Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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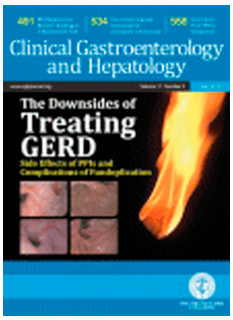

Long-term gastrointestinal sequelae following COVID-19: A prospective follow-up cohort study

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Long-term gastrointestinal sequelae following COVID-19

320 COVID-19 infected

FGID/DGBI

Asymptomatic

(n= 27)
8.4%

6 improved

(n= 21)
6.6%

n= 293

n= 299

Control Group-A (n= 320)
Control Group-B (n= 280)

none developed symptoms

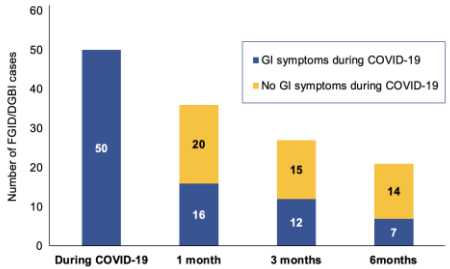
3 months **6 months**

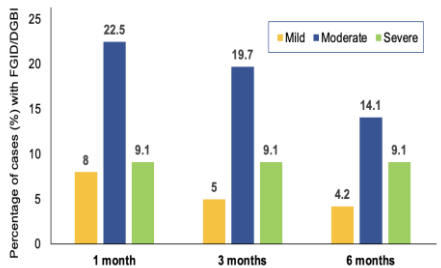
PI-FGID/DGBI: **18**

Isolated Carbohydrate malabsorption: **8**
(1 positive for IMO)

Malabsorption Syndrome: **1**

Predictive risk factors





Clinical Gastroenterology and Hepatology

TITLE: Long-term gastrointestinal sequelae following COVID-19: A prospective follow-up cohort study

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- **Bhaskar Kante** (Supervision: Supporting; Writing – review & editing: Supporting)
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Abstract:

Background and Aims: COVID-19 is associated with long-term gastrointestinal sequelae; however, prospective longitudinal data are sparse. We prospectively studied the frequency, spectrum and risk factors of post infection functional gastro-intestinal disorders/disorders of gut-brain interaction (PI-FGID/DGBI) following COVID-19.

Methods: 320 cases with COVID-19 and two control groups: (Group-A) 320 healthy spouses/family controls and (Group B) 280 healthy COVID serology-negative controls were prospectively followed up at 1,3 and 6 months using validated Rome IV criteria to evaluate the frequency of PI-FGID/DGBI.

Results: Of 320 cases**,** at 1 month, 36 (11.3%) developed FGID symptoms. Persistent symptoms were noted in 27 (8.4%) at 3 months, and in 21 (6.6%) at 6 months. At 3 months, 8 (2.5%) had irritable bowel syndrome, 7 (2.2%) had functional diarrhea, 6 (1.9%) had functional dyspepsia, 3 (0.9%) had functional constipation, 2 (0.6%) had FD-IBS overlap, and 1 (0.3%) had functional abdominal bloating/distension. Among symptomatic individuals at 3 months, 8 (29.6%) were positive for isolated carbohydrate malabsorption, 1 (3.7%) was positive for post infection malabsorption syndrome (PI-MAS) and 1 (3.7%) was positive for Intestinal methanogen overgrowth (IMO). None of the healthy controls developed FGID up to 6 months of follow up ($p<0.01$). Predictive factors at 3 and 6 months were severity of infection ($p<0.01$) and presence of GI symptoms at the time of infection ($p<0.01$).

Conclusion: COVID-19 led to significantly higher number of new onset PI-FGID/DGBI compared to healthy controls at 3 and 6 months of follow-up. If further investigated some patients can be diagnosed with underlying malabsorption.

Keywords: COVID-19; Functional Gastro-Intestinal Disorders (FGID); Long COVID; Post infection-irritable bowel syndrome (PI-IBS)

Introduction: COVID-19 is a multisystem disease with predominantly respiratory involvement. Gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain are seen in approximately 12-20%(1). There is evidence that fecal-oral transmission is possible and that viral RNA can persist in stool samples even after nasopharyngeal samples have become negative(2). A proportion of patients recovering from COVID-19 can have either prolonged systemic symptoms or develop new symptoms termed as 'Long COVID' or 'Post-acute COVID-19 syndrome'(PACS)(3). It is defined as persistence of/ongoing symptoms after recovery beyond 4 weeks of infection, which cannot be attributed to any other diagnosis(4).

Functional gastrointestinal disorders (FGID), now called disorders of gut-brain interaction (DGBI) by the Rome foundation are encountered both in gastroenterology practice and in the community. A Rome foundation global study in 2021 found the prevalence of FGID to be over 40% across 33 countries(5). Studies have shown that IBS(irritable bowel syndrome) may follow an episode of gastroenteritis, and is referred to as post-infection IBS(6). Post infection FGID/DGBI are multifactorial conditions driven primarily by an abnormality in gut-brain interaction. In the recent past, a micro-organic basis, including small intestinal bacterial overgrowth (SIBO), altered gut permeability and persistence of low grade of immune activation has been reported(7). After infectious diarrhea by various pathogens, around 10–30% of patients continue to have symptoms suggestive of IBS(8). On further exploration, several studies have shown that a proportion of these patients have features suggestive of malabsorption and SIBO(9). Since post infection FGID/DGBI is a clinical diagnosis made by Rome criteria, a patient with mild malabsorption syndrome (MAS) could be missed. Hence exclusion of malabsorption by appropriate investigations is important.

Most of the prior studies done on post-COVID-19 FGID lacked recruitment of prospective controls. Gastro-intestinal symptoms on follow-up were mainly self-reported without use of validated questionnaires. In addition, none of the studies explored the link of FGID following COVID-19 with post infection MAS/SIBO. We prospectively studied the frequency, spectrum and predictive risk factors of PI-FGID/DGBI following COVID-19 compared to uninfected controls and family members.

METHODS

Study Design: This prospective cohort study was conducted from April 2021 to January 2022. It consisted of two cohorts: A case group which included patients admitted at All India Institute of Medical Sciences, New Delhi, a dedicated COVID care center. These patients were recruited post-discharge in April-May 2021during the second wave dominated by the delta variant (irrespective of severity), with documented infection by reverse-transcriptase polymerase chain reaction (RT-PCR) or cartridge based-nucleic acid amplification testing (CB-NAAT). The other cohort included two groups. Group-A included age matched spouses/family members of the case group sharing the same dietary and environmental factors. Group-B included COVID serology negative healthcare workers at our institution. Both cases and control groups A and B had no prior history of COVID-19 or FGID (as per Rome-IV criteria). Cases and controls with inflammatory bowel disease, major psychiatric illness, GI malignancies, history of abdominal surgeries or on immunosuppressive therapy were excluded. Follow up was carried out either in person or by telephone using a self-administered/interviewer-based questionnaire (Rome IV questionnaire). The questionnaire was made available in RED-Cap (Research Electronic Data Capture) software for online administration. Electronic informed consent was obtained from each study participant. Subjects who fulfilled the criteria of various FGID in the case and control groups at 3 months, were further investigated by lab based and endoscopic methods to assess for MAS/SIBO. The study protocol was approved by the Institute Ethics Committee (Ref no: IECPG 766/23.12.2020).

Definitions: Diagnosis of FGID/DGBI was made using the Rome IV criteria(10). Analysis was done in the symptomatic at 3 months considering the latest update of Rome-IV which specifies time duration of 6 months as not mandatory to establish diagnosis(11). We performed a hydrogen breath test as a surrogate marker for small intestinal bacterial overgrowth (SIBO). Diagnosis of malabsorption syndrome (MAS) required demonstration of malabsorption of at least two unrelated nutrients(9). A D-Xylose test was performed for evaluation of carbohydrate malabsorption. Relevant blood tests were also done. Severity of COVID-19 was based on the clinical guidelines of the NIHof Health (NIH)(12).

Techniques: a) **D-Xylose test**(13)**:** After obtaining basal breath sample following an overnight fast, a 5-gram dose of D-Xylose was used. Urine was collected for 5 hours, starting from the time the dose was given. The fasting blood, timed blood, and 5-hour urine samples were tested for xylose concentrations. Value less than 1gram/5gm/5hr was considered positive. b) **Glucose Hydrogen breath test**(14)**:** Glucose hydrogen breath test was done by a breath analyzer to detect SIBO. Breath hydrogen concentration was measured in the expired air at fasting state and sequentially at 15-min interval for 3h after 70-g glucose/8 oz of water administration orally. A rise in breath hydrogen concentration above 12 ppm of basal value was considered positive for SIBO. A rise in breath methane concentration above 10 ppm of basal value during the test was considered positive for intestinal methanogen overgrowth (IMO). c) **Endoscopic duodenal biopsy**(15)**:** Biopsies were taken during esophagogastroduodenoscopy and were subjected to histological examination after hematoxylin and eosin staining using standard techniques. Villous height and crypt depth ratio of >3:1, <3:1 and $\leq$1:1 was considered as normal, partial, and total villous atrophy respectively.

Statistical analysis:

Sample size calculation: Based on prior studies, the incidence of PI-IBS following episodes of acute gastroenteritis was estimated around 15%. Keeping the risk difference of 0.10, with alpha error of 5% and power 90%, 187 patients and controls each would be required. Assuming a 40% drop out rate, a total of 262 subjects were required in both case and control groups.

Data Analysis: Statistical software SPSS (version 20, SPSS Inc. Chicago, IL) was used for statistical analyses. Normally distributed continuous variables were expressed as mean (standard deviation), and continuous variables with skewed distribution were expressed as median (range). The incidence of FGID/DGBI was calculated as proportion with 95% confidence interval (CI). Shapiro–Wilk test was used to check the normal distribution of the data. Categorical data were presented as proportions. Sub-group analysis by univariate analysis was done. A two tailed p-value of < 0.05 was considered significant.

Results:

Baseline demographic and clinical profile: The study included 416 post COVID-19 recovered patients, of whom 66 were excluded due to non-availability of a COVID-19 negative spouse/family member, and 30 were lost to follow up. Hence, a total of 320 cases and 320 controls in group-A and 280 controls in group-B were analysed. The mean age was 38.02 ± 11.4 years in the case group, 37.94 ± 11.9 years in control group-A and 38.47 ± 11.7 years in control group-B. Based on COVID disease severity, 238 (74.3%) had mild, 71 (22.1%) had moderate and 11 (3.4%) had severe disease. The baseline characteristics are shown in Table 1.

Baseline GI symptoms: During COVID-19, 50 (15.6%) among the 320 patients developed gastrointestinal complaints. The predominant symptom was diarrhea in 23 (7.2%) followed by abdominal pain in 16 (5.0%) and nausea with vomiting in 11 (3.4%).

PI-FGID/DGBI in COVID-19 patients and healthy controls: At 1 month, 36 (11.3%) among the 320 cases developed FGID-like symptoms. At 3 months, 27 (8.4%) persisted to have symptoms and 9 improved. At 6 months, another 6 improved and 21 (6.6%) had persistent symptoms. No new patients in the case group developed symptoms on follow-up. Out of the various reported FGID as per Rome IV Questionnaire at 3 months, 8 (2.5%) had irritable bowel syndrome, 7 (2.2%) had functional diarrhea, 6 (1.9%) had functional dyspepsia, 3 (0.9%) had functional constipation, 2 (0.6%) had FD-IBS overlap, and 1 (0.3%) had functional abdominal bloating/distension. Among patients with IBS and FD-IBS overlap, IBS-Diarrhea predominant (7/10) was most common followed by IBS-Mixed (2/10) and IBS-Constipation predominant (1/10). Among healthy controls in both group-A and B, none developed PI-FGID/DGBI at 3 and 6 months of follow up ($p<0.01$) (Figure 1)

Predictive risk factors: Moderate-severe COVID-19 was associated with development of FGID ($p<0.01$) (Supplementary Figure 1). Presence of gastro-intestinal symptoms during COVID-19 and at 1 month, was also a predictive risk factor ($p<0.01$) (Table 2). At 3 and 6 months of follow up among FGID patients, 12 (44.4%) and 7 (33.3%) had GI symptoms during COVID-19 respectively, while the remaining did not have GI symptoms at baseline (Figure 2).

Tests for MAS/SIBO: Patients who had FGID symptoms at 3 months were followed up until 6 months and underwent additional lab/endoscopic tests. Out of the 27 patients who had persistent symptoms at 3 months, 8 (29.6%) had isolated carbohydrate malabsorption (positive D-xylose test) and 1 (3.7%) had 2 positive tests fulfilling criteria for MAS (positive D-Xylose test + low B12). One (3.7%) patient had IMO (intestinal methanogen overgrowth) as documented by methane production on hydrogen breath test. Symptomatic patients who underwent endoscopy with biopsies had normal small intestinal histology (Table 3).

Discussion: This prospective cohort study with six months of follow up showed (i) Patients with COVID-19 have a higher probability of developing functional gastro-intestinal disorders/disorders of gut-brain interaction (FGID/DGBI) (ii) Moderate and severe forms of infection pose greater risk than mild ones (iii) Presence of gastro-intestinal symptoms during COVID-19 is associated with a higher frequency of development of FGID/DGBI (iv) PI-FGID can be concomitant with underlying malabsorption/small intestinal bacterial overgrowth (MAS/SIBO/IMO) that can be detected if appropriate tests are used.

Post-infection irritable bowel syndrome (PI-IBS) is a common disorder in which symptoms begin after an episode of infective gastroenteritis. As per Rome criteria, PI-IBS is diagnosed if 2 out of 4 criteria are present: 1) Fever 2) Diarrhea 3) Vomiting 4) Positive stool culture which suggests acute infectious gastroenteritis, with symptoms developing immediately after resolution with no evidence of IBS prior to the episode(16). The first formal description of PI-IBS was published in 1962 by Chaudhary and Truelove(17). Various studies have reported incidence of PI-IBS to range between 5% to 32%(8). Similar to above criteria, Max Schmulson and colleagues (18) proposed criteria for post-COVID-19 FGID/DGBI as: Symptoms fulfilling Rome IV criteria for any FGID/DGBI in the past 3 months, with symptom onset at least 6 months before diagnosis associated with: 1) Previous COVID-19 infection confirmed by SARS-CoV-2 real-time PCR. 2) Symptom development immediately after resolution of acute infection. 3) Should not meet criteria for FGID before onset of acute illness. A systematic review of 45 studies, comprising 21,000 individuals with enteritis followed up for 3 months to 10 years, found a pooled prevalence of IBS at 12 months to be 10.1%(6). Our study found that 36 (11.3%)

among the 320 developed FGID-like symptoms at 1 month, 27 (8.4%) and 21 (6.6%) had persistent symptoms at 3 and 6 months, respectively, similar to prior studies.

Based on prior experiences with viral gastroenteritis, it was hypothesized that COVID-19 could be followed by the development of FGID/DGBI(18). We showed that at 3 months, 8 (2.5%) had irritable bowel syndrome, 7 (2.2%) had functional diarrhea, 6 (1.9%) had functional dyspepsia, 3 (0.9%) had functional constipation, 2 (0.6%) had FD-IBS overlap, and 1 (0.3%) had functional abdominal bloating/distension. Among patients with IBS and FD-IBS overlap, IBS-Diarrhea predominant was most common. Our findings are similar to those of recent studies exploring the surge of FGID/DGBI(18). A multicenter study done in India and Bangladesh showed at 6 months following infection, 15 (5.3%), 6 (2.1%), and 5 (1.8%) of the 280 COVID-19 patients developed IBS, UD and IBS-UD overlap respectively(19). Various studies on post COVID-19 FGID/DGBI are summarized in Table 4 (19)(20)(21)(3)(22)(23)(24).

The pathophysiology underlying the development of PI-IBS following COVID-19 is not fully understood, although proposed theories include persistent sub-clinical inflammation, changes in the permeability of the gut barrier and alteration in gut microflora(25). Prior studies showed inflammation could persist for several months to years leading to prolonged intestinal dysfunction(26). Persistence of low-grade inflammation with gut dysbiosis appears to be the most important trigger for FGID following infection. A prospective study followed up 106 patients with post-acute COVID-19 syndrome (PACS) and found that gut microbiota at baseline could predict the occurrence of PACS. Non-PACS COVID-19 patients had recovering gut microbiota as compared to those who developed PACS(27). Though research is in its early stages, preliminary data reveal enrichment of opportunistic pathogens and depletion of commensal flora following infection with COVID-19(27).

Recent studies also suggest some patients with IBS could have underlying malabsorption and SIBO(28). As all three entities have overlapping presentations, it is expected that many true cases of MAS and SIBO could be missed(7). In the past, following an episode of acute gastroenteritis around 10–30% patients were reported to develop post-infectious malabsorption syndrome (PI-MAS), which is also referred to as tropical sprue(9). Pimentel et.al have validated novel biomarkers for identifying IBS-D, especially the post-infectious subtype. They found titers of anti-cytolethal distending toxin B and anti-vinculin antibody levels to be much higher when compared to other causes of diarrhea(29). Another study also showed higher antibody titers in IBS compared to healthy controls, and titers were higher in IBS-D and M compared to IBS-C (30). In a RCT of 80 patients with IBS, 15 (19%) had SIBO on upper gut aspirate culture(31). In one meta-analysis of 12 studies comprising 1,921 patients with IBS, pooled prevalence of SIBO was 54%(32). An Indian study done by Rana and colleagues showed the prevalence of SIBO to be 11.1% in IBS(33). A prospective cohort study studied the outcomes of 345 patients who had recovered from infectious gastroenteritis. Among those having FGID, two out of 23 had underlying MAS, diagnosed by lab-based tests(34). Due to lack of controls in many studies, the exact causal relationship between PI-IBS and MAS/SIBO could not be effectively demonstrated. Our study showed that among the 27 patients who fulfilled criteria for FGID at 3 months, 8 (29.6%) had one positive test for carbohydrate malabsorption (D-Xylose test) and 1 (3.7%) had two positive tests . For SIBO none were positive, however 1 (3.7%) had increased methane production (>10ppm) on glucose hydrogen breath test and was labelled as IMO (intestinal methanogen overgrowth). Hence further studies are required to explore this association.

Considering the benign and self-resolving nature of post infection FGID, management options have not been extensively explored and include symptom-based treatment. A recent study showed mast cell activation as one of

the important mechanisms of Long COVID, and therapies directed against it may benefit symptoms(35). For example, H1/H2 blockers may lead to symptomatic improvement in patients with Long COVID(36).

The results of our study reconfirm that PI-IBS has a good prognosis, considering the improvement of symptoms in patients over time. Another important observation is that the incidence of PI-IBS was similar to published evidence on COVID-19(19) and norovirus (37)(38). Hence, it is plausible that post COVID-19 FGID behaves in a manner similar to other viral gastroenteritis, with comparable overall prognosis.

A notable strength of our study is the recruitment of age and sex matched controls who are family members of cases, sharing the same environmental and dietary conditions. A second control group-B was also included who were serology negative for COVID-19. Another strength is the use of Rome IV criteria to diagnose FGID/DGBI.

Our study has certain limitations. Patients were infected predominantly by the delta variant; thus, it is not known whether the results can be extrapolated to other COVID variants. Though a COVID antibody negative control group-B was recruited, there is still a possibility of asymptomatic infection which could be detected by spike protein and T-cell testing(39). Though psychiatric co-morbidities are important risk factors for FGID, we have excluded subjects with major psychiatric illnesses considering that heightened distress during pandemic times could lead to false positive results. Another limitation is that the mechanisms of post-COVID-19 FGID were not evaluated.

In conclusion, at 6 months of follow up, COVID-19 infection led to development of various FGID/DGBI. The long-term course of these symptoms and the underlying microbiome alterations may help unravel the pathophysiological mechanisms.

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Parameter	COVID-19 cases	Control group-A	Control group-B	p value
Number	320	320	280	
Age (mean in years)	38.02 ± 11.4 years	37.94 ± 11.9 years	38.47 ± 11.7 years	0.87 (Group-A) 0.76 (Group-B)
Gender				
Males	163 (50.9%)	175 (54.6%)	172 (61.4%)	0.88 (Group-A)
Females	157 (49.0%)	145 (45.3%)	108 (38.5%)	
Co-Morbidities				0.17 (Group-A) 0.33 (Group-B)
Diabetes	27 (8.4%)	16 (5.0%)	12 (4.2%)	
Hypertension	37 (11.5%)	21 (6.6%)	21 (7.5%)	
CAD	8 (2.5%)	5 (1.5%)	0	
CKD	4 (1.2%)	1 (0.3%)	0	
Test to confirm				
RT-PCR	275 (85.9%)			
CB-NAAT	45 (14.1%)			
Severity of COVID-19				
Mild	238 (74.3%)	-	-	
Moderate	71 (22.1%)	-	-	
Severe	11 (3.4%)	-	-	

CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CB-NAAT, Cartridge based- Nucleic acid amplification test; RT-PCR, Reverse Transcriptase-Polymerase chain reaction

Table 1

Parameter	FGID (n=27)	No FGID (n=293)	p value
Age (mean in years)	35.58 ± 10.8	38.33 ± 12	0.19
Gender (females)	14 (51.9%)	143 (48.8%)	0.7
Presence of Co-morbidity	3 (11.1%)	56 (19.1%)	0.3
Severity of COVID-19			
Mild	12 (44.4%)	226 (77.1%)	
Moderate	14 (51.9%)	57 (19.5%)	**<0.01**
Severe	1 (3.7%)	10 (3.5%)	
G.I symptoms during COVID-19	12 (44.4%)	38 (13%)	**<0.01**

Table 2

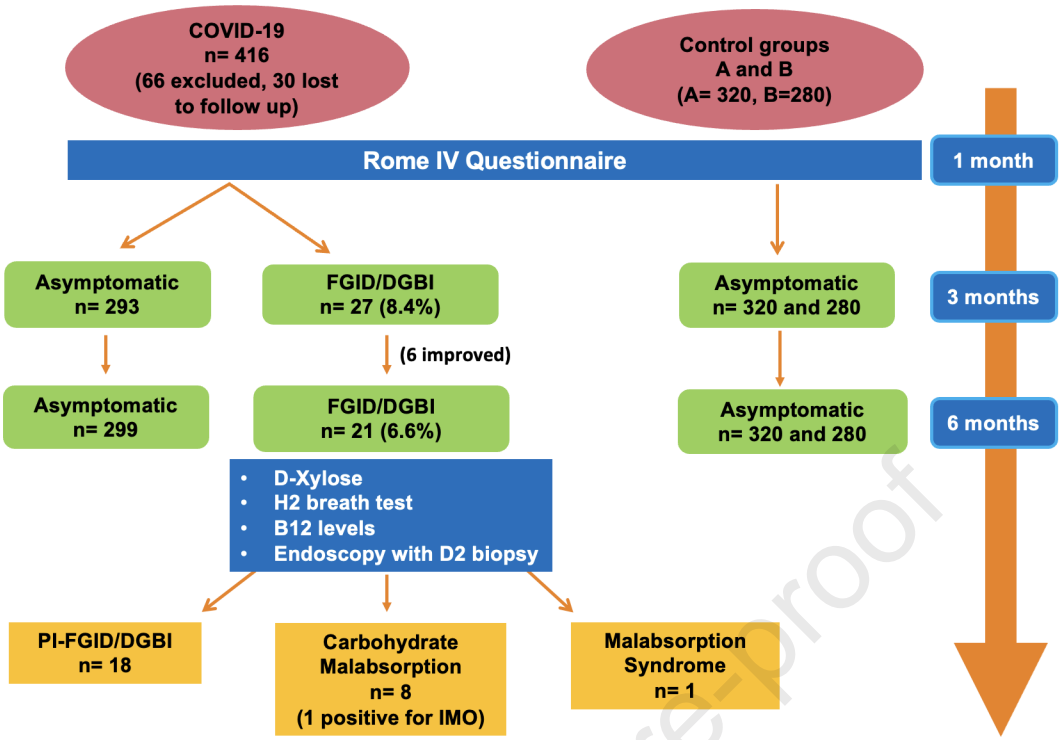
S. No	Age/Sex	Type of FGID/DGBI	D-Xylose gram/5gram/5hr (positive)	Hydrogen breath test	Hemoglobin (g/dl)	Albumin (g/dl)	B12 (pg/ml)	UGIE with biopsy
1	35/M	IBS-C	0.55	Negative	15.5	5.3	432	Normal
2	68/M	Functional Dyspepsia	0.62	Negative	13.1	3.5	362	Normal
3	42/F	FAB/D	0.91	Negative	13.3	4.1	214	Normal
4 **(IMO)**	20/F	IBS-M/FD	0.76	Methane producer	13.3	4.4	224	Normal
5	23/M	Functional diarrhea	0.88	Negative	15.0	5.3	240	Normal
6	40/F	IBS-D/FD	0.23	Negative	12.3	4.3	450	Normal
7	36/F	IBS-M	0.42	Negative	12.3	4.1	1492	Normal
8	46/F	Functional dyspepsia	0.88	Negative	14.0	4.9	422	Normal
9 **(MAS)**	37/M	Functional dyspepsia	0.96	Negative	13.8	4.1	186	Normal

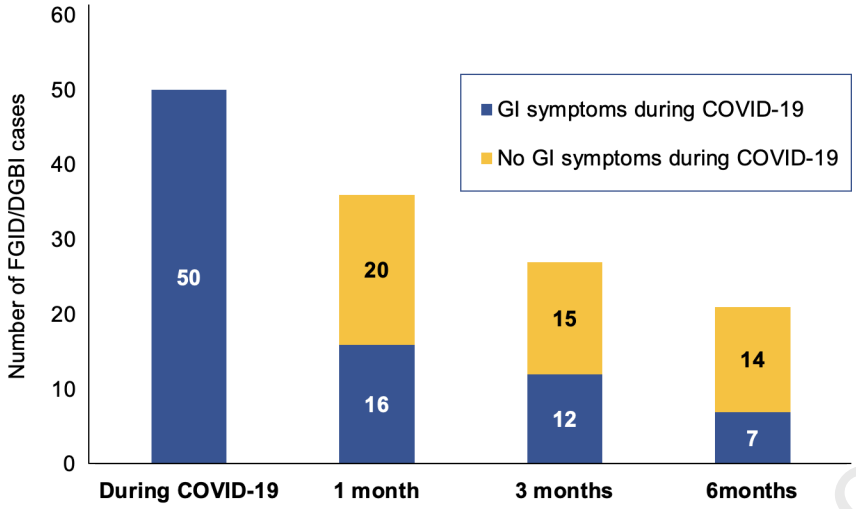
FD, Functional dyspepsia; FAB/D, Functional abdominal bloating/distension; IMO, Intestinal Methanogen Overgrowth; IBS-C, Irritable bowel syndrome-Constipation; IBS-M, Irritable bowel syndrome-Mixed; Irritable bowel syndrome-Diarrhea; MAS, Malabsorption syndrome

Table 3

Study	Number of patients/controls	Frequency of IBS/ FGIDs in cases	Frequency of IBS/ FGIDs in controls	Follow-up (months)	Comments
Ghoshal at al. (2021)[19]	280/264	IBS: 5.3% UD: 2.1% IBS-UD overlap: 1.8%	IBS: 0.3%	6	Historical controls No investigations done for MAS
Velez et al. (2022)[20]	200/no controls	IBS: 29% FD: 1% Overlap: 9.5%	-	6	No controls
Blackett et.al (2022)[21]	1783/no controls	GI symptoms: 29%	-	6	No controls
Ziyad Al-Aly et. al (2021)[3]	33,940 break-through infections v/s controls	Increased G.I disturbances	-	6	Self-reported questionnaire No investigations done for MAS
Oshima et. al (2020)[22]	5157/no controls	FD: 8.5% IBS: 16.6% FD-IBS: 4%	-	6	No controls
Nakov et. al (2021)[23]	1896/980	FGID: 36%		6	Controls not well defined No investigations done for MAS
Noviello et. al (2021)[24]	164/183	IBS: 26.2%	IBS: 25.1%	5	Controls not well defined No investigations done for MAS

Table 4





What you need to know:

Background:

- SARS-CoV-2 is primarily a respiratory pathogen, but can infect the gastro-intestinal tract. Post-infection functional gastro-intestinal disorders/disorders of gut-brain interaction (FGID/DGBI) can occur after COVID-19.
- There is paucity of data from prospective studies evaluating the occurrence of post-COVID-19 FGID/DGBI.

Findings:

- This study shows that Post-COVID-19 FGID/DGBI is present in about 7% of patients after 6 months of follow-up.
- This is the first study to explore concomitant malabsorption among FGID patients, finding that around 30% have isolated carbohydrate malabsorption.

Implications for patient care:

- Familiarising with this entity will enable clinicians to better recognize and manage Post-COVID-19 FGID/DGBI, potentially minimizing unnecessary testing.

Supplementary Figure 1: Bar graph depicting baseline severity of infection during follow-up among FGID/DGBI patients