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. The management of FGIMD represents a major social and economic burden accounting for significant healthcare utilization and costs. The coronavirus disease 2019 (COVID-19) pandemic has led to an unprecedented disruption in healthcare including reduced and delayed access and availability 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 and GI symptoms are common among patients with COVID-19. Prior studies have focused on the epidemiology and clinical outcomes of COVID-19 in patients with inflammatory bowel disease, cirrhosis, and pancreatic diseases. 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. 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. 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.

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

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.
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, antplatelets, 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 | 747 | 22 | 0.522 |
| Female, no. (%) | 1823 | 1762 | 61 | 0.739 |
| **BMI, kg/m²** | 26.6 (±7.2) | 26.6 (±7.2) | 27.3 (±7.2) | 0.378 |
| BMI ≥30.0 (Obese) | 613 | 592 | 21 | 0.719 |
| **Race** | | | | |
| White, no. (%) | 1529 | 1486 | 43 | 0.176 |
| Hispanic, no. (%) | 337 | 326 | 11 | 0.945 |
| Black, no. (%) | 131 | 126 | 5 | 0.682 |
| Asian, no. (%) | 290 | 282 | 8 | 0.649 |
| Pacific Islander, no. (%) | 19 | 17 | 2 | 0.069 |
| Native American, no. (%) | 15 | 14 | 1 | 0.445 |
| Unknown, no. (%) | 271 | 258 | 13 | 0.115 |
| **Clinical features** | | | | |
| Fever, no. (%) | 312 | 295 | 17 | 0.016 |
| Cough, no. (%) | 506 | 476 | 30 | <0.001 |
| Nasal Congestion, no. (%) | 51 | 48 | 3 | 0.272 |
| Sore throat, no. (%) | 227 | 218 | 9 | 0.494 |
| Dyspnea, no. (%) | 524 | 496 | 28 | 0.002 |
| Fatigue, no. (%) | 430 | 412 | 18 | 0.204 |
| Myalgia, no. (%) | 214 | 208 | 6 | 0.730 |
| Pneumonia, no. (%) | 19 | 8 | 11 | <0.001 |
| **Gastrointestinal symptoms, no. (%)** | | | | |
| Abdominal pain, no. (%) | 801 | 786 | 15 | 0.010 |
| Nausea/vomiting, no. (%) | 577 | 557 | 20 | 0.683 |
| Diarrhea, no. (%) | 345 | 330 | 15 | 0.194 |
| Constipation, no. (%) | 464 | 454 | 10 | 0.157 |
| Melena, no. (%) | 59 | 58 | 1 | 0.158 |
| GI Bleed, no. (%) | 44 | 43 | 1 | 0.224 |
| Hematemesis, no. (%) | 19 | 18 | 1 | 0.426 |
| Weight loss, no. (%) | 151 | 149 | 2 | 0.177 |
| Anosmia, no. (%) | 4 | 2 | 2 | 0.080 |
| Parageusia, no. (%) | 3 | 2 | 1 | 0.137 |
| **Past medical history** | | | | |
| Irritable bowel syndrome (IBS) | | | | |
| Total, no. (%) | 1574 | 1517 | 57 | 0.242 |
| Diarrhea-predominant IBS, no. (%) | 406 | 385 | 21 | 0.014 |
| Constipation predominant IBS, no. (%) | 196 | 191 | 5 | 0.590 |
| Mixed IBS, no. (%) | 972 | 941 | 31 | 0.520 |
| **Gastroparesis** | | | | |
| Total, no. (%) | 749 | 726 | 23 | 0.220 |
| Diabetic gastroparesis, no. (%) | 206 | 196 | 10 | 0.160 |

(Continues)
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

| 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                           | 530                               | 13                              | 0.228   |
| Functional dyspepsia               |                               |                                   |                                 |         |
| Total, no. (%)                     | 1187                          | 1158                              | 29                              | 0.044   |
| Current Smoker                     |                               |                                   |                                 |         |
| Yes, no. (%)                       | 106                           | 97                                | 9                               | 0.002   |
| No, no. (%)                        | 2486                          | 2412                              | 74                              | 0.891   |
| Current alcohol use                |                               |                                   |                                 |         |
| Yes, no. (%)                       | 1807                          | 1767                              | 40                              | <0.001  |
| No, no. (%)                        | 785                           | 742                               | 43                              | 0.518   |
| Hypertension                       |                               |                                   |                                 |         |
| Yes, no. (%)                       | 1236                          | 1189                              | 47                              | 0.097   |
| No, no. (%)                        | 1356                          | 1320                              | 36                              | 0.337   |
| Diabetes mellitus                  |                               |                                   |                                 |         |
| Yes, no. (%)                       | 660                           | 633                               | 27                              | 0.133   |
| No, no. (%)                        | 1932                          | 1876                              | 56                              | 0.276   |
| Medications                        |                               |                                   |                                 |         |
| PPI, no. (%)                       | 521                           | 508                               | 13                              | 0.305   |
| H2 Blocker, no. (%)                | 103                           | 99                                | 4                               | 0.689   |
| Steroids, no. (%)                  | 298                           | 290                               | 8                               | 0.590   |
| Buspirone, no. (%)                 | 29                            | 28                                | 1                               | 0.940   |
| Dicyclomine, no. (%)               | 64                            | 62                                | 1                               | 0.014   |
| Loperamide, no. (%)                | 39                            | 38                                | 1                               | 0.820   |
| Mirtazapine, no. (%)               | 60                            | 59                                | 1                               | 0.494   |
| Opioid, no. (%)                    | 441                           | 431                               | 10                              | 0.221   |
| SSRI, no. (%)                      | 238                           | 229                               | 9                               | 0.594   |
| SNRI, no. (%)                      | 131                           | 125                               | 6                               | 0.358   |
| TCA, no. (%)                       | 99                            | 96                                | 3                               | 0.921   |
| Aspirin, no (%)                    | 99                            | 96                                | 3                               | 0.921   |
| Antiplatelets, no. (%)             | 23                            | 22                                | 1                               | 0.381   |
| Anticoagulant, no. (%)             | 145                           | 141                               | 4                               | 0.755   |
| NSAIDs, no. (%)                    | 253                           | 242                               | 11                              | 0.276   |
### 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

| 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 |
| 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 (1.22%) | 44 (1.70%) | 0.143 | 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%) | 2 (0.08%) | 0.2780 | 0 (0.00%) | 1 (1.20%) | 0.288 |
| 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)
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

### Table 2 (Continued)

| Clinical variables | All FGIMD patients (N = 2592) | 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 | 793 | 933 | 0.133 | 50 | 0.683 |
| Inpatient hospitalization (number of visits) | 933 | 1296 | <0.0001 | 903 | 1296 | 0.887 | 37 | 0.019 |
| Outpatient clinic (number of visits) | 12,390 | 14,723 | <0.0001 | 11,993 | 14,200 | <0.0001 | 393 | 0.168 |
| CT scans (number) | 467 | 602 | 0.002 | 427 | 602 | <0.0001 | 16 | 0.211 |
| EGDs (number) | 259 | 251 | <0.0001 | 251 | 251 | <0.0001 | 4 | 0.060 |
| Colonoscopies (number) | 104 | 104 | <0.0001 | 104 | 104 | <0.0001 | 3 | 0.006 |

of steroids, loperamide, buspirone, SSRIs, SNRIs, TCAs, or NSAIDs in either group.
(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\textsuperscript{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\textsuperscript{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,\textsuperscript{17} we speculate that the stress and anxiety associated with the COVID-19 pandemic\textsuperscript{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\textsuperscript{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
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.

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.

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.

Although gastrointestinal symptoms have been shown to be prevalent among patients with COVID-19, 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.

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. 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. Furthermore, patients with IBS may have increased susceptibility to infections as a significant proportion of IBS is thought to be post-infectious. Patients with IBS-D may be more susceptible to COVID-19 infection due to decreased immune function possibly mediated through increased T-cell exhaustion. 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 and COVID-19 severity and death 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.

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. 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 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
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.\textsuperscript{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.\textsuperscript{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
| Clinical variables                  | Simple logistic regression |          | Multiple logistic regression |          |
|------------------------------------|---------------------------|----------|-----------------------------|----------|
|                                    | 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     |
| Male sex                           | 0.85                      | 0.52-1.40| 0.522                       | 0.90     |
| White race                         | 0.74                      | 0.48-1.15| 0.178                       | 1.00     |
| Obesity                            | 1.10                      | 0.66-1.81| 0.719                       | 1.00     |
| Current smoker                     | 3.50                      | 1.79-15.56| <0.001                     | 3.13     |
| Current alcohol use                | 0.39                      | 0.25-0.61| <0.001                     | 0.26     |
| Hypertension                       | 1.45                      | 0.93-2.26| 0.099                       | 1.50     |
| Diabetes mellitus                  | 1.43                      | 0.89-2.28| 0.135                       | 0.86     |
| Fever                              | 1.93                      | 1.12-3.34| 0.018                       | 1.02     |
| Cough                              | 1.78                      | 1.53-3.82| <0.001                     | 1.83     |
| 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     |
| 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     |
| Abdominal pain                     | 0.48                      | 0.27-0.85| 0.012                       | 0.75     |
| 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     |
| Total gastroparesis                | 0.72                      | 0.43-1.22| 0.222                       | 1.34-4.19| 0.003 |
| Diabetic gastroparesis             | 1.62                      | 0.82-3.18| 0.164                       | 1.36     |
| Functional dyspepsia               | 0.63                      | 0.54-0.95| 0.045                       | 0.46     |
| Proton pump inhibitor              | 0.73                      | 0.40-1.33| 0.307                       | 0.58     |
| H2 blocker                         | 1.23                      | 0.44-3.43| 0.689                       | 1.55     |
| 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)
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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