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Factors Associated With Chronic De Novo Post-Coronavirus Disease Gastrointestinal Disorders in a Metropolitan US County

The first coronavirus disease 2019 (COVID-19) pandemic surge harshly impacted the medically underserved populations of the urbanized northeastern United States. SARS-CoV-2 virions infect the gastrointestinal (GI) tract, and GI symptoms are common during acute infection.[1] Post-COVID syndromes increasingly are recognized as important public health considerations.[2] Postinfectious disorders of gut–brain interaction (DGBIs; formerly known as functional gastrointestinal disorders) can occur after enteric illness; the COVID-19 pandemic is anticipated to provoke DGBI development[3] within a rapidly evolving post-COVID framework of illness. Here, we evaluate factors associated with DGBI-like post-COVID gastrointestinal disorders (PCGIDs) in our hospital's surrounding communities comprised predominantly of racial/ethnic minorities and those of reduced socioeconomic status.

A longitudinal cohort study was performed of ambulatory patients identified retrospectively as being COVID-19–infected from April through September 2020. Potential participants were mailed a brochure before initial screening telephone calls (in English and Spanish, and were offered a cash raffle incentive for participation). Screening telephone calls occurred 6 months after diagnosis at our hospital's respiratory illness clinics, examining for PCGIDs. Subjects were asked to recall if they suffered from dyspeptic or bowel symptoms before COVID-19 infection; despite the inherent limitation, this decision was taken to reduce data loss given uneven patient contact with our hospital before their COVID-19 diagnosis. Eligibility criteria included protocolized GI symptom assessment at COVID-19 diagnosis, speaking English or Spanish, participation in telephone screening, and the capability of providing consent. Patients with organic/structural conditions explaining dyspeptic or bowel symptoms were excluded (Supplementary Methods).

Our primary outcome was incident functional dyspepsia (FD)-like and irritable bowel syndrome (IBS)-like PCGIDs present for at least 3 months, no earlier than 6 months after a COVID-19 diagnosis using modified Rome IV questions (when answering yes to recurrent complaints of >/ 1 of 4 dyspepsia symptoms and yes to recurrent complaints of at least 2 of 3 bowel symptoms) in patients reporting an absence of FD-like and IBS-like symptoms before COVID. Secondary outcomes in patients meeting PCGID criteria were GI symptom and psychological distress scores on patient-reported outcome measures (Supplementary Methods) including versions validated in Spanish.[4–8] Socioeconomic disadvantage was estimated using patient ZIP codes as previously described.[9]

We used univariable and multivariable methods to determine factors associated with incident chronic FD- or IBS-like post-COVID symptoms, with the latter controlling for confounders by logistic regression adjusted for age, race/ethnicity, sex, history of depression/anxiety, GI symptoms at COVID-19 diagnosis, subsequent hospitalization resulting from COVID-19 infection after ambulatory diagnosis, pandemic-related income losses, or perceived pandemic-related personal distress. We also evaluated the relationship between GI symptom severity and anxiety/depression using Pearson correlation.

Of the 891 patients diagnosed with COVID-19 during clinic visits, 459 met eligibility criteria, with a screening completion rate of 59.3% (Supplementary Figure 1). Of the 272 individuals completing screening, 72 recalled FD- and/or IBS-like symptoms before their COVID-19 diagnosis, resulting in a final analyzed cohort of 200. In our cohort, 39.5% developed de novo PCGIDs. Racial/ethnic minority communities represented 86.5% of the cohort (particularly Latinos/Latinas, 67.5%) living in disadvantaged ZIP codes (96.5%) (Supplementary Table 1). A total of 77 patients had FD-like complaints and 21 patients had IBS-like complaints (including 19 with overlap) (Supplementary Figure 1).

After multivariable adjustment, both female sex (odds ratio, 2.38; 95% CI, 1.20–4.84) and a history of depression or anxiety (odds ratio, 3.27; 95% CI, 1.65–6.58) were associated independently with incident FD- and IBS-like PCGIDs (Figure 1*A*). Factors including stressors (lost income, being hospitalized after an ambulatory COVID-19 diagnosis, or knowing individuals who became ill enough to require hospitalization or died of COVID-19) were not associated. Those with GI symptoms at COVID-19 diagnosis were as likely to have PCGIDs as those without GI symptoms. Among those with new-onset dyspeptic or bowel complaints, there was a correlation between psychological distress and GI symptom severity

Abbreviations used in this paper: **COVID-19, coronavirus disease 2019; DGBI, disorders of gut–brain interaction; FD, functional dyspepsia; GI, gastrointestinal; IBS, irritable bowel syndrome; PCGID, post–coronavirus disease gastrointestinal disorders.**

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(R = 0.34; $P < .01$ for FD-like PCGID; R = 0.57, $P < .01$ for IBS-like PCGID) (Figure 1*B* and *C*).

Unsurprisingly, given the demographics in our metropolitan county, we evaluated a cohort comprised primarily of Latino/Latina patients residing in disfavored locales. In ambulatory COVID-19 patients, we show a heavy burden (39.5%) of de novo PCGIDs in this predominantly medically underserved community. Our results represent some of the earliest data suggesting that FD- and IBS-like PCGIDs are of clinical concern. Although the provoking event is presumed to be viral infection of the digestive tract, the independent association of sex and anxiety/depression with the risk of developing post-COVID GI symptoms is similar to what has been reported in DGBIs. Because neuropsychiatric complications occur after COVID,[10] the association with anxiety/depression becomes even more critical given the correlation we note here between increased psychological distress and GI symptom severity. That chronic dyspepsia and bowel symptoms were as likely to occur in patients with GI symptoms during COVID-19 diagnosis as those without GI symptoms warrants further investigation. It is anticipated in some participants that FD- and IBS-like PCGIDs, once present for 6-months, will progress to meet formal Rome criteria for FD and IBS.

We acknowledge several limitations to this work, including a relatively small cohort, potential recall bias related to pre-COVID GI symptoms, and possible selection bias both in terms of those who could not be reached by telephone and those willing to complete telephone screening. In addition, we did not evaluate for other DGBI-like post-COVID conditions and recognize the lack of a comparator cohort. However, these limitations are balanced by unique strengths, notably: (1) protocolized GI symptom assessment during COVID-19 infection vs larger studies with variable COVID-19 GI symptom intake; (2) engaging historically marginalized communities (especially normally excluded non-English speakers); (3) querying DGBI-related factors such as trauma and financial distress not consistently collected in clinical care; and (4) use of patient-reported outcome measures not routinely deployed in larger databases to assess symptom severity (vs the presence or absence of symptoms).

Having found an association between female sex, anxiety/depression, and chronic post-COVID GI distress, we highlight important factors to be studied

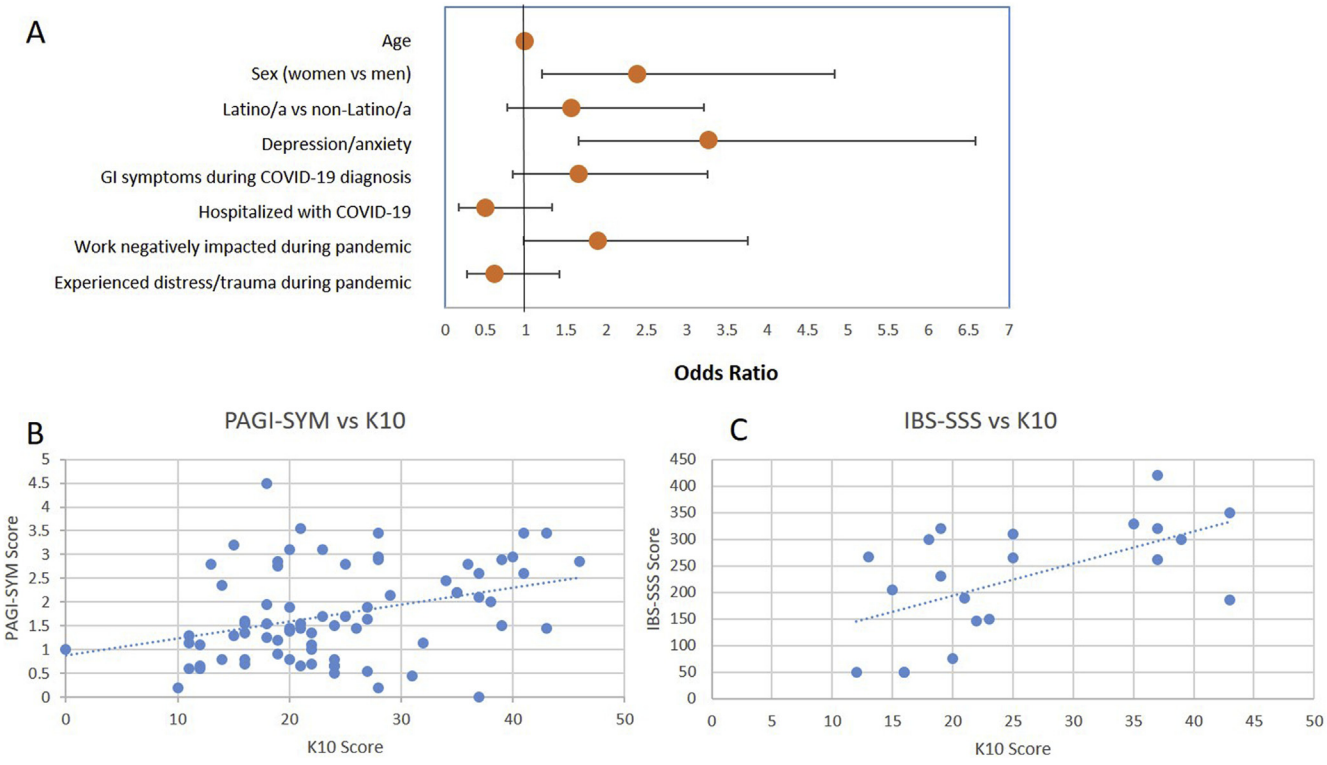

Figure 1. Factors associated with de novo functional dyspepsia (FD)- and irritable bowel syndrome (IBS)-like symptoms after coronavirus disease 2019 (COVID-19) infection and correlation between psychological distress and gastrointestinal symptom severity. (*A*) Logistic regression comparing those with de novo gastrointestinal (GI) symptoms after infection and those without symptoms showed a significant association between chronic gastrointestinal symptoms and female sex as well as a history of depression and anxiety. Correlation was noted both between psychological distress (by the Kessler Psychological Distress Scale [K10]) and the (*B*) Patient Assessment of Gastrointestinal Disorders–Symptom Severity (PAGI-SYM) gastrointestinal index in patients meeting criteria for functional dyspepsia and the (*C*) Irritable Bowel Syndrome–Symptom Severity Score (IBS-SSS) index in patients meeting criteria for IBS.

in future population-wide studies of PCGIDs and potential post-COVID DGBIs. Given barriers to research in historically underserved communities, sufficiently recruited control populations will be needed to reduce confounding from social determinants of health.

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and the Suffolk County COVID-19 Gastrointestinal Symptom Assessment

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Conflicts of interest
The authors disclose no conflicts.

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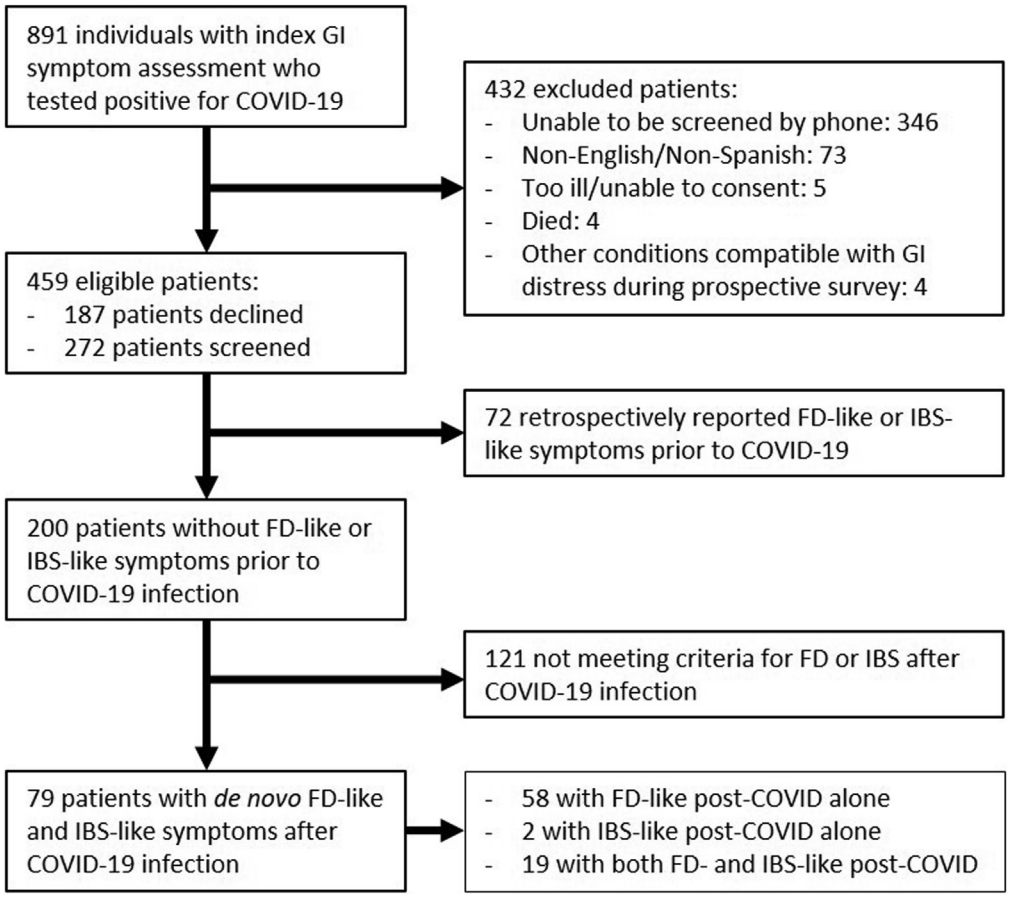
Supplementary Methods

In retrospective fashion we assembled a cohort of patients diagnosed with COVID-19 who underwent protocolized GI symptom screening during ambulatory testing at respiratory illness clinics during the first surge of the COVID-19 pandemic from April–September 2020. We targeted such patients because they had clear assessment for the presence or absence of GI symptoms during their COVID-19 infection using a standardized form developed at our institution in the electronic medical record (Epic Systems Corporation, Verona, WI). Patients who did not undergo systematic assessment for the absence or presence of GI symptoms were not included. Prior COVID-19 GI symptom studies have been limited by predominantly recruiting hospitalized patients; we targeted a cohort of patients diagnosed in the ambulatory setting who were more likely to reflect a more typical illness course during and after COVID-19 infection vs those admitted with severe disease.

Our county is highly urbanized and includes an increased percentage of communities-of-color and greater poverty rates relative to our state (Supplementary Table 1). Preferred language was obtained from the electronic medical record for the purposes of determining language of screening telephone calls and mailed brochures. Screening surveys were administered prospectively 6 months after the COVID-19 diagnosis, although patients were asked retrospectively about the presence or absence of dyspeptic or bowel symptoms before the COVID-19 infection. Although 272 patients completed the survey, 72 retrospectively reported FD-like and IBS-like symptoms before infection (Supplementary Figure 1). The 4 patients who were excluded because of organic illness had diagnoses of *Helicobacter pylori*, pancreatitis, and pregnancy (which were believed to be better explanations for GI distress).

Rome IV–styled questions consisted of the following prompts for dyspepsia including versions generated in Spanish: (1) bothersome fullness in your stomach after eating, (2) getting full too quickly when you eat, (3) bothersome upper abdominal or stomach pain above the belly button, and (4) bothersome upper abdominal or stomach burning above the belly button. Patients were deemed to have FD-like symptoms if they answered yes to any of these 4 dyspepsia-related questions (either before COVID-19 or after COVID-19 infection). Similarly, Rome IV–styled questions consisted of the following prompts for bowel disturbance: (1) recurrent/repeated abdominal or stomach pain related to bowel movements (when pooping) that gets better or gets worse with bowel movements, (2) recurrent/repeated abdominal or stomach pain associated with change in stool frequency (bowel movements occurring more often or less often), and (3) recurrent/repeated abdominal pain associated with a change in the way stool looks. If patients stated the presence of at least 2 of these 3, they were determined to have IBS-like symptoms (either before COVID-19 or after COVID-19 infection).

Patient-reported outcome measures used in patients who had FD-like and IBS-like complaints included the following: (1) Patient Assessment of Gastrointestinal Disorders–Symptom Severity score for those with incident FD, (2) the Irritable Bowel Syndrome–Symptom Severity Score for those with incident IBS, and (3) the Kessler Psychological Distress Scale. These are patient-reported outcome measures that are well established in the study of patients with disordered gut–brain interaction.



Supplementary Figure 1. Progression of patients screened for gastrointestinal (GI) symptoms during coronavirus disease 2019 (COVID-19) infection and logistic regression of patient characteristics. A total of 200 patients without any dyspeptic or bowel symptoms before their COVID-19 infection comprised the analyzed cohort. Seventy-nine patients (39.5%) developed new chronic dyspeptic and bowel symptoms after their COVID-19 infection, meeting criteria for functional dyspepsia (FD)-like or irritable bowel syndrome (IBS)-like post-COVID GI disorders, while 121 did not meet the criteria for these conditions.

Supplementary Table 1. Characteristics of COVID-19 Cohort by GI Symptom Status

	No FD- or IBS-like post- COVID, n (%)	FD-and/or IBS-like post-COVID, n (%)	*P* value
Age, *y*	48	46	.35
Sex			
Women	65 (53.7)	60 (75.9)	**<.01**
Men	56 (46.3)	19 (24.1)	
Language			
English	64 (52.9)	51 (64.6)	.10
Spanish	57 (47.1)	28 (35.4)	
Self-identified race/ethnicity			
Hispanic	75 (62.0)	60 (75.9)	
Non-Hispanic black	15 (12.4)	6 (7.6)	
Non-Hispanic white	21 (17.4)	6 (7.6)	.15
Asian	1 (0.8)	2 (2.5)	
Multiple identity/other	9 (7.4)	5 (6.3)	
Socioeconomic status (ZIP code)			
<100% living wage	116 (95.9)	77 (97.5)	.55
>100% living wage	5 (4.1)	2 (2.5)	
GI symptoms at COVID-19 diagnosis			
GI symptoms present	35 (28.9)	29 (36.7)	.25
GI symptoms absent	86 (71.1)	50 (63.3)	

NOTE. Patients were queried 6 months after their COVID-19 diagnosis using modified Rome IV criteria to assess for post-COVID GI distress that was FD- or IBS-like. The majority of patients came from racial/ethnic minority communities, including those of disadvantaged socioeconomic status. There was an even balance between Spanish and English speakers. Female sex was associated with an increased incidence of FD-like and/or IBS-like post-COVID GI disorders. Having GI symptoms as a component of COVID-19 diagnosis was not related to having post-COVID GI complaints. GI symptoms in FD-and/or IBS-like post COVID: abdominal pain: 8/79 (10.1%); nausea: 13/79 (16.5%); vomiting: 6/79 (7.6%); diarrhea: 19/79 (24.1%). GI symptoms in no FD-and/or IBS-like post COVID: abdominal pain: 7/121 (5.8%); nausea: 17/121 (14.0%); vomiting: 5/121 (4.1%); diarrhea: 24/121 (19.8%).

COVID-19, coronavirus disease 2019; FD, functional dyspepsia; GI, gastrointestinal; IBS, irritable bowel syndrome.