon, had worse outcomes. These patients had higher requirement of ICU level of care, lower rates of discharges home, higher rates of discharges to other facilities, and higher rates of mortality. Patients who presented with only GI symptoms were older and had more comorbidities. After controlling for these variables via the CCI on multiple logistic regression, the Only-GI cohort was found to have less discharges home compared to those in the Mixed-Sxs cohort (OR 0.38; 95% CI: 0.15–0.99).

In the diagnostic work-up for the patients in our study, nearly all patients in both the Only-GI and the Mixed-Sxs cohorts received both CXR's and CT chest imaging. This was likely to rule out COVID-19 pneumonia prior to triaging patients from the Emergency Department as chest imaging was recommended as an adjunct to diagnostic tools for COVID-19 in symptomatic patients.[20] Notably, patients who presented solely with GI symptoms received a significantly higher number of abdominal X-rays and CTAP on admission. Although Bhayana et al[21] describe that patients with COVID-19 are more likely to have bowel-wall thickening, pneumatosis, and portal venous gas on imaging, most of the patients in both cohorts had no significant findings on either abdominal X-ray or CTAP. Interestingly, both CXR and CT chest imaging studies showed similar rates of infiltrates/consolidations and evidence of viral/atypical pneumonia, respectively, between both cohorts. Evidence of pulmonary disease on imaging in the absence of any non-GI symptoms is unexpected as fever, dry cough, and fatigue are often the first signs of COVID-19 pneumonia.[22] Additionally, most of the

deaths in both cohorts were found to be secondary to acute hypoxic respiratory failure. One possible explanation for the presence of pulmonary disease in the absence of respiratory symptoms may be due to systemic spread of the SARS-CoV-2 after a primary GI infection. Studies have shown that the SARS-CoV-2 ACE2 protein cell receptor is present in the GI tract and that these receptors are similar to those found in the respiratory system.[23,24] Evidence of viremia with SARS-CoV-2 has also been documented, which suggests the possibility of inter-organ dissemination of SARS-CoV-2.[25] We hypothesize that patients with COVID-19 who present solely with GI symptoms may initially be infected with SARS-CoV-2 in the GI tract with subsequent systemic spread of the virus to other organs. Asymptomatic respiratory infection found incidentally on imaging in patients who present initially with only GI symptoms may be the earliest signs of systemic spread of SARS-CoV-2 to the pulmonary system. Therefore, although the World Health Organization currently recommends against the use of diagnostic chest imaging in asymptomatic patients, it may be worthwhile to screen for pulmonary disease in COVID-19 patients who present solely with GI manifestations to rule out the possibility of systemic spread of COVID-19.[20] Prompt diagnosis of COVID-19 in patients with GI manifestations is imperative given the possibility of systemic spread, pulmonary involvement, and progression of disease. Patients who presented solely with GI symptoms may have had delays in treatment for COVID-19 as other etiologies for the GI symptoms may have been initially considered given the significant amount of diagnostic abdominal imaging studies obtained for this cohort.

The main strengths of this study include the large sample size (n = 750) and use of electronic medical record to capture accurate testing and outcomes. To the best of our knowledge, this is the first study to assess characteristics and outcomes in patients with COVID-19 presenting solely with GI symptoms and in the absence of non-GI symptoms. The main limiting factors of this study include its retrospective nature and its single center study design. Another limiting factor to this study was the small sample size of patients who presented with solely GI symptoms (n = 21). The patient population also only included those who were admitted to the hospital and did not include those in the outpatient setting. Future research is needed to further characterize clinical presentations and outcomes of those with COVID-19 who present with only GI symptoms. This is especially important with the discovery of different variants of SARS-CoV-2 such as the delta variant which has been documented as being more severe than the alpha variant.[26]

In conclusion, COVID-19 should be considered on the differential diagnosis in patients who present with GI symptoms without a clear etiology. The presence of GI symptoms in patients with other COVID-19 symptoms are associated with better clinical outcomes when compared with patients who only present with extra-GI symptoms. However, isolated GI symptoms in the absence of non-GI symptoms, although uncommon, are associated with worse outcomes likely because COVID-19 pneumonia is undetected. Prompt diagnosis of COVID-19 in these patients who present with GI symptoms is important given the possibility of pulmonary involvement.

Author contributions

Jun Song: planned study, performed chart review, organized and analyzed data, wrote manuscript.

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