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Gastrointestinal symptoms and healthcare utilization have increased among patients with functional gastrointestinal and motility disorders during the COVID-19 pandemic

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has led to unprecedented disruptions in healthcare. Functional gastrointestinal and motility disorders (FGIMD) are associated with significant healthcare utilization. The clinical implications of these healthcare disruptions due to the COVID-19 pandemic on clinical outcomes in patients with FGIMD are unclear.

Methods: We performed a retrospective study of patients with three common FGIMD (irritable bowel syndrome [IBS], gastroparesis, functional dyspepsia [FD]) tested for SARS-CoV-2 to describe alterations in gastrointestinal symptoms, medication use, and healthcare utilization during and before the pandemic and factors associated with COVID-19.

Key Results: The prevalence of COVID-19 during the pandemic (03/2020–09/2020) was 3.20% (83/2592) among patients with FGIMD, 3.62% in IBS (57/1574), 3.07% in gastroparesis (23/749), and 2.44% in FD (29/1187) at our institution. Patients with FGIMD had increased abdominal pain, nausea/vomiting, diarrhea, constipation, and weight loss ($p < 0.001$) along with increased proton pump inhibitor, H2 blocker, and opioid use ($p < 0.0001$). Both inpatient hospitalizations and outpatient visits ($p < 0.0001$) and number of diagnostic tests including cross-sectional imaging ($p = 0.002$), and upper and lower endoscopies ($p < 0.0001$) were significantly higher during the pandemic as compared to 6 months prior. Diarrhea-predominant IBS was positively (OR 2.37, 95% CI 1.34–4.19, $p = 0.003$) associated with COVID-19, whereas functional dyspepsia was negatively (OR 0.46, 95% CI 0.27–0.79, $p = 0.004$) associated.

Conclusions & Inferences: Patients with common functional gastrointestinal and motility disorders have reported more gastrointestinal symptoms during the COVID-19 pandemic with concurrent increased medication use and healthcare utilization.

KEYWORDS
COVID-19, functional dyspepsia, functional GI and motility disorders, gastroparesis, healthcare utilization, irritable bowel syndrome, SARS-COV-2

1 | INTRODUCTION

Functional gastrointestinal and motility disorders (FGIMD) or disorders of gut-brain interactions and motility disorders are highly prevalent with more than 40% of persons estimated to be affected worldwide.[1] The management of FGIMD represents a major social and economic burden accounting for significant healthcare utilization and costs.[2] The coronavirus disease 2019 (COVID-19) pandemic has led to an unprecedented disruption in healthcare including reduced[3,4] and delayed access and availability[5] to non-COVID-19 services. The clinical ramifications of these healthcare disruptions due to the COVID-19 pandemic on clinical outcomes in patients with FGIMD are unclear.

There has been great interest in understanding the epidemiology of COVID-19 in patients with gastrointestinal diseases as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to infect the gastrointestinal (GI) tract[6] and GI symptoms are common among patients with COVID-19.[7,8] Prior studies have focused on the epidemiology and clinical outcomes of COVID-19 in patients with inflammatory bowel disease,[9,10] cirrhosis,[11] and pancreatic diseases.[12] Although FGIMD are prevalent, there are currently limited epidemiological studies exploring the clinical outcomes of COVID-19 in patients with FGIMD as well as the impact of the pandemic on these patients. This is especially important and clinically relevant as there have been some reports of COVID-19 exacerbating FGIMD or gastrointestinal motility. For example, a recent case report detailed COVID-19 presenting as a severe diabetic gastroparesis flare.[13] In a case series of 141 patients with COVID-19 admitted to the intensive care unit, about 55.8% of patients developed an ileus, whereas 2.9% developed Ogilvie's syndrome.[14] The primary aim of this study was to describe changes in gastrointestinal symptoms, medication use, and healthcare utilization in patients with three common FGIMD (irritable bowel syndrome [IBS], gastroparesis, functional dyspepsia [FD]) during and before the COVID-19 pandemic. Our secondary aims were to determine the prevalence and clinical factors associated with COVID-19 in patients with these FGIMD.

Key Points

- The coronavirus disease 2019 (COVID-19) pandemic has led to unprecedented disruptions in health care, and gastrointestinal symptoms are common among patients with COVID-19.
- How the COVID-19 pandemic has altered gastrointestinal symptoms and healthcare utilization among patients with functional gastrointestinal and motility disorders (FGIMD) is unclear.
- The clinical predictors of COVID-19 in patients with FGIMD are unknown.
- The COVID-19 pandemic is associated with increased gastrointestinal symptoms (abdominal pain, nausea/vomiting, diarrhea, constipation, and weight loss), medication use (pump inhibitor, H2 blocker, and opioid use), and healthcare utilization (outpatient visits, hospitalizations, imaging, endoscopy) in patients with FGIMDs.
- Among patients with FGIMDs, current smoker status, cough, pneumonia, and diarrhea-predominant IBS are positive predictors of COVID-19 while current alcohol use and functional dyspepsia as negative predictors.

2 | METHODS

2.1 | Patient selection

We performed a retrospective analysis of data collected from consecutive patients whose SARS-CoV-2 testing was performed by a laboratory at Stanford University between March 15, 2020, and September 30, 2020, and received emergency department, outpatient, or inpatient care at any Stanford Healthcare facility. We included all SARS-CoV-2 tests including those performed in the outpatient setting. Our institution initially reserved testing for symptomatic patients, however, later expanded testing for asymptomatic individuals who required testing prior to procedures or for employment. Our cohort included both symptomatic and asymptomatic individuals. We evaluated the association of the COVID-19 pandemic on rates of GI symptoms, medication use, and healthcare utilization, prevalence, and prevalence and clinical predictors of COVID-19 among patients with three common FGIMD (IBS, gastroparesis, FD). All SARS-CoV-2 RNA testing was performed using samples from a nasopharyngeal swab. The clinical sensitivity of the COVID-19 test at our institution is 96% and clinical specificity approaches 100%. Our study was approved by the Stanford University Institutional Review Board (Protocol 55975). We included patients with FGIMD based on International Classification of Diseases 10 (ICD-10) code documentation. These disorders included IBS (IBS-D ICD K58.0, IBS-C ICD K58.1, IBS-mixed ICD K58.2), gastroparesis (ICD K31.84, diabetic gastroparesis ICD E10.43, E11.43, E13.43), and FD (ICD K30).

2.2 | Data collection

Severe acute respiratory syndrome coronavirus 2 symptoms were assessed by standardized questionnaires for screening. Patient-reported symptoms related to SARS-CoV-2 and gastrointestinal symptoms were assessed by physicians as part of standard of care (eg, review of systems) and recorded by ICD codes. We collected clinical data including age, sex, ethnicity, body mass index (BMI), smoking status, alcohol use, essential hypertension (ICD I10), diabetes mellitus (ICD E08-E13), infectious symptoms including fever (ICD 780.6x), cough (ICD R05), nasal congestion (ICD R09.81), sore throat (ICD 784.1), dyspnea (ICD R06.xx), fatigue (ICD G93.3, R53.8x), body pain/myalgia (ICD M79.1), viral pneumonia (ICD J12), and gastrointestinal symptoms including diarrhea (ICD R19.7), constipation (ICD

K59.xx), abdominal pain (ICD R10.xx), nausea/vomiting (ICD R11.xx), melena (ICD K92.1), GI bleed (ICD K92.2), hematemesis (ICD K92.0), weight loss (ICD R63.4, 783.2), and anosmia/loss of smell (ICD R43.0), and parageusia/loss or disturbance in taste (ICD R43.2). For all included patients, we obtained data regarding medication use (proton pump inhibitors (PPI), H2 blockers, steroids, buspirone, dicyclomine, loperamide, mirtazapine, opioids, selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA), aspirin, antiplatelets, anticoagulants, and non-steroid anti-inflammatory drugs (NSAID). Medication use was determined by inpatient provider orders or outpatient prescriptions by healthcare providers. We were unable to capture over-the-counter medication use as this was not coded in our electronic medical record. We also assessed healthcare utilization by measuring the number of (emergency department) ED visits, inpatient hospitalizations, outpatient clinic visits, number of CT scans of abdomen and/or pelvis, number of esophagogastroduodenoscopies (EGD), and number of colonoscopies. For all data, we evaluated a 6-month period both before (September 01, 2019–March 14, 2020) and during the COVID-19 pandemic (March 15, 2020–September 30, 2020), using March 15, 2020, as the index start date of COVID-19 testing at Stanford. All data were automatically extracted from the electronic medical record (EMR) using both the Stanford Research Repository (STARR) tools and a custom Python script (Python 3.7, Python Software Foundation).

2.3 | Statistical analysis

We compared rates of gastrointestinal complaints, medication use, and healthcare utilization (ED visits, inpatient hospitalizations, outpatient clinic visits, CT scans, EGDs, and colonoscopies) 6 months before (September 01, 2019–March 14, 2020) and during the COVID-19 pandemic (March 15, 2020–September 30, 2020). To evaluate seasonal variation as a potential confounder, we performed a sensitivity analysis comparing GI symptoms, medication use, and healthcare utilization in FGIMD patients 1 year before the pandemic (March 15, 2019–September 30, 2019) and during the pandemic (March 15, 2020–September 30, 2020).

Dichotomous variables were analyzed for outcomes using the chi-square test or the Fisher exact test where appropriate, and continuous variables were analyzed using *t*-tests if normally distributed, or the Wilcoxon test if non-normally distributed. Subgroup analyses among patients with IBS, gastroparesis, and FD were also performed for all analyses. We used logistic regression to determine factors associated with COVID-19 infection in this patient population. We first used simple logistic regression to determine association. All variables with $p < 0.05$ in simple logistic regression, demographics (age, sex, ethnicity), and variables with a demonstrated relationship with COVID-19 in the literature (hypertension, diabetes, PPI, and H2 blockers) were included in a multiple logistic regression model. All statistical and data analysis was done using Stata/IC version 15.1 for Windows (StataCorp).

3 | RESULTS

3.1 | Baseline characteristics of patients with FGIMD undergoing SARS-CoV-2 testing

From 03/15/2020 to 09/30/2020, we included 2592 patients with FGIMD who underwent SARS-COV-2 testing. During the same time period, the SARS-CoV-2 RNA positive rate (COVID-19) was 4.23% (7440/175,540) in our institution. From the 175,440 patients tested, the rate of positive SARS-CoV-2 was higher ($p < 0.05$) among patients with one or more risk factors for COVID-19 (including hypertension, diabetes, obesity, cardiovascular disease, autoimmune disease, etc.) at 5.75% (4265/74,178) versus 3.13% for patients without any risk factors (3175/101,362). The prevalence of COVID-19 in our FGIMD cohort was 3.20% (83/2592), 3.62% in IBS (57/1574), 3.07% in gastroparesis (23/749), and 2.44% in FD (29/1187). The prevalence of COVID-19 among patients with FGIMD was lower compared to patients in the entire cohort tested with COVID-19 risk factors (3.20% vs 5.75%, $p < 0.05$) but comparable to patients in the cohort tested without COVID-19 risk factors (3.20% vs 3.13%, $p = 0.878$). The prevalence of COVID-19 was 5.17% in IBS-D (21/406), 2.55% in IBS-C (5/196), and 3.00% in IBS-M (31/1032). The prevalence of COVID-19 was 4.85% (10/206) in patients with diabetic gastroparesis versus 1.66% (9/543) in patients with idiopathic gastroparesis ($p = 0.054$). Table 1 summarizes the baseline characteristics of patients FGIMD tested for SARS-CoV-2. Our final cohort consisted of 2592 patients with FGIMD (1574 with IBS, 749 with gastroparesis, 1187 with FD, with some patients with overlapping diagnoses). The mean age was 52.3 years old, 70.3% were female, and 58.4% were white.

3.2 | Gastrointestinal symptoms in patients with FGIMD 6 months before and during the COVID-19 pandemic

Table 2 and Figure 1 summarize rates of gastrointestinal symptoms among patients with FGIMD 6 months before and during pandemic. Patients with FGIMD had increased abdominal pain (23.77% vs 30.90%, $p < 0.0001$), nausea/vomiting (16.36% vs 22.26%, $p < 0.0001$), diarrhea (10.11% vs 13.31%, $p < 0.0001$), constipation (13.39% vs 17.90%, $p < 0.0001$), and weight loss (4.32% vs 5.83%, $p = 0.01$) in the 6 months during the pandemic (March 15, 2020–September 30, 2020) compared to 6 months prior. Subgroup analyses based on FGIMD (Figure 1) revealed similar trends with a few noteworthy exceptions. Weight loss was only significantly higher in IBS patients and not in patients with gastroparesis or FD and diarrhea was not increased in patients with gastroparesis during the pandemic. On the other hand, despite the comparable rate of GI bleeding in FGIMD, patients with IBS had increased rates of melena and hematemesis during the pandemic (Figure 1). Conversely, FGIMD patients with positive COVID-19 reported only increased rates of diarrhea (6.02% vs 18.07%, $p = 0.017$) during the pandemic,

TABLE 1 Baseline characteristics of patients with functional gastrointestinal and motility disorders tested for SARS-CoV-2

Clinical variables	All FGIMD patients ($N = 2592$)		SARS-CoV−2 RNA negative ($N = 2509$)		SARS-CoV−2 RNA positive ($N = 83$)		*p*-value
Age, years (mean ± SD)	52.3 (±19.6)		52.3 (±19.6)		50.6 (± 21.1)		0.480
Sex							
Male, no. (%)	769	29.67%	747	29.77%	22	26.51%	0.522
Female, no. (%)	1823	70.33%	1762	70.23%	61	73.49%	
BMI, kg/m^2 (mean ± SD)	26. 6(±7.2)		26.6 (±7.2)		27.3 (±7.2)		0.378
BMI ≥30.0 (Obese)	613	23.65%	592	22.86%	21	25.30%	0.719
Race							
White, no. (%)	1529	58.40%	1486	59.23%	43	51.81%	0.176
Hispanic, no. (%)	337	14.22%	326	12.99%	11	13.25%	0.945
Black, no. (%)	131	5.56%	126	5.02%	5	6.02%	0.682
Asian, no. (%)	290	11.95%	282	11.24%	8	9.64%	0.649
Pacific Islander, no. (%)	19	0.94%	17	0.68%	2	2.41%	0.069
Native American, no. (%)	15	0.67%	14	0.56%	1	1.20%	0.445
Unknown, no. (%)	271	8.26%	258	10.28%	13	15.66%	0.115
Clinical features							
Fever, no. (%)	312	12.04%	295	11.76%	17	20.48%	0.016
Cough, no. (%)	506	19.52%	476	18.97%	30	36.14%	<0.001
Nasal Congestion, no. (%)	51	1.97%	48	1.91%	3	3.61%	0.272
Sore throat, no. (%)	227	8.76%	218	8.69%	9	10.84%	0.494
Dyspnea, no. (%)	524	20.22%	496	19.77%	28	33.73%	0.002
Fatigue, no. (%)	430	16.59%	412	16.42%	18	21.69%	0.204
Myalgia, no. (%)	214	8.26%	208	8.29%	6	7.23%	0.730
Pneumonia, no. (%)	19	0.73%	8	0.32%	11	13.25%	<0.001
Gastrointestinal symptoms, no. (%)							
Abdominal pain, no. (%)	801	30.90%	786	31.33%	15	18.07%	0.010
Nausea/vomiting, no. (%)	577	22.26%	557	22.20%	20	24.10%	0.683
Diarrhea, no. (%)	345	13.31%	330	13.15%	15	18.07%	0.194
Constipation, no. (%)	464	17.90%	454	18.09%	10	12.05%	0.157
Melena, no. (%)	59	2.28%	58	1.05%	1	1.20%	0.158
GI Bleed, no. (%)	44	1.70%	43	1.70%	1	1.20%	0.224
Hematemesis, no. (%)	19	0.73%	18	0.72%	1	1.20%	0.426
Weight loss, no. (%)	151	5.83%	149	5.94%	2	2.41%	0.177
Anosmia, no. (%)	4	0.15%	2	0.08%	2	2.41%	0.080
Parageusia, no. (%)	3	0.12%	2	0.08%	1	1.20%	0.137
Past medical history							
Irritable bowel syndrome (IBS)							
Total, no. (%)	1574	60.73%	1517	60.46%	57	68.67%	0.242
Diarrhea-predominant IBS, no. (%)	406	15.66%	385	15.34%	21	25.30%	0.014
Constipation predominant IBS, no. (%)	196	7.56%	191	7.61%	5	6.02%	0.590
Mixed IBS, no. (%)	972	37.50%	941	37.50%	31	37.35%	0.520
Gastroparesis							
Total, no. (%)	749	28.90%	726	28.94%	23	27.71%	0.220
Diabetic gastroparesis, no. (%)	206	7.95%	196	7.81%	10	12.05%	0.160

(Continues)

TABLE 1 (Continued)

Clinical variables	All FGIMD patients (*N* = 2592)		SARS-CoV–2 RNA negative (*N* = 2509)		SARS-CoV–2 RNA positive (*N* = 83)		*p*-value
Idiopathic gastroparesis, no. (%)	543	20.95%	530	21.12%	13	15.66%	0.228
Functional dyspepsia							
Total, no. (%)	1187	45.79%	1158	46.15%	29	34.94%	0.044
Current Smoker							
Yes, no. (%)	106	4.09%	97	3.87%	9	10.84%	0.002
No, no. (%)	2486	95.91%	2412	96.13%	74	89.16%	
Current alcohol use							
Yes, no. (%)	1807	69.71%	1767	70.43%	40	48.19%	<0.001
No, no. (%)	785	30.29%	742	29.57%	43	51.81%	
Hypertension							
Yes, no. (%)	1236	47.69%	1189	47.39%	47	56.63%	0.097
No, no. (%)	1356	52.31%	1320	52.61%	36	43.37%	
Diabetes mellitus							
Yes, no. (%)	660	25.46%	633	25.23%	27	32.53%	0.133
No, no. (%)	1932	74.54%	1876	74.77%	56	67.47%	
Medications							
PPI, no. (%)	521	20.10%	508	20.25%	13	15.66%	0.305
H2 Blocker, no. (%)	103	3.97%	99	3.95%	4	4.82%	0.689
Steroids, no. (%)	298	11.50%	290	11.56%	8	9.64%	0.590
Buspirone, no. (%)	29	1.12%	28	1.12%	1	1.20%	0.940
Dicyclomine, no. (%)	64	2.47%	62	2.47%	1	1.20%	0.141
Loperamide, no. (%)	39	1.50%	38	1.51%	1	1.20%	0.820
Mirtazapine, no. (%)	60	2.31%	59	2.35%	1	1.20%	0.494
Opioid, no. (%)	441	17.01%	431	17.18%	10	12.05%	0.221
SSRI, no. (%)	238	9.18%	229	9.13%	9	10.84%	0.594
SNRI, no. (%)	131	5.05%	125	4.98%	6	7.23%	0.358
TCA, no. (%)	99	3.82%	96	3.83%	3	3.61%	0.921
Aspirin, no (%)	99	3.82%	96	3.83%	3	3.61%	0.921
Antiplatelets, no. (%)	23	0.89%	22	0.87%	1	1.20%	0.381
Anticoagulant, no. (%)	145	5.59%	141	5.62%	4	4.82%	0.755
NSAIDs, no. (%)	253	9.76%	242	9.65%	11	13.25%	0.276

though sample size was small, and the effect was mainly driven from patients with IBS. Otherwise, patients with gastroparesis and FD who were COVID-19 positive did not report any significant increase in GI symptoms during the pandemic.

3.3 | Association of COVID-19 pandemic with medication use and healthcare utilization in patients with FGIMD 6 months before and during COVID-19 pandemic

Table 2 summarizes rates of medication use (Figure 2), ED visits, inpatient hospitalizations, outpatient clinic visits, CT scans, EGD, and colonoscopy (Figure 3) in patients with FGIMD 6 months before and during the pandemic. In general, we saw a significant increase in healthcare utilization and medication prescriptions during the pandemic among all patients with FGIMD. These differences were only limited to the patients with negative COVID-19 test and otherwise not seen in FGIMD patients who tested positive for COVID-19.

Compared to the 6 months preceding the pandemic, rate of opioid use was significantly higher across all FGIMD groups (IBS, gastroparesis, and FD). Of commonly prescribed GI medications, H2 blocker use was also significantly higher in patients with IBS, gastroparesis, and FD while PPI use was significantly higher only in patients with FD and antispasmodic use was higher only in patients with gastroparesis. These differences in medicine use were not seen in patients with positive COVID-19. There were no significant changes in use

TABLE 2 Gastrointestinal symptoms, medication use, and healthcare utilization 6 months before and during COVID-19 pandemic in patients with functional gastrointestinal and motility disorders

	All FGIMD patients ($N = 2592$)			SARS-CoV–2 RNA negative ($N = 2509$)			SARS-CoV–2 RNA positive ($N = 83$)		
Clinical variables	**6 months before COVID–19**	**6 months during COVID–19**	***p*-value**	**6 months before COVID–19**	**6 months during COVID–19**	***p*-value**	**6 months before COVID–19**	**6 months during COVID–19**	***p*-value**
Gastrointestinal symptoms (% of patients)									
Abdominal pain, no. (%)	616 (23.77%)	801 (30.90%)	<0.0001	599 (23.87%)	786 (31.33%)	<0.0001	17 (20.48%)	15 (18.07%)	0.696
Nausea/vomiting, no. (%)	424 (16.36%)	578 (22.26%)	<0.0001	409 (16.30%)	552 (22.20%)	<0.0001	15 (18.07%)	20 (24.10%)	0.344
Diarrhea, no. (%)	262 (10.11%)	345 (13.31%)	<0.0001	257 (10.24%)	330 (13.15%)	0.0013	5 (6.02%)	15 (18.07%)	0.017
Constipation, no. (%)	347 (13.39%)	464 (17.90%)	<0.0001	339 (13.51%)	454 (18.09%)	<0.0001	8 (9.64%)	10 (12.05%)	0.620
Melena, no. (%)	39 (1.51%)	59 (2.28%)	0.054	38 (1.52%)	59 (2.35%)	0.1313	1 (1.21%)	0 (0.00%)	0.319
GI bleed, no. (%)	31 (1.12%)	44 (1.70%)	0.077	40 (1.16%)	44 (1.75%)	0.0770	0 (0.00%)	0 (0.00%)	1.000
Hematemesis, no. (%)	11 (0.42%)	19 (0.73%)	0.143	11 (0.44%)	19 (0.76%)	0.1430	0 (0.00%)	0 (0.00%)	1.000
Weight loss, no. (%)	112 (4.32%)	151 (5.83%)	0.014	110 (4.38%)	148 (5.94%)	0.0128	2 (2.41%)	2 (2.41%)	0.999
Anosmia, no. (%)	(0) 0.00%	4 (0.15%)	0.125	0 (0.00%)	2 (0.08%)	0.2780	0 (0.00%)	2 (2.41%)	0.127
Parageusia, no. (%)	(0) 0.00%	3 (0.12%)	0.111	0 (0.00%)	2(0.08%)	0.3250	0 (0.00%)	1 (1.20%)	0.288
Medication use (% of patients)									
PPI (%)	521 (20.10%)	623 (24.04%)	0.001	508 (20.25%)	609 (24.27%)	0.0006	13 (15.66%)	14 (16.87%)	0.835
H2 Blocker (%)	103 (3.97%)	172 (6.64%)	<0.0001	99 (3.95%)	168 (6.70%)	<0.0001	4 (4.82%)	4 (4.82%)	1.000
Steroids (%)	298 (11.50%)	327 (12.62%)	0.216	290 (11.56%)	318 (12.67%)	0.2259	8 (9.64%)	9 (10.84%)	0.799
Buspirone (%)	29 (1.12%)	39 (1.51%)	0.222	28 (1.12%)	37 (1.48%)	0.2613	1 (1.21%)	2 (2.41%)	0.563
Dicyclomine (%)	64 (2.47%)	77 (2.97%)	0.267	64 (2.55%)	77 (3.07%)	0.2669	0 (0.00%)	0 (0.00%)	1.000
Loperamide (%)	39 (1.51%)	45 (1.74%)	0.509	38 (1.52%)	43 (1.71%)	0.5755	1 (1.21%)	2 (2.41%)	0.563
Mirtazapine (%)	60 (2.32%)	81 (3.13%)	0.073	59 (2.35%)	80 (3.19%)	0.0709	1 (1.21%_	1 (1.21%)	1.000
Opioid (%)	441 (17.01%)	631 (23.46%)	<0.0001	431 (17.18%)	590 (23.52%)	<0.0001	10 (12.05%)	18 (21.69%)	0.098
SSRI (%)	238 (9.18%)	262 (10.11%)	0.259	229 (9.13%)	241 (9.96%)	0.3131	9 (10.84%)	12 (14.46%)	0.487
SNRI (%)	131 (5.05%)	122 (4.71%)	0.562	125 (4.98%)	116 (4.62%)	0.5525	6 (7.23%)	6 (7.23%)	1.000
TCA (%)	99 (3.82%)	108 (4.17%)	0.523	96 (3.83%)	105 (4.19%)	0.5171	3 (3.61%)	3 (3.61%)	1.000
Aspirin (%)	108 (4.17%)	99 (3.82%)	0.523	96 (3.83%)	145 (5.78%)	0.0012	3 (3.61%)	5 (6.02%)	0.472
Antiplatelets (%)	23 (0.89%)	45 (1.74%)	0.007	23 (0.92%)	44 (1.75%)	0.0098	0 (0.00%)	1 (1.21%)	0.319
Anticoagulant (%)	153 (5.59%)	169 (6.52%)	0.162	141 (5.62%)	165 (6.58%)	0.1569	4 (4.82%)	4 (4.82%)	1.000
NSAIDs (%)	253 (9.76%)	243 (9.38%)	0.637	242 (9.65%)	234 (9.33%)	0.7000	11 (13.25%)	9 (10.84%)	0.636

(Continues)

TABLE 2 (Continued)

Clinical variables	All FGIMD patients (N = 2592)			SARS-CoV-2 RNA negative (N = 2509)			SARS-CoV-2 RNA positive (N = 83)		
	6 months before COVID-19	6 months during COVID-19	p-value	6 months before COVID-19	6 months during COVID-19	p-value	6 months before COVID-19	6 months during COVID-19	p-value
Healthcare utilization									
Emergency department (number of visits)	752	881	0.1074	703	803	0.1183	50	59	0.683
Inpatient hospitalization (number of visits)	933	1296	<0.0001	903	1296	<0.0001	37	39	0.887
Outpatient clinic (number of visits)	12,390	14,723	<0.0001	11,993	14,200	<0.0001	383	528	0.168
CT scans (number)	467	596	0.002	427	602	<0.0001	16	8	0.211
EGD (number)	259	492	<0.0001	251	477	<0.0001	4	5	0.779
Colonoscopy (number)	104	259	<0.0001	100	251	<0.0001	3	4	0.060

of steroids, loperamide, buspirone, SSRIs, SNRIs, TCAs, or NSAIDs in either group.

In terms of healthcare utilization, FGIMD patients had increased rates of inpatient hospitalizations (0.36 vs 0.50, $p < 0.0001$), outpatient clinic visits (4.78 vs 5.68, $p < 0.0001$), CT scans (0.18 vs 0.23, $p = 0.002$), EGDs (0.10 vs 0.19, $p < 0.0001$), and colonoscopies (0.04 vs 0.10, $p < 0.0001$). These findings only applied to patients who tested negative for SARS-CoV-2. In those who tested positive for SARS-CoV-2, there were no statistical differences, but sample size was small.

Rate of outpatient visits and endoscopies were significantly higher among patients with IBS, gastroparesis, and FD. Significantly more FD patients had also undergone cross-sectional imaging of abdomen and pelvis. Somewhat surprisingly gastroparesis patients unlike the IBS and FD patients did not show increased rates of inpatient hospitalizations (Figure 2). These differences were limited to patients with negative COVID-19. We conducted a sensitivity analysis of seasonally matched data from 1 year prior to the pandemic to determine if seasonality was a confounder in our main analysis. Again, similar trends were seen, with higher gastrointestinal symptom burden, medication prescription, and health care utilization during the pandemic as compared to before the pandemic.

3.4 | Clinical factors associated with COVID-19 among patients with FGIMD

Table 3 summarizes the simple and multiple logistic regression predictors of COVID-19 among the cohort of patients with FGIMD. In simple regression analysis, current smoking (OR 3.50, 95% CI 1.79–15.60) and IBD-D (OR 1.87, 95% CI 1.13–3.10) were positive risk factors for COVID-19 and symptoms of fever (OR 1.93, 95% CI 1.12–3.34), cough (OR 1.78, 95% CI 1.53–3.82), dyspnea (OR 2.07, 95% CI 1.30–3.29), and presence of pneumonia (OR 47.76, 95% CI 18.65–122.32) were associated with increased odds of positive COVID-19 test. In our cohort, active alcohol use (OR 0.39, 95% CI 0.25–0.61) and FD (OR 0.63, 95% CI 0.54–0.95) were negatively associated with COVID-19 and presence of abdominal pain (OR 0.48, 95% CI 0.27–0.85) was less likely to be associated with positive COVID-19. In multiple regression analysis, current smoking (OR 3.13, 95% CI 1.38–7.09) and IBS-D (OR 2.37, 95% CI 1.34–4.19) were the only independent risk factors for COVID-19 whereas patients with current alcohol use (OR 0.26, 95% CI 0.15–0.44) and FD (OR 0.46, 95% CI 0.27–0.79) had decreased risk of COVID-19. Symptoms of cough (OR 1.83, 95% CI 1.06–3.16) and pneumonia (OR 38.62, 95% CI 12.37–120.59) were independent predictors of positive COVID-19.

Subgroup analyses revealed similar trends to the combined group with a few noteworthy exceptions. In patients with IBS, smoking was not associated with risk of COVID-19, whereas PPI use was associated with decreased risk of COVID-19 (OR 0.31, 95% CI 0.10–0.98). In patients with gastroparesis, diabetes mellitus (OR 6.86, 95% CI 1.52–30.85) and fatigue (OR 5.20, 95% CI 1.40–19.28) were associated with increased risk of COVID-19, whereas abdominal pain

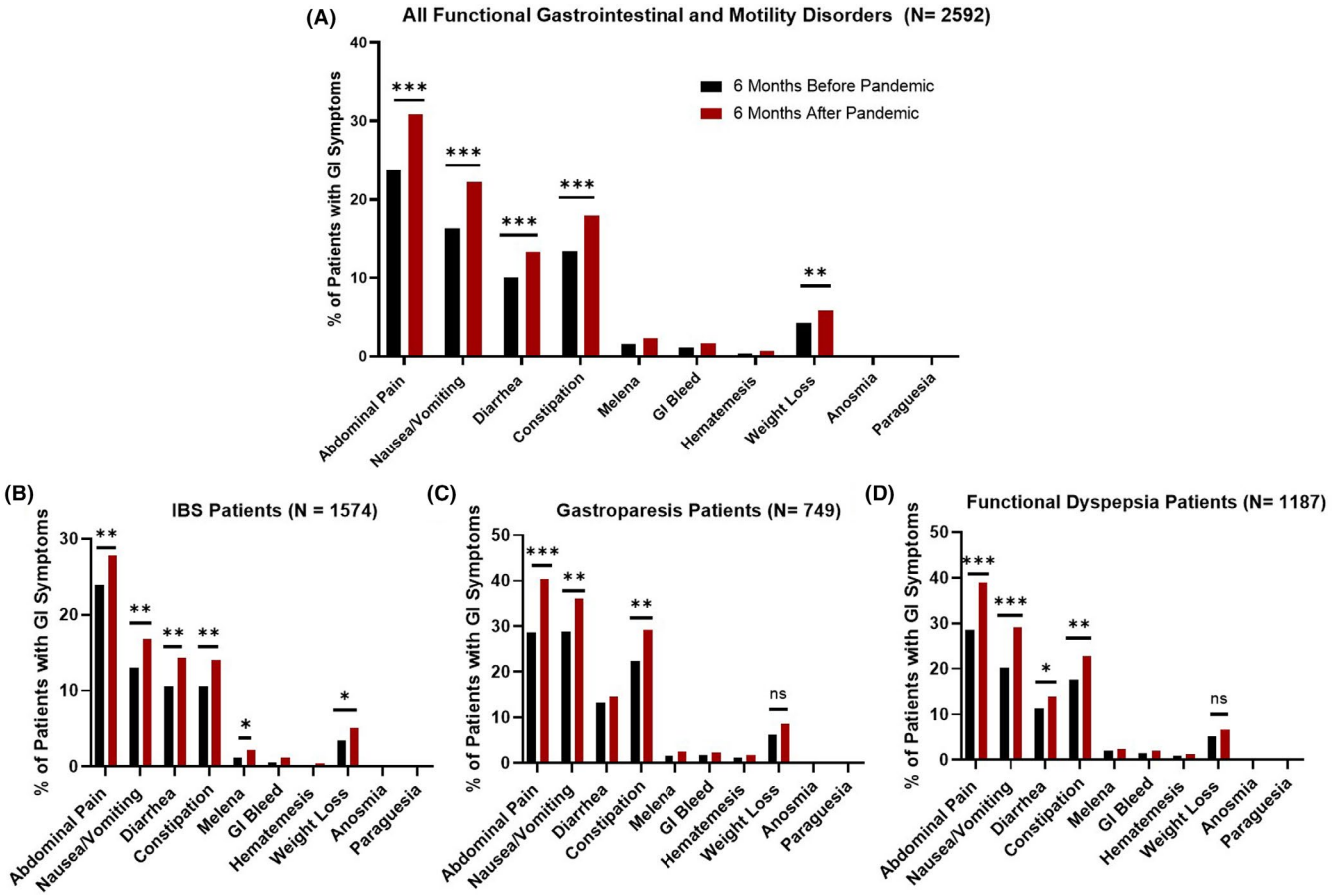

FIGURE 1 Gastrointestinal SYMPTOMS in Patients with Functional Gastrointestinal and Motility Disorders Before and After the COVID-19 Pandemic. (A) All FGIMD Patients, (B) IBS Patients, (C) Gastroparesis Patients, (D) Functional Dyspepsia Patients

(OR 0.24, 95% CI 0.06–0.94) was associated with decreased risk of COVID-19. In patients with FD, alcohol use was not an independent predictor of COVID-19.

4 | DISCUSSION

In this retrospective study of over 2500 patients with common FGIMD (IBS, gastroparesis, and FD), we report for the first time that the COVID-19 pandemic has led to increased gastrointestinal complaints, medication use, and healthcare utilization overall. We demonstrate that the prevalence of COVID-19 in patients with FGIMD is 3.20% (IBS 3.62%, gastroparesis 3.07%, FD 2.44%). Finally, we show that active smoking and IBS-D were independent risk factors for COVID-19 in this cohort of patients with FGIMD, and symptoms of cough, dyspnea, and pneumonia were predictive of COVID-19.

Our study revealed patients with FGIMD developed increased gastrointestinal symptoms, medication use, and healthcare utilization during the pandemic. We found that this was independent of COVID-19 infection, as diarrhea was the only symptom that had increased with COVID-19. Our data suggest that patients with FGIMD had increased GI burden during the COVID-19 pandemic. Our results are consistent with a recent population-based survey from Japan[15] which demonstrated that patients with FD, IBS, and FD-IBS overlap reported worsening of gastrointestinal symptoms during the COVID-19 pandemic. Our increased outpatient clinic visits among patients with FGIMD are also similar with findings by Schmulson et al[16] which reported an increase in number of consultations for patients with FGIMD despite a significant decrease in elective endoscopic and physiological procedures during the COVID-19 pandemic. Given the role of brain-gut interactions in FGIMD,[17] we speculate that the stress and anxiety associated with the COVID-19 pandemic[18] may have contributed to FGIMD exacerbation. Although we were unable to objectively measure psychologic factors in our FGIMD patients, the study by Oshima et al[15] demonstrated that patients with FGIMD had increased anxiety and depression scores by validated questionnaires compared to non-FD/IBS patients in their survey. In our FGIMD cohort, worsening of GI symptoms paralleled increase in use of opioid medications and acid blockers. However, use of neuromodulators did not increase in our FGIMD patients suggesting that pharmacological interventions may be underutilized in this cohort during the COVID-19 pandemic. Of note, we only detected nonsignificant increases in medication use among patients with FGIMD and COVID-19 as this was likely due to a small sample size compared to COVID-19 negative patients. We also found that steroid use did not increase among patients with FGIMD and

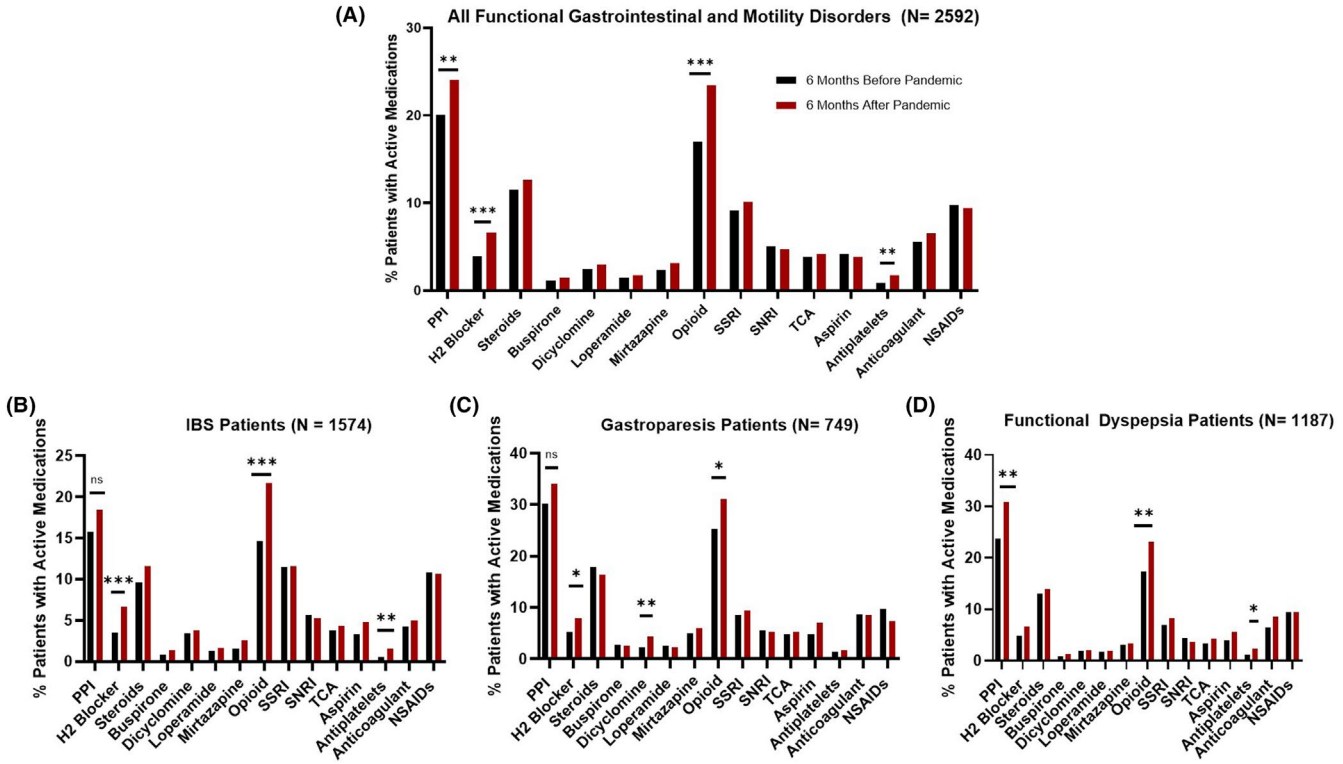

FIGURE 2 Medication Use in Patients with Functional Gastrointestinal and Motility Disorders Before and After the COVID-19 Pandemic. (A) All FGIMD Patients, (B) IBS Patients, (C) Gastroparesis Patients, (D) Functional Dyspepsia Patients

COVID-19 as this likely reflected a mild COVID-19 disease course in our patients with no patients developing cytokine storm where steroids may be beneficial.

It is conceivable that the imposed changes in lifestyle during the pandemic also affected the FGIMD symptoms. For many of patients in this cohort, diet, eating habits, sleep, and exercise that are known to impact the FGIMD symptoms were possibly affected during the pandemic by stay-at-home orders, remote work, and access to bathrooms.[19] Other factors related to the pandemic that may explain our findings include widespread use of telehealth along with the disruptions in endoscopy and GI motility testing.[20] Future studies should focus on understanding the long-term sequelae of the COVID-19 pandemic on FGIMD and the clinical implications of post-infectious (COVID-19) FGIMD.[21]

Although gastrointestinal symptoms have been shown to be prevalent among patients with COVID-19,[8] gastrointestinal symptoms were not associated with COVID-19 in our FGIMD cohort. We found that acid suppression medications were not associated with risk of COVID-19 in FGIMD patients, which contrasts with a prior study demonstrating an increased risk of COVID-19 with PPI use.[22,23] Our study found that type of FGIMD may be associated with COVID-19. Patients with IBS-D were more likely to develop COVID-19, whereas patients with FD were less likely to develop COVID-19. The mechanisms that mediate the risks of COVID-19 with IBS-D and FD are unclear but may reflect underlying differences in pathogenesis. Increased intestinal permeability has been shown in patients with IBS-D and post-infectious IBS.[24] Intestinal barrier dysfunction inherent in IBS may be contributing to increased risk of COVID-19. For example, a recent study demonstrated that disruption of gut barrier integrity plays a role in the development of severe COVID-19.[25] Furthermore, patients with IBS may have increased susceptibility to infections as a significant proportion of IBS is thought to be post-infectious.[26] Patients with IBS-D may be more susceptible to COVID-19 infection due to decreased immune function possibly mediated through increased T-cell exhaustion.[27] It is unclear why patients with FD have decreased risk of COVID-19. Given that a diagnosis of gastroparesis did not confer increased or decreased risk to COVID-19, gastric-specific factors may be less related to COVID-19 risks.

We also highlight several interesting findings in our study. First, our study revealed that current smoker status was independently associated with increased risk of COVID-19 in our cohort of patients with FGIMD. This finding is consistent with prior studies in the general population showing an increased risk of symptomatic COVID-19[28] and COVID-19 severity and death[29] in smokers. The mechanism of this association is unclear but is speculated to be related to increased ACE2 expression in the lung mucosa of smokers.[29] Second, we showed that opioid use significantly increased in patients with FGIMD during the pandemic. Our findings parallel reported U.S. trends showing increased rates of opioid overdose during the pandemic.[30] Increased opioid use in our cohort of FGIMD may suggest exacerbation of chronic pain associated with their functional GI disorder and increased prescription possibly from non-specialist clinicians who may not be aware of diagnoses

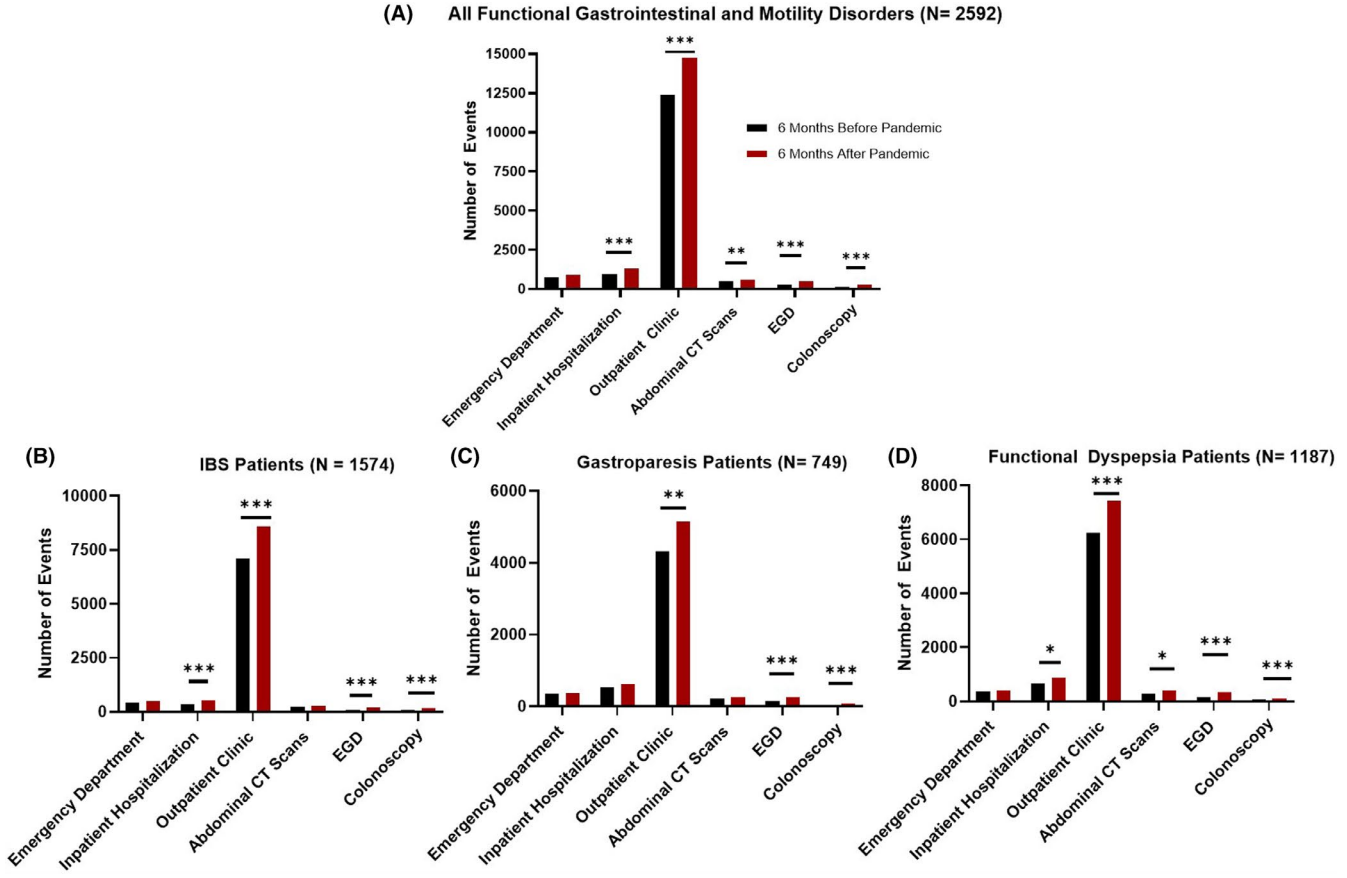

FIGURE 3 Healthcare Utilization in Patients with Functional Gastrointestinal and Motility Disorders Before and After the COVID-19 Pandemic. (A) All FGIMD Patients, (B) IBS Patients, (C) Gastroparesis Patients, (D) Functional Dyspepsia Patients

of FGIMD. Another explanation is that patients with FGIMD who have concurrent opioid use disorders may have experienced substance abuse relapse due to disruptions in healthcare and lack of prior support by providers.[31] Third, we demonstrated a significant increase in antiplatelet use among patients with FGIMD during the pandemic. This is interesting given the high incidence of thrombotic complications reported in patients with severe COVID-19.[32] The reason for this increase is not entirely clear. The increase in antiplatelet use is unlikely from increased thrombotic events among patients with FGIMD as there was not a concurrent increase in anticoagulant therapy. It may be possible that increased use of antiplatelet may be from medical conditions unrelated to COVID-19 or may reflect prophylaxis use in patients with high risk for thrombotic events.

Our study has several strengths. First, our findings are novel. To our knowledge, this is the first study to assess the impact of the pandemic on healthcare utilization in FGIMD patients during the COVID-19 pandemic and explore prevalence and factors associated with COVID-19. Second, our study is highly relevant and timely. Our understanding of the COVID-19 pandemic on patients with gastrointestinal disorders is rapidly evolving with many unknowns. Our study fills in a major gap in the literature as there are limited data on COVID-19 in patients with FGIMD. Third, our sample size was large. We included over 2500 patients which gave us sufficient power to adjust for multiple confounders in our multiple regression model as well as to perform more detailed subgroup analysis in the different FGIMD. Finally, our findings may inform and impact clinical practice. We highlight trends in increased GI symptoms and healthcare utilization among patients FGIMD during the COVID-19 pandemic which warrants further investigation and likely intervention to improve FGIMD flares during the pandemic. Our study has limitations that warrant attention. First, our study was retrospective and observational. Our findings provide only associations and cannot establish causation or exclude the possibility of residual, unmeasured confounders. Second, we were unable to capture over-the-counter medication use as this was not coded in our electronic medical record. We acknowledge that our reported rates of medication use may be underestimated. Third, our study was single center. Our results may not reflect the clinical practice at other medical centers, thus limiting the generalizability of our findings. Finally, our data were based on ICD codes. We thus cannot exclude the possibility of misclassification and selection bias using these codes.

In conclusion, we demonstrate that the COVID-19 pandemic has led to increased gastrointestinal complaints, medication use, and healthcare utilization in patients with three common FGIMD. We demonstrate that the prevalence of COVID-19 in FGIMD is comparable to patients without risk factors for COVID-19 and identify IBS-D as positively associated with COVID-19 whereas FD is

TABLE 3 Clinical factors associated with COVID-19 in patients with functional gastrointestinal and motility disorders (*N* = 2592)

	Simple logistic regression			Multiple logistic regression		
Clinical variables	**Odds ratios (OR)**	**95% CI**	***p*-value**	**Odds ratios (OR)**	**95% CI**	***p*-value**
Age	1.00	0.98–1.01	0.444	0.99	0.98–1.00	0.086
Male sex	0.85	0.52–1.40	0.522	0.90	0.53–1.53	0.698
White race	0.74	0.48–1.15	0.178	1.00	0.61–1.64	0.997
Obesity	1.10	0.66–1.81	0.719			
Current smoker	3.50	1.79–15.56	<0.001	3.13	1.38–7.09	0.006
Current alcohol use	0.39	0.25–0.61	<0.001	0.26	0.15–0.44	<0.001
Hypertension	1.45	0.93–2.26	0.099	1.50	0.86–2.62	0.155
Diabetes mellitus	1.43	0.89–2.28	0.135	0.86	0.43–1.70	0.666
Fever	1.93	1.12–3.34	0.018	1.02	0.52–2.01	0.957
Cough	1.78	1.53–3.82	<0.001	1.83	1.06–3.16	0.029
Nasal congestion	1.92	0.59–6.30	0.281			
Sore throat	1.28	0.63–2.59	0.496			
Dyspnea	2.07	1.30–3.29	0.002	1.39	0.80–2.42	0.245
Fatigue	1.41	0.83–2.40	0.207			
Myalgia	0.86	0.37–2.00	0.730			
Pneumonia	47.76	18.65–122.32	<0.001	38.62	12.37–120.59	<0.001
Abdominal pain	0.48	0.27–0.85	0.012	0.75	0.41–1.36	0.338
Nausea/vomiting	1.11	0.67–1.86	0.683			
Diarrhea	1.46	0.82–2.58	0.197			
Constipation	0.62	0.32–1.21	0.161			
Melena	0.79	0.11–5.85	0.820			
GI bleed	0.68	0.09–5.02	0.708			
Hematemesis	1.60	0.21–12.08	0.650			
Weight loss	0.39	0.10–1.61	0.193			
Anosmia	1.08	0.88–1.21	0.879			
Parageusia	1.02	0.91–1.17	0.957			
Total irritable bowel syndrome	1.21	0.75–1.96	0.443			
Diarrhea-predominant IBS	1.87	1.13–3.10	0.016	2.37	1.34–4.19	0.003
Total gastroparesis	0.72	0.43–1.22	0.222			
Diabetic gastroparesis	1.62	0.82–3.18	0.164	1.36	0.56–3.31	0.504
Functional dyspepsia	0.63	0.54–0.95	0.045	0.46	0.27–0.79	0.004
Proton pump inhibitor	0.73	0.40–1.33	0.307	0.58	0.29–1.15	0.116
H2 blocker	1.23	0.44–3.43	0.689	1.55	0.54–4.44	0.415
Steroids	0.82	0.39–1.71	0.590			
Buspirone	1.08	0.15–8.04	0.940			
Dicyclomine	1.00	0.06–3.40	0.451			
Loperamide	0.79	0.11–5.85	0.820			
Mirtazapine	0.51	0.07–3.70	0.502			
Opioid	0.66	0.34–1.29	0.224			
SSRI	1.21	0.60–2.45	0.595			
SNRI	1.49	0.64–3.48	0.361			
TCA	0.94	0.29–3.04	0.921			

(Continues)

TABLE 3 (Continued)

	Simple logistic regression			Multiple logistic regression		
Clinical variables	Odds ratios (OR)	95% CI	*p*-value	Odds ratios (OR)	95% CI	*p*-value
Aspirin	0.92	0.32–3.06	0.821			
Antiplatelets	1.32	0.18–9.88	0.788			
Anticoagulant	0.85	0.31–2.36	0.755			
NSAIDs	1.43	0.75–2.74	0.278			

negatively associated. Future prospective studies are warranted to validate these observations.

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CONFLICT OF INTEREST

Authors have no conflicts of interests or financial disclosures relevant to this manuscript.

AUTHOR CONTRIBUTIONS

JG and LN planned and designed the study; JG, TZ, and JW extracted data and performed the statistical analyses, ESB assisted with background literature review and manuscript. TZ, ESB, AG, LB, AH, and LN provided critical review of the manuscript; JG drafted the manuscript; all authors interpreted the results and contributed to critical review of the manuscript; and JG had full access to the study data and takes responsibility for the integrity of the data and accuracy of the analysis.

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