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ORIGINAL ARTICLE

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Gastrointestinal symptoms and the severity of COVID-19: Disorders of gut–brain interaction are an outcome

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Abstract

Background: Many of the studies on COVID-19 severity and its associated symptoms focus on hospitalized patients. The aim of this study was to investigate the relationship between acute GI symptoms and COVID-19 severity in a clustering-based approach and to determine the risks and epidemiological features of post-COVID-19 Disorders of Gut–Brain Interaction (DGBI) by including both hospitalized and ambulatory patients.

Methods: The study utilized a two-phase Internet-based survey on: (1) COVID-19 patients' demographics, comorbidities, symptoms, complications, and hospitalizations and (2) post-COVID-19 DGBI diagnosed according to Rome IV criteria in association with anxiety (GAD-7) and depression (PHQ-9). Statistical analyses included univariate and multivariate tests.

Results: Five distinct clusters of symptomatic subjects were identified based on the presence of GI symptoms, loss of smell, and chest pain, among 1114 participants who tested positive for SARS-CoV-2. GI symptoms were found to be independent risk factors for severe COVID-19; however, they did not always coincide with other severity-related factors such as age >65 years, diabetes mellitus, and Vitamin D deficiency. Of the 164 subjects with a positive test who participated in Phase-2, 108 (66%) fulfilled the criteria for at least one DGBI. The majority (n = 81; 75%) were new-onset DGBI post-COVID-19. Overall, 86% of subjects with one or more post-COVID-19 DGBI had at least one GI symptom during the acute phase of COVID-19, while 14% did not. Depression (65%), but not anxiety (48%), was significantly more common in those with post-COVID-19 DGBI.

Conclusion: GI symptoms are associated with a severe COVID-19 among survivors. Long-haulers may develop post-COVID-19 DGBI. Psychiatric disorders are common in post-COVID-19 DGBI.

KEYWORDS
anxiety, COVID-19, depression, gastrointestinal/digestive symptoms, patient clustering, post-COVID disorders of gut–brain interaction (DGBI)

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1 | INTRODUCTION

A cluster of pneumonia cases was first documented in Wuhan, Hubei Province in China, in December 2019. These incidents were later found to be attributable to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] This pathogen has been responsible for a global pandemic of unprecedented consequences. More than 218 million confirmed cases with SARS-CoV-2 have been reported worldwide, and about 4.52 million lives were lost through September 2021. Vaccines have been developed and are being distributed throughout the world as a prophylactic measure to generate immunity and prevent COVID-19. However, there are disparities in vaccination coverage worldwide, and vaccine hesitancy is a major public health problem. Efforts are still underway to discover and approve safe and efficacious treatments.

We still have not identified all the pathways of SARS-CoV-2 behavior. Many important questions remain, such as why some individuals are severely affected and some remain asymptomatic, which patients develop antibodies post-infection, and how long after infection or vaccination does immunity from antibodies last. Diabetes, obesity, hypertension, coronary artery disease, and older ages are some risk factors believed to be associated with severe COVID-19.[2,3] Post-COVID-19 conditions that are present 4 or more weeks after SARS-CoV-2 infection are new and unknown entities which have been recognized by health authorities.[4]

Most studies on COVID-19 focus on hospitalized patients. Acute gastrointestinal (GI) symptoms have been reported in up to 40% of patients with COVID-19.[5-8] How GI symptoms affect the severity and outcome of COVID-19 is still controversial. While some studies showed that GI symptoms are associated with a severe COVID-19 course, others showed that GI manifestations account for a less-severe disease.[9-13] Moreover, it appears that GI symptoms and sequelae are common after resolution of the acute COVID-19 illness.[14,15] It has been proposed that these sustained symptoms fulfill a specific GI diagnosis, namely Disorders of Gut–Brain Interaction (DGBI), [16] which has been also explored in a recent study.[17]

Without any presumption in favor of GI symptoms as a predictive factor of the severity or outcome, the current study pooled and clustered a large group of COVID-19 survivors based on their symptoms to understand which factors are associated with a more severe COVID-19 course. Moreover, it explored the risks and epidemiological features of post-COVID-19 DGBI.

Key points

- COVID-19 may manifest with gastrointestinal (GI) symptoms. Whether these symptoms are associated with a severe outcome has been mostly studied in hospitalized patients. Furthermore, it has been posited that Disorders of Gut–Brain Interaction (DGBI) are a sequela of COVID-19.
- This work proposes an unsupervised clustering of COVID-19 patients based on the appearance of symptoms. GI symptoms, loss of smell, and chest pain are the most discriminative findings. During the acute phase, GI symptoms were associated with a more severe COVID-19.
- The results of this study reconfirm the occurrence of post-COVID-19 DGBI among COVID-19 long haulers. It also reveals that these post-COVID-19 disorders may or may not be associated with the presence of GI symptoms during the acute phase.

2 | METHODS

2.1 | Study design

This cross-sectional study was approved by the Texas Tech University Health Sciences Center (TTUHSC) El Paso and University of British Columbia Institutional Review Boards, including waiver of written informed consent owing to the de-identification of the data and consisted of two phases: Phase-1 focused on acute GI symptoms and was conducted between November 2020 and March 2021 by utilizing the data generated through an Internet-based survey designed in the Qualtrics platform in both English and Spanish. It consisted of 42 questions about patients' demographics, comorbidities, symptoms, and hospitalization and took <10 min to complete. Phase-2 studied the development of post-COVID-19 DGBI/Functional Gastrointestinal Disorders based on Rome IV criteria. It consisted of questions on demographics, comorbidities, and acute symptoms and included the standardized Rome IV Adult Questionnaire, the Patient Health Questionnaire-9 (PHQ-9) for depression, and General Anxiety Disorder-7 (GAD-7) for Anxiety questionnaire.[18,19] Phase-2 was in English on the Qualtrics platform and was conducted between March and August 2021.

Recruitment was through advertising on the TTUHSC El Paso website, and through postings on social media platform accounts (Facebook, LinkedIn, and Instagram) of the investigators and online patient support groups. Duplicate responses were not allowed based on the Qualtrics platform. By reading the introduction of the survey and agreeing to proceed, the participants consented to be a part of this anonymous study.

2.2 | Patient population

For Phase-1, adults (≥18 years old) with a history of positive or negative COVID-19 test (PCR and/or antibodies) results and with/without COVID-19 symptoms were included. For Phase-2, subjects with PCR-confirmed COVID-19 at least 6 months before the study with current GI symptoms were invited to participate. Phase-1 and Phase-2 were independently conducted. Therefore, subjects who

participated in Phase-2 may or may not have participated in Phase-1 as well.

2.3 | Outcome assessment

In Phase-1, the presence of the following symptoms was analyzed as binary variables: fever, chills, shortness of breath, cough, sputum, bloody sputum, chest pain, chest discomfort, nasal congestion, sore throat, fatigue, red eye, headache, abdominal pain, body ache, nausea /vomiting, diarrhea, loss of taste, loss of smell, skin rash, cyanosis, dizziness, and loss of appetite. The severity of pulmonary and extrapulmonary symptoms was categorically ranked from 1 (minimal) to 5 (very severe) according to the patients' self-assessment. A severe disease was defined in the presence of any of the following factors (combined or alone): shortness of breath (with the severity of 4 or 5), hospitalization, intensive care unit (ICU) admission, being on ventilator support, receiving remdesivir, and acute complications including acute kidney failure, thromboembolism, gastrointestinal bleeding, pancreatitis, and acute liver dysfunction based on the patients' own report. Acute complications including acute kidney failure and thromboembolism were based on what patients were notified by their doctors and if these developments were recorded in their discharge summary or medical record.

For Phase-2, the diagnosis of DGBI was made by analyzing the valid Rome IV Adult Questionnaire as described previously.[20] The Rome IV Adult Questionnaire classifies the DGBI according to the target organ, and each group includes several diagnostic categories: A. Esophageal (e.g., chest pain, functional heartburn, reflux hypersensitivity, globus, and functional dysphagia); B. Gastroduodenal (e.g., functional dyspepsia, belching disorder, nausea and vomiting disorders, and rumination syndrome); C. Bowel (e.g., irritable bowel syndrome [IBS], functional abdominal bloating and distension, functional constipation, functional diarrhea, unspecified functional bowel disorder, and opioid-induced constipation); D. Centrally mediated abdominal pain disorders (e.g., centrally mediated abdominal pain syndrome [CAPS], narcotic bowel syndrome [NBS]/opioid-induced GI hyperalgesia); E. Functional gallbladder and sphincter of Oddi [SO] (e.g., functional gallbladder disorder, functional biliary SO disorder, and functional pancreatic SO disorder); and F. Anorectal and pelvic floor (e.g., fecal incontinence, functional anorectal pain, *levator ani* syndrome, unspecified functional anorectal pain, proctalgia fugax, functional defecation disorders).[20] For the diagnosis of post-COVID-19 DGBI, those diagnosed with at least one DGBI prior to the acute COVID-19 were excluded.

Anxiety and depression were assessed using the Generalized Anxiety Disorder Assessment (GAD-7) and the Patient Health Questionnaire (PHQ-9) instruments, respectively.[18,19] The total score (TS) for one was used to determine the severity and was calculated by summation of scores to the individual questions (0–3), where 0 represented "not at all", 1: "several days", 2: "more than half the days", and 3: "nearly every day". Anxiety was graded as follows: mild (TS: 5–9), moderate (TS: 10–14), and severe (TS: 15–21).[19] Depression was graded as follows: mild (TS: 5–9), moderate (TS: 10–14), moderately severe (TS: 15–19), and severe (20–27).[18]

2.4 | Statistical and data analysis

In Phase-1, to identify patients with similar symptomatic patterns (referred to as patient clusters), we have used hierarchical clustering, which is an unsupervised machine-learning technique, to cluster the data based on the distances between data points by continuously merging the closest ones until all data samples are merged into one cluster. Detailed information about the analysis is presented in the supplementary material section. In Phase-2, a logistic regression analysis was used. More information on this has been provided in the supplementary material section.

All the analyses of this study were conducted using Python (version 3.9.4). In addition, Pandas (version 1.2.4) was used for data loading and preprocessing, and the cluster maps were plotted using Seaborn (version 0.11.1) which uses SciPy (version 1.6.2) underneath for calculating the dendrograms of hierarchical clustering.

3 | RESULTS

3.1 | Phase-1, Acute phase of COVID-19

A total of 2222 subjects completed the survey, of which 1780 (80.1%) were tested for SARS-CoV-2 with PCR and/or antibodies, while 442 (19.9%) were not tested (although they reported symptoms of COVID-19). Among tested subjects, 1114 (62.6%) cases were positive, and 666 (37.4%) had negative results. Among the subjects that reported to be tested, only 8 (0.7%) were included based on the antibody criteria before November 2020 when vaccines were not available yet. Of the positive cases, 1092 (98%) reported to be symptomatic, and 401 (60.2%) of those with negative results also claimed that they experienced COVID-19 symptoms. The demographic data and comorbidities among these groups are presented in Table 1. From symptomatic positive, symptomatic negative, and symptomatic without test cohorts, 70, 88, and 102 participants had not provided enough information about their symptoms and severity, respectively. Therefore, they were excluded from further analysis. The countries of residence for responders are shown in Table S1.

The multivariate analysis according to the baseline demographics and comorbidities revealed that age greater than 65 years, diabetes, asthma, and Vitamin D deficiency were associated with a more severe COVID-19 in positive-tested symptomatic patients. (Table S2).

Using hierarchical clustering, symptomatic patients with positive test results fell into one of five distinct clusters mainly based on the presence of GI symptoms, loss of smell, and chest pain, while the presence of other symptoms was not distinctive. These clusters included 1: GI symptoms and loss of smell; 2: No GI symptoms, with loss of smell and chest pain; 3: No GI symptoms and no loss of smell; 4: GI symptoms with no loss of smell; 5: No GI symptoms or chest

TABLE 1 Demographic data and comorbidities among participants

	Symptomatic with positive test	Symptomatic with negative test	Symptomatic without testing	Chi-square *p*-value
Number of subjects	1092	401	442	
Over 65 years old	9%	10%	11%	0.81
BMI more than 30	38%	29%	24%	**<0.001**
Male	17%	20%	19%	0.81
Smoker	14%	26%	33%	**<0.001**
Marijuana user	12%	22%	22%	**<0.001**
Heavy alcohol user	8%	11%	9%	0.76
Diabetic	8%	7%	5%	0.81
Hypertensive	23%	21%	16%	0.11
Asthmatic	17%	17%	14%	0.81
Vitamin D deficient	30%	36%	23%	**0.004**
With inflammatory bowel disease	4%	4%	3%	0.81
Having shortness of breath	56%	56%	52%	0.81
Severe shortness of breath	26%	33%	28%	0.35
Hospitalized	15%	6%	4%	**<0.001**
Admitted to ICU	5%	1%	1%	**<0.001**
Intubated	2%	0.5%	0.2%	**0.01**

Note: The significane of bold value indicate *p*-values.

pain, with loss of smell (Figure 1). A severe disease was significantly more prevalent among clusters with GI symptoms (Clusters 1 and 4), while Clusters 3 and 5 (with no GI symptoms) had a less severe COVID-19 illness. Loss of smell and no chest pain were associated with the least severity among this study group (Table 2). In concordance with severity, hospitalization was more common among subjects in Cluster 4. Shortness of breath was significantly more common among Clusters 1 and 2, but severe shortness of breath was only more common in Cluster 1 with GI symptoms. Cluster 5 with loss of smell and no GI symptoms or chest pain had the least disease severity with the least frequent hospitalizations and presence of shortness of breath, suggesting a negative association between the loss of smell and disease severity in the absence of GI symptoms (Table 2).

Specifically in relation to GI symptoms, the presence of abdominal pain in Clusters 1 and 4 was associated with a severe COVID-19, while nausea and vomiting were associated with a severe disease only in Cluster 1. In contrast, in Cluster 4, age >65 years and Vitamin D deficiency were associated with a severe illness (Table 3).

The symptomatic cases with negative SARS-CoV-2 test were also clustered according to their symptoms. Although clusters were still separable based on the presence of GI symptoms, loss of smell, and chest pain, (Figure S1), they were somehow different from those of subjects with positive testing. A severe disease was significantly more prevalent among clusters with GI symptoms including abdominal pain and nausea (Clusters 1 and 2), while the cluster defined by no chest pain and no GI symptoms (Cluster 5) had a less severe disease course. In addition, an unexplained cluster (Cluster 4) characterized by GI symptoms, mostly diarrhea, was visible. This cluster was less enriched and was associated with a milder disease. Shortness of breath was more common in Cluster 2 which was dominated by loss of smell and chest pain, similar to Cluster 2 in symptomatic subjects with positive tests. Severe shortness of breath was also more common in Clusters 1 and 2 with GI symptoms. The absence of chest pain was also associated with less prevalent shortness of breath and a lesser disease severity (Table S3). In Cluster 2, hypertension was significantly more common among those with severe COVID-19 (Table S4).

3.2 | Phase-2, Post-COVID-19

One hundred and sixty-four subjects with a positive SARS-CoV-2 test completed the survey (70% women, 14% men, and 16% did not specify their sex). Age-group distribution was ≤65 years old: 79%, >65 years old: 4%, did not report their age: 17%, and BMI <25: 21%, and >30: 38%. Hospitalization was reported by 24%, no hospitalization by 60%, and the rest did not report hospitalization status. Diabetes was reported by 6.7% of respondents and Vitamin D deficiency by 11%.

In total, 108 (66%) subjects fulfilled Rome IV criteria for at least one DGBI; the majority of them (81 subjects; 75%) developed this DGBI post-COVID-19. The most common post-COVID-19 DGBI were functional dyspepsia in 38 subjects (postprandial distress syndrome [PDS]: 16, epigastric pain syndrome [EPS]: 7, and mixed: 15), followed by IBS in 26 subjects (IBS with diarrhea [IBS-D]: 7, IBS with

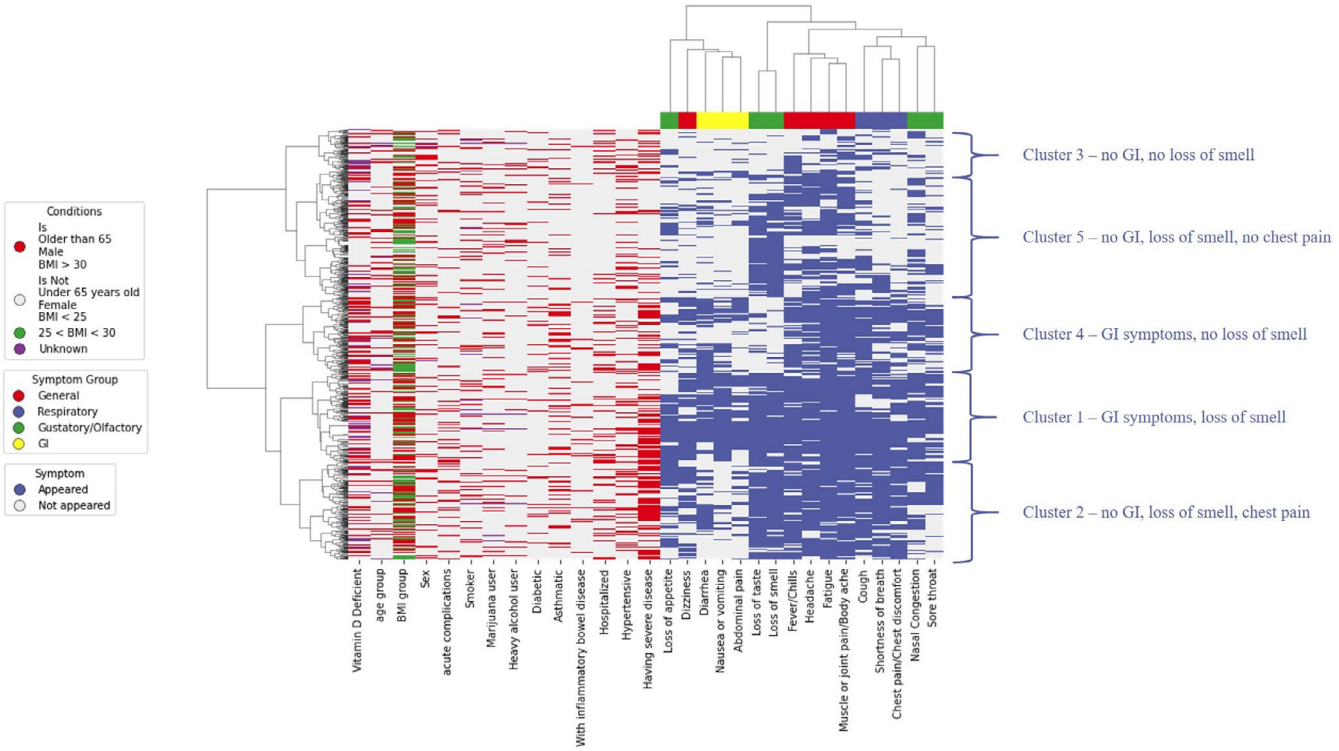

FIGURE 1 Clustering of symptomatic patients with positive SARS-CoV-2 test results according to their symptoms. Each row indicates a subject with positive SARS-CoV-2 test result, while the columns show the presence of both symptoms and comorbidities for each subject. The columns on the left specify the comorbidities and demographic information of each subject. The columns on the right indicate the appearance of symptoms on which the hierarchical clustering was applied (the subject clustering dendrogram is seen on the left side of the figure). Symptoms are divided into four main categories including GI (gastrointestinal), Respiratory, Gustatory/Olfactory, and General, each one identified by a different color box on the top of the right side of the figure, and the co-occurrence frequency of symptoms is shown above these color boxes by using the hierarchical clustering dendrogram

constipation [IBS-C]: 4, mixed IBS [IBS-M]: 14, and unsubtyped IBS [IBS-U]: 1) (Table 4).

Age greater than 65 years, male sex, diabetes, hypertension, and obesity were not associated with the development of post-COVID-19 DGBI. According to the logistic regression analysis, a higher household income was associated with decreased odds of developing post-COVID-19 functional esophageal disorders, mainly functional heartburn, reflux hypersensitivity, and functional dysphagia (Table 13).

Among subjects with at least one post-COVID-19 DGBI, 86% reported having at least one GI symptom during the acute disease phase, and among those, 64%, 63%, and 79% reported having abdominal pain, nausea/vomiting, and diarrhea, respectively. As for post-COVID-19 DGBI subjects who were hospitalized during the acute phase, 92% reported having at least one GI symptom during the acute disease phase; 79%, 71%, and 87% reported abdominal pain, nausea/vomiting, and diarrhea during the acute phase, respectively. The presence of abdominal pain in the acute phase increased the odds of post-COVID-19 functional dyspepsia, while nausea/vomiting increased the odds of post-COVID-19 reflux hypersensitivity and functional dyspepsia. In addition, loss of taste in the acute phase increased the odds of post-COVID-19 DGBI in general, while loss of smell was protective against developing post-COVID-19 DGBI, post-COVID-19 functional dyspepsia, and post-COVID-19 reflux hypersensitivity (Table 13).

Among all included subjects with positive test result in the Phase-2 study, 33% and 45% had anxiety and depression, respectively. Mild, moderate, and severe anxieties were present in 17%, 5%, and 11% of all subjects with positive test results, respectively, while mild, moderate, moderately severe, and severe depression were present in 15%, 14%, 9%, and 7% of the cases, respectively. Among subjects with post-COVID-19 DGBI, 48% reported anxiety and 65% reported depression (Figure 2). However, the rate of anxiety in subjects with post-COVID-19 DGIB was 24%, 9%, and 15% for mild, moderate, and severe cases, respectively. For depression, it was 23%, 18%, 14%, and 10% for mild, moderate, moderately severe, and severe cases, respectively. Depression, but not anxiety, was significantly more common in post-COVID-19 DGBI compared with the whole study group.

4 | DISCUSSION

We present the results of an Internet-based survey on COVID-19 comorbidities, acute symptoms, complications, and hospitalization and long-COVID GI symptoms with significant representation of

TABLE 2 Demographic features, comorbidities, and symptom relevance among clusters of symptomatic participants with positive SARS-CoV-2 test results with Chi-square enrichment *p*-values

Demographic, comorbidities, and symptom characteristics	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Total positive symptomatic group
	Frequency in % (*p*-value)					
Over 65 years old	5.6% (0.28)	6.9% (0.99)	15% (0.08)	11% (0.77)	8% (0.95)	9%
BMI less than 25	27% (0.69)	26% (0.99)	34% (0.33)	18.6% (0.22)	35% (0.39)	28%
BMI more than 30	43% (0.69)	36% (0.99)	29% (0.33)	45% (0.22)	30% (0.39)	38%
Male	11% (0.18)	8.5% (0.45)	**27% (0.01)**	17% (0.92)	21.7% (0.42)	16%
Smoker	13% (0.99)	18.8% (0.92)	15.2% (0.97)	10% (0.76)	16% (0.88)	14%
Marijuana user	10.5% (0.92)	8.5% (0.97)	16.4% (0.76)	14% (0.88)	13% (0.95)	12%
Heavy alcohol user	4% (0.15)	11% (0.93)	**14% (0.04)**	6% (0.78)	10% (0.65)	8%
Diabetic	8% (0.99)	5% (0.97)	6% (0.97)	12.2% (0.17)	3% (0.30)	7.5%
Hypertensive	28% (0.18)	22% (0.99)	18.6% (0.85)	21% (0.92)	16% (0.39)	23%
Asthmatic	18% (0.99)	18% (0.99)	17% (0.97)	25% (0.23)	12.4% (0.39)	18%
Vitamin D Deficient	34% (0.64)	26% (0.99)	28% (0.97)	38% (0.32)	**17.4% (0.01)**	30%
With inflammatory bowel disease	4.6% (0.99)	3% (0.99)	2% (0.78)	7% (0.28)	1.8% (0.55)	4%
Diarrhea	**77% (<0.001)**	**0% (<0.001)**	**0% (<0.001)**	**77% (<0.001)**	**0% (<0.001)**	45%
Abdominal pain	**53% (<0.001)**	**0% (<0.001)**	**0% (<0.001)**	**47% (<0.001)**	**0% (<0.001)**	29%
Nausea or vomiting	**63% (<0.001)**	**0% (<0.001)**	**0% (<0.001)**	**54% (<0.001)**	**0% (<0.001)**	35%
Having shortness of breath	**73% (<0.001)**	**78% (0.006)**	**39% (<0.001)**	60% (0.92)	**27% (<0.001)**	59%
Severe shortness of breath	**36% (<0.001)**	33% (0.8)	**14% (0.01)**	30% (0.78)	**6% (<0.001)**	26.4%
Hospitalized	17% (0.99)	13% (0.99)	12% (0.85)	**27% (<0.001)**	**5% (<0.001)**	16%
Admitted to ICU	5% (0.99)	6% (0.99)	6% (0.97)	9% (0.35)	2% (0.39)	5%
Intubated	3% (0.99)	0% (0.83)	4% (0.88)	5% (0.35)	0.6% (0.51)	2.7%
Acute complications	15% (0.61)	11% (0.99)	8% (0.65)	18% (0.23)	**4% (0.01)**	12.5%
Having severe disease	**48% (<0.001)**	41% (0.99)	**25% (0.01)**	**51% (0.01)**	**12.5% (<0.001)**	38.8%
Number of subjects	403	104	160	193	162	1022

Note: Data format: ratio of subject with the condition (*p*-value of Chi-squared test). Entries that passed the statistical significance ($p \leq 0.05$) are highlighted in bold. Clusters included 1: With GI symptoms and loss of smell; 2: No GI symptoms, but with loss of smell and chest pain; 3: No GI symptoms and no loss of smell; 4: With GI symptoms but no loss of smell; 5: No GI symptoms or chest pain, but with loss of smell.

TABLE 3 Multivariate logistic regression analysis and ratio of severe cases among symptomatic patients with positive SARS-CoV-2 test results

Demographic, comorbidities, and symptom characteristics	Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
	SCR (*p*)	CI	SCR (*p*)	CI	SCR (*p*)	CI	SCR (*p*)	CI	SCR (*p*)	CI
Over 65 years old	43% (0.96)	[−0.91, 0.96]	71% (0.13)	[−0.46, 3.73]	32% (0.29)	[−0.55, 1.85]	**80% (0.01)**	**[0.36, 3.0]**	23% (0.12)	[−0.35, 2.93]
BMI < 25	40% (0.41)	[−0.86, 0.35]	33% (0.71)	[−1.5, 1.02]	24% (0.07)	[−0.11, 2.38]	36% (0.55)	[−1.42, 0.76]	16% (0.08)	[−0.2, 2.91]
BMI more than 30	50% (0.94)	[−0.52, 0.57]	44% (0.83)	[−1.03, 1.3]	30% (0.07)	[−0.11, 2.39]	57% (0.47)	[−0.51, 1.1]	15% (0.68)	[−1.27, 1.95]
Male	40% (0.8)	[−0.81, 0.63]	17% (0.44)	[−3.28, 1.4]	18% (0.73)	[−1.26, 0.88]	53% (0.55)	[−0.72, 1.34]	9% (0.85)	[−1.56, 1.3]
Smoker	47% (0.58)	[−0.51, 0.9]	39% (0.91)	[−1.3, 1.4]	5% (0.19)	[−4.04, 0.78]	41% (0.71)	[−1.0, 1.47]	17% (0.28)	[−0.64, 2.18]
Marijuana user	42% (0.38)	[−1.04, 0.4]	66% (0.37)	[−1.5, 4.0]	9% (0.46)	[−2.33, 1.07]	37% (0.09)	[−1.96, 0.14]	10% (0.73)	[−1.99, 1.39]
Heavy alcohol user	35% (0.4)	[−1.5, 0.6]	22% (0.3)	[−3.78, 1.18]	12% (0.99)	[−1.75, 1.77]	45% (0.67)	[−1.77, 1.14]	0% (0.96)	[−469, 445]
Diabetic	54% (0.47)	[−0.52, 1.1]	60% (0.18)	[−0.66, 3.51]	44% (0.21)	[−0.65, 2.87]	62% (0.61)	[−0.82, 1.39]	25% (0.2)	[−0.95, 4.45]
Hypertensive	42% (0.13)	[−0.9, 0.1]	40% (0.26)	[−2.27, 0.62]	35% (0.18)	[−0.37, 1.97]	53% (0.3)	[−1.39, 0.43]	15% (0.83)	[−1.26, 1.57]
Asthmatic	60% (0.09)	[−0.07, 1.1]	65% (0.08)	[−0.15 2.48]	29% (0.22)	[−0.47, 2.01]	58% (0.36)	[−0.44, 1.22]	**26% (0.05)**	**[0.01, 2.93]**
Vitamin D deficient	51% (0.57)	[−0.3, 0.6]	56% (0.08)	[−0.13 2.2]	23% (0.79)	[−0.89, 1.17]	**64% (0.01)**	**[0.17, 1.73]**	8% (0.23)	[−2.85, 0.69]
With inflammatory bowel disease	55% (0.97)	[−0.98, 1.03]	100% (0.97)	[−738, 764]	0% (0.96)	[−500, 478]	66% (0.43)	[−0.88, 2.03]	0% (0.97)	[−466, 447]
Diarrhea	48% (0.33)	[−0.27, 0.8]	NA	NA	NA	NA	53% (0.65)	[−0.68, 1.09]	NA	NA
Abdominal pain	**54% (0.03)**	**[0.05, 0.95]**	NA	NA	NA	NA	**63% (0.01)**	**[0.25, 1.71]**	NA	NA
Nausea or vomiting	**53% (0.01)**	**[0.14, 1.1]**	NA	NA	NA	NA	48% (0.5)	[−1.01, 0.49]	NA	NA
Number of subjects	347		90		135		157		149	

Note: Entries that passed the statistical significance ($p \leq 0.05$) are highlighted in bold. Clusters included; 1: With GI symptoms and loss of smell; 2: No GI symptoms, but with loss of smell and chest pain; 3: No GI symptoms and no loss of smell; 4: With GI symptoms but no loss of smell; 5: No GI symptoms or chest pain, but with loss of smell.

Abbreviations: CI, Confidence Interval of the Factor in the Logistic Regression; *p*, *p*-value of the Factor in the Logistic Regression; SCR, Severe Cases Ratio.

survivors that were not hospitalized, mainly residing in the United States. Using an unsupervised machine learning technique, we identified five subgroups of COVID-19 patients based on symptomatology data and investigated their relationship with COVID-19 outcomes and comorbidities. Interestingly, the presence or absence of GI symptoms, loss of smell, and chest pain were the most defining features of the five patient clusters. A severe disease course was significantly more prevalent among clusters with GI symptoms including abdominal pain and nausea. The presence of GI symptoms which predicted a severe COVID-19 did not always coincide with factors such as age older than 65, diabetes, asthma, and Vitamin D deficiency, which were also associated with a greater illness severity. In addition, in a subgroup of subjects, our study showed that Rome IV DGBI may develop after COVID-19. The risk factors of post-COVID-19 DGBI were not the same as those for acute COVID-19 (e.g., age greater than 65 years, diabetes, and obesity). As for risk factors for specific diagnostic categories of DGBI, we found that a higher household income was protective against reflux hypersensitivity, functional heartburn, and functional dysphagia, while abdominal pain as well as nausea and vomiting increased the risk of functional dyspepsia. Additionally, a BMI lower than 25 decreased the risk for post-COVID-19 DGBI. Finally, anxiety and depression were common in post-COVID-19 DGBI.

TABLE 4 The frequency of disorders of Gut–Brain Interaction (DGBI) before and after COVID-19

	DGBI[a]	
	Post-COVID-19	Pre-COVID-19
Functional chest pain	17	2
Functional heartburn	11	8
Reflux hypersensitivity	9	6
Globus	3	0
Functional dysphagia	16	1
Functional dyspepsia	38	1
Belching disorders	8	0
Cyclic vomiting syndrome	5	1
Rumination syndrome	9	0
Irritable bowel syndrome	26	17
Functional constipation	9	7
Functional diarrhea	12	1
Functional abdominal bloating/distention	12	5
Opioid-induced constipation	0	2
Centrally mediated abdominal pain	1	3
Fecal incontinence	6	1
Functional anorectal pain	0	1
Functional defecation disorders	0	1

[a]Some patients may have multiple DGBI.

The constellation of gastrointestinal symptoms recognized in COVID-19 patients includes anorexia, diarrhea, abdominal pain, and vomiting. These symptoms can occur in conjunction with the more well-known respiratory symptoms or without them.[5] Patients infected with SARS-CoV-2 were noted to have disruption of their gut microbiome, related to an immune activation evidenced by elevation in inflammatory cytokine levels including interleukin-2 (IL-2) and interleukin-18 (IL-18).[21]

Several meta-analyses have investigated the prevalence of GI symptoms in COVID-19 patients.[7,22-25] The most recent one which included 78,798 SARS-CoV-2 positive patients from 158 studies reported diarrhea in 16.5%, nausea in 9.7%, vomiting in 1.5%, and abdominal pain in 4.5% of the patients.[22] Most of the included studies in these meta-analyses are from China, and overall, the body of literature indicates a higher prevalence of GI symptoms in studies outside of China.[5,26] A study from New York on a total of 1,059 patients diagnosed with COVID-19 revealed that 22% had diarrhea, 7% had abdominal pain, 16% had nausea, and 9% had vomiting.[24] In addition, 33% of patients had at least one GI manifestation.[27] In another study from New York, among the 278 COVID-19-positive patients, 97 (35%) had GI symptoms, which was associated with an increased odds for testing positive for SARS-CoV-2.[13] A study from California reported GI symptoms in 31.9% of patients, including loss of appetite in 22.3%, nausea/vomiting in 12%, and diarrhea in 12%.[28] In a multicenter study from Massachusetts on 318 hospitalized patients with confirmed COVID-19, diarrhea was present in 33.7%, nausea in 26.4%, vomiting in 15.4%, and abdominal pain in 14.5%.[29] In our study, of those with positive tests for COVID-19, 45%, 43%, and 36% had diarrhea, nausea and vomiting, and abdominal pain, respectively. These numbers are much higher compared with previous studies including those from the United States. The above finding could be interpreted by the differences in study settings and population, as most of our subjects were not hospitalized.

Whether the presence of GI symptoms impacts the severity and outcome of COVID-19 has been investigated in several meta-analyses.[6,22,25,30-32] One meta-analysis which included 21 studies with 5285 patients showed that abdominal pain was associated with a near 2.8-fold increased risk of severe COVID-19; for nausea/vomiting and diarrhea, no strong association with severe COVID-19 was observed. This meta-analysis which was mainly based on hospitalized COVID-19 patients revealed unstable results during sensitivity analysis for some of the odds ratios and was dominated by studies from China, as only three studies conducted outside China were included.[31] Thus, geographical differences may limit the generalizability of the study results. One of the most recent meta-analyses on the severity of COVID-19 in the presence of GI symptoms, which included 158 studies, showed that the presence of GI symptoms and elevated liver enzymes did not affect mortality or ICU admission rate. This study found geographical variability in GI mortality among COVID-19 patients.[22] In contrast, our study found that the presence of GI symptoms was associated with a severe COVID-19, namely

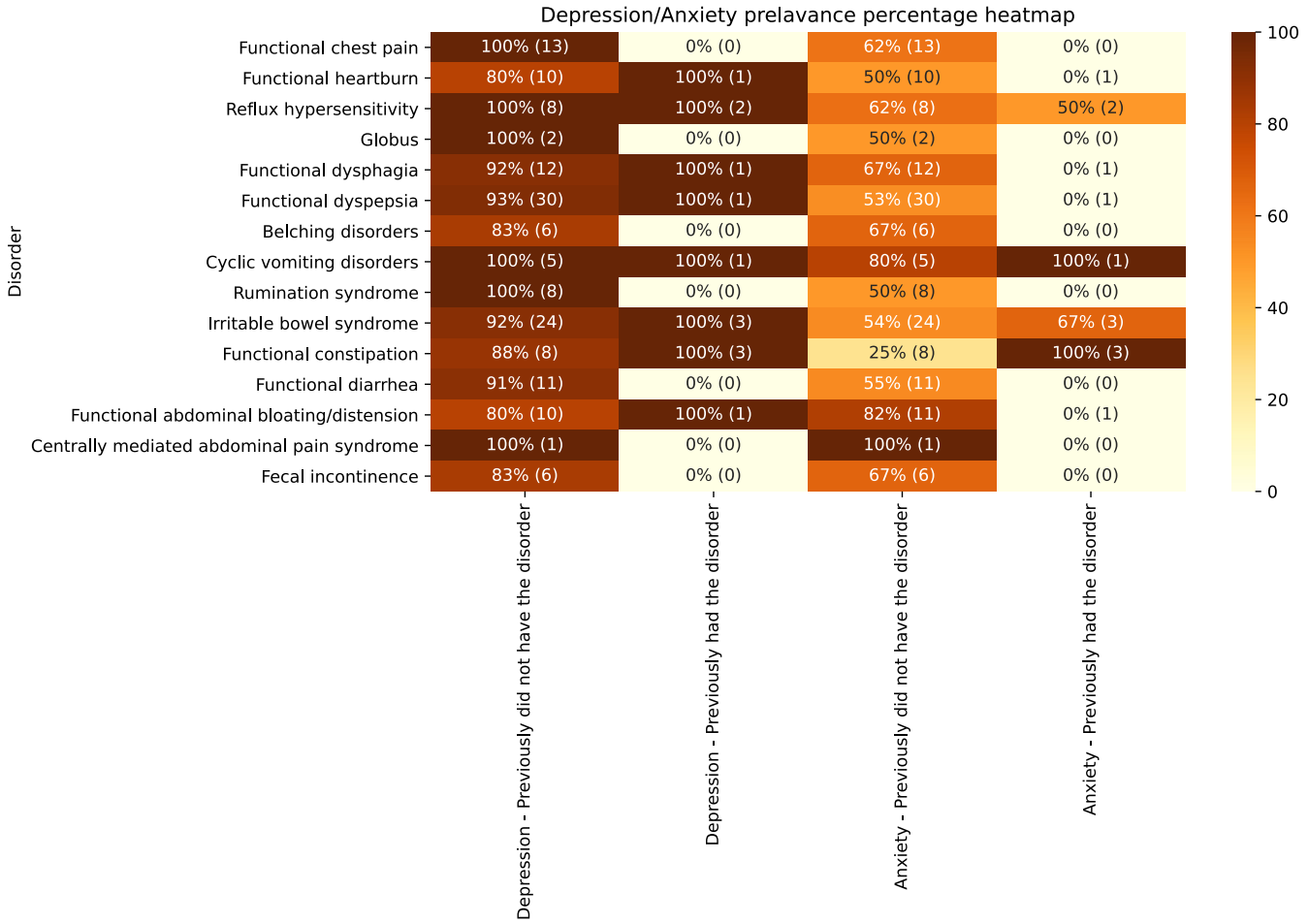

FIGURE 2 Distribution of depression/anxiety Post-COVID-19 versus Pre-COVID-19. Numbers in the parenthesis specify the number of patients in each group who completed GAD-7 and PHQ-9 questionnaires. % indicates the rate of anxiety and depression in each group

hospitalization, without any significant effect on ICU admission and intubation rate.

While our study endeavored to highlight the acute symptoms of COVID-19 and determine whether those manifestations heralded the intensity of the disease course in these said patients, it is important to recognize comorbidities and other factors which were associated with more severe disease progression and outcomes. We have found that age older than 65, heavy alcohol intake, diabetes, asthma, and Vitamin D deficiency were associated with a more severe COVID-19. These findings align with previously reported data. For example, one meta-analysis studied variables in severe and non-severe COVID-19 patients and showed that the average age in the severe COVID-19 cohort was greater than that of the non-severe counterparts, and male sex was also determined to be a risk factor. Regarding preexisting comorbidities, diabetes, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease (COPD) were linked with severe COVID-19.[33] Another meta-analysis echoed the previously described findings. These authors documented a notable prevalence of diabetes, hypertension, cardiovascular disease, and malignancy among COVID-19 patients. Furthermore, the prevalence of diabetes and hypertension increased significantly when assessing the critically ill pool of COVID-19 patients.[34] In another systematic review and meta-analysis, the investigators reported that age >75 years, male sex, and severe obesity were factors associated with adverse outcomes in COVID-19. They also found that active cancer was associated with an elevated risk of severe outcome. Interestingly though, this study found that diabetes and hypertension did not confer an increased risk of severe outcomes.[35] One research group disclosed that in their meta-analysis, while Vitamin D deficiency did not correspond with an increased risk of SARS-CoV-2 infection, severe COVID-19 cases revealed an increased prevalence of Vitamin D deficiency compared with mild cases. Moreover, Vitamin D deficiency was associated with increased hospitalization and mortality due to COVID-19.[36] Some may be surprised that according to another study, asthma was not identified as a risk factor in the development of severe COVID-19.[37] The key point in our study was that clusters with more severe disease did not always possess the comorbidities which are generally associated with severe COVID-19, suggesting that the prediction of severity based on GI symptoms is a unique phenomenon that does not necessarily need to coincide with any comorbidity in order to transpire.

Post-COVID-19 DGBI have been defined as the presence of Rome IV criteria for any DGBI in the past 3 months, with symptom onset at least 6 months before diagnosis associated with previously

confirmed SARS-CoV-2 infection and symptom development immediately after resolution of acute SARS-CoV-2 infection, while criteria for DGBI before the onset of acute illness should have not been met.[16] Our study documented the characteristics of post-COVID-19 DGBI patients as a unique entity. As proposed in the previous definition for post-COVID-19 DGBI,[16] many cases of DGBI found, herein, emerged right after COVID-19.[16] The prevalence and underlying mechanisms of this new entity are unknown. A recently published study from the U.S. found that among 147 patients at a median of 106 days after discharge following hospitalization due to COVID-19, 16% had new GI symptoms. Among 285 survivors, 40% reported new GI symptoms.[14] In a study from China on 1655 subjects, 80 reported diarrhea or vomiting 6 months after COVID-19.[38] Sustained new bowel control problems were reported after COVID-19 in 3 out of 100 hospitalized patients in a UK-based study.[39] A study from France on 150 patients with noncritical COVID-19 reported diarrhea and vomiting in 17% and 12% of the studied cases 30 and 60 days after discharge, respectively.[40] In a recent study by Ghoshal et al, from 280 COVID-19 patients in India and Bangladesh who were followed up for 6 months, 15, 6, and 5 patients developed IBS, uninvestigated dyspepsia (UD), and IBS-UD overlap, respectively; the frequency of post-COVID-19 DGBI development among patients with asymptomatic COVID-19 was same as that of healthy controls.[17] Our study reiterated the presence of post-COVID-19 DGBI in a different population and study design. Recruitment differences due to online data collection of those mainly with post-COVID-19 GI issues, the inclusion of all types of DGBI rather than IBS and dyspepsia which was done in the earlier study,[17] and inclusion of patients with more severe COVID-19 rather than those with mild forms of disease could explain the higher rate of post-COVID-19 DGBI in the current study.

While post-infection DGBI were first reported after bacterial infections (mainly gastroenteritis), viruses may also trigger these conditions. Those viruses predominantly affect the GI tract, causing GI symptoms. As SARS-CoV-2 also affects the GI tract in the acute phase, it is reasonable to consider post-COVID-19 DGBI a post-infection condition.[16] As for the underlying mechanism for the post-COVID-19 DGBI, it is possibly related to the high expression of the angiotensin-converting enzyme-2 (ACE2) in the gut epithelial cells, a receptor that is required for the SARS-CoV-2 virus to infect human cells.[41] The infection of the gut epithelial cells triggers an increase in permeability, a low-grade inflammation with calprotectin secretion,[42] and dysbiosis.[43] Mediators of the low-grade inflammation can stimulate the enteric nerves with projections to the central nervous system, factors that together with the stress of having COVID-19, anxiety, and depression, can generate symptoms of post-COVID-19 DGBI.[16] In fact, these mechanisms have been described and postulated for other post-infection-DGBI, such as PI-IBS.[44]

Based on a recent meta-analysis which included 73 articles, the prevalence of anxiety and depressive symptoms and disorders in patients with IBS was 39.1% and 23%, respectively.[45] Our study showed that the prevalence of anxiety and depression were high in post-COVID-19 DGBI, supporting the concept that post-traumatic stress and other psychological factors may be associated with its underlying mechanisms. The association between psychological factors and post-COVID-19 DGBI was also confirmed in the study by Ghoshal et al.[17]

Abdominal pain and nausea/vomiting in the acute phase increased the odds of post-COVID-19 functional dyspepsia. Changes in inflammatory signaling, neuronal plasticity, and signaling in the GI tract may explain the chronic changes.[16] In addition, loss of taste increased the odds of post-COVID-19 DGBI, while loss of smell was protective against post-COVID-19 DGBI. As outlined above in Phase-1 of this study, loss of smell was also associated with a less severe COVID-19. Ghoshal et al. reported both loss of smell and taste as the risk factors of post-COVID-19 DGBI.[17] The differences between our findings and that of Ghoshal et al. could be related to the aforementioned population differences, or even related to the unique coronavirus variants which may have affected the subjects in the two studies. As hypothesized by Ghoshal et al, the association between the development of post-COVID-19 DGBI and loss of taste or smell could be explained by the involvement of the GI tract and central nervous system in COVID-19 and the cross talk between enteric and central nervous systems.[17]

Limitations of this study include the fact that women were the predominant respondents. Subjects completed the survey anonymously and the subjects could not be followed up. On the other hand, the large sample size overcomes many limitations. Additionally, we did not have access to patients' medical charts, which prevented us from obtaining laboratory and other objective data. As some subjects completed the survey after their recovery, there is a possibility of recall bias. And lastly, because of the nature of our survey, we do not have any data from patients who did not survive COVID-19.

In conclusion, among survivors, GI symptoms were associated with more severe COVID-19 symptoms during the acute phase of the illness. This association was independent of the presence of any comorbidity which could affect the severity of COVID-19 itself. Future analysis of the available records should address whether this phenomenon was also present among those who died of COVID-19. In addition, post-COVID-19 DGBI is a new entity which deserves further investigations to determine its prevalence, long-term prognosis, and treatment. While some of the cases with post-COVID-19 DGBI had GI symptoms during the acute phase, some appeared in those with no acute GI symptoms.

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CONFLICTS OF INTEREST

The authors do not have anything to disclose in relation to the current paper.

AUTHOR CONTRIBUTIONS

MJS, AB, and MB designed the study. IS, JB, KE, SS, AR, MJS, AB, and MB recruited the study subjects. RN, MJS, AB, and MB analyzed the data. RN, IS, IA, SE, ASa, JS, MZ, AR, RWM, MJS, AB, and MB interpreted the results. RN, IS, IA, SE, MZ, AR, AB, and MB reviewed the literature. RN, ASh, IS, JB, SS, MJS, AR, AB, and MB drafted the manuscript. AB and MB validated the data. All authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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