Original research

Post COVID-19 irritable bowel syndrome

Giovanni Marasco,[1,2] Cesare Cremon,[1,2] Maria Raffaella Barbaro,[1] Giulia Cacciari,[1,2] Francesca Falangone,[3] Anna Kagramanova,[4] Dmitry Bordin,[4,5,6] Vasile Drug,[7] Egidia Miftode,[8] Pietro Fusaroli ,[9] Salem Youssef Mohamed,[10] Chiara Ricci,[11] Massimo Bellini,[12] Mohammed Masudur Rahman,[13] Luigi Melcarne,[14] Javier Santos ,[15] Beatriz Lobo,[15] Serhat Bor,[16] Suna Yapali,[17] Deniz Akyol,[18] Ferdane Pirincci Sapmaz,[19] Yonca Yilmaz Urun,[20] Tugce Eskazan,[21] Altay Celebi,[22] Huseyin Kacmaz,[23] Berat Ebik,[24] Hatice Cilem Binicier,[25] Mehmet Sait Bugdayci,[26] Munkhtsetseg Banzragch Yağcı,[27] Husnu Pullukcu,[18] Berrin Yalınbas Kaya,[20] Ali Tureyen,[20] İbrahim Hatemi,[21] Elif Sitre Koc,[17] Goktug Sirin,[22] Ali Riza Calıskan,[23] Goksel Bengi,[25] Esra Ergun Alıs,[28] Snezana Lukic,[29] Meri Trajkovska,[30] Keren Hod,[31] Dan Dumitrascu,[32] Antonello Pietrangelo,[33] Elena Corradini,[33] Magnus Simren,[34] Jessica Sjölund ,[34] Navkiran Tornkvist,[34] Uday C Ghoshal ,[35] Olga Kolokolnikova,[36] Antonio Colecchia,[37] Jordi Serra,[38] Giovanni Maconi ,[39] Roberto De Giorgio ,[40] Silvio Danese ,[41] Piero Portincasa,[42] Antonio Di Sabatino ,[43] Marcello Maggio,[44] Elena Philippou,[45] Yeong Yeh Lee ,[46] Daniele Salvi,[2] Alessandro Venturi,[1] Claudio Borghi,[1,2] Marco Zoli,[2] Paolo Gionchetti,[1,2] Pierluigi Viale,[1,2] Vincenzo Stanghellini ,[1,2] Giovanni Barbara ,[1,2] the GI-COVID19 study group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-328483).

For numbered affiliations see end of article.

Correspondence to
Dr Giovanni Barbara, Azienda Ospedaliero-Universitaria di Bologna IRCCS, Bologna, Emilia-Romagna, Italy;
giovanni.barbara@unibo.it

Received 15 August 2022
Accepted 23 November 2022
Published Online First
9 December 2022

Check for updates

© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Marasco G, Cremon C, Barbaro MR, *et al*. *Gut* 2023;**72**:484–492.

ABSTRACT

Objectives The long-term consequences of COVID-19 infection on the gastrointestinal tract remain unclear. Here, we aimed to evaluate the prevalence of gastrointestinal symptoms and post-COVID-19 disorders of gut–brain interaction after hospitalisation for SARS-CoV-2 infection.

Design GI-COVID-19 is a prospective, multicentre, controlled study. Patients with and without COVID-19 diagnosis were evaluated on hospital admission and after 1, 6 and 12 months post hospitalisation. Gastrointestinal symptoms, anxiety and depression were assessed using validated questionnaires.

Results The study included 2183 hospitalised patients. The primary analysis included a total of 883 patients (614 patients with COVID-19 and 269 controls) due to the exclusion of patients with pre-existing gastrointestinal symptoms and/or surgery. At enrolment, gastrointestinal symptoms were more frequent among patients with COVID-19 than in the control group (59.3% vs 39.7%, p<0.001). At the 12-month follow-up, constipation and hard stools were significantly more prevalent in controls than in patients with COVID-19 (16% vs 9.6%, p=0.019 and 17.7% vs 10.9%, p=0.011, respectively). Compared with controls, patients with COVID-19 reported higher rates of irritable bowel syndrome (IBS) according to Rome IV criteria: 0.5% versus 3.2%, p=0.045. Factors significantly associated with IBS diagnosis included history of allergies, chronic intake of proton pump inhibitors and presence of dyspnoea. At the 6-month follow-up, the rate of patients with COVID-19 fulfilling the criteria for depression was higher than among controls.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The long-term consequences of COVID-19 infection on the gastrointestinal tract remain unclear.
⇒ Similarly, if SARS-CoV-2 may be a risk factor for disorders of gut–brain interaction is unknown.

WHAT THIS STUDY ADDS

⇒ At the 12-month follow-up, compared with controls, patients with COVID-19 reported higher rates of postinfection irritable bowel syndrome (IBS) according to Rome IV criteria.
⇒ Factors significantly associated with new IBS diagnosis included dyspnoea during the acute phase, history of allergies and chronic intake of proton pump inhibitors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ COVID-19 is associated with an increased risk of long-term gastrointestinal symptoms, including postinfection IBS.
⇒ Given the high prevalence of COVID-19 at the global level, an increase in new-onset disorders of gut–brain interaction should be expected due to COVID-19.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

Conclusion Compared with controls, hospitalised patients with COVID-19 had fewer problems of constipation and hard stools at 12 months after acute infection. Patients with COVID-19 had significantly higher rates of IBS than controls.
Trial registration number NCT04691895.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, has spread globally with over 533 million confirmed cumulative cases, and more than 6 million cumulative deaths, as reported by the WHO on 15 June 2022.[1] The clinical course of COVID-19 can range from asymptomatic infection to rapidly progressing and life-threatening disease.[2] Older people and those with underlying medical conditions are more likely to develop serious illness.[3] Despite vaccination,[4 5] new virus variants[6 7] lead to cyclic contagion peaks that are a cause of concern.

Additionally, the so-called long COVID-19 is an emerging entity burdening health systems worldwide,[8] consisting of residual effects after SARS-CoV-2 infection, such as fatigue, dyspnoea, chest pain, cognitive disturbances, arthralgia and reduced quality of life.[9] A recent metanalysis including 57 studies, with 250 351 COVID-19 survivors, reported long-term sequelae, including pulmonary impairment, neurological disorders, mental health disorders, functional mobility impairments, and general and constitutional symptoms.[10] Long-term and postacute digestive symptoms included abdominal pain, anorexia, diarrhoea and vomiting.[10] We recently reported[2] that compared with non-infected controls, SARS-CoV-2 infection was associated with diarrhoea, nausea and other gastrointestinal symptoms. Moreover, at 1 month after the initial assessment, patients with COVID-19 had a greater prevalence of nausea and acid regurgitation compared with controls.

The hypothetical mechanisms responsible for gastrointestinal COVID-19 symptoms and their long-term presence support the involvement of cellular damage, inflammation, gut dysbiosis, enteric nervous system dysfunction and a prothrombosis state induced by the virus.[9 11] Moreover, long-term gastrointestinal COVID-19 symptoms may resemble postinfection (PI) disorders of gut–brain interaction (DGBI).[12] Indeed, acute gastroenteritis following infection with bacterial or viral pathogens is the strongest known risk factor for irritable bowel syndrome (IBS) development, the so-called PI IBS (PI-IBS).[13] Compared with IBS induced by bacterial infections and other DGBI, fewer studies have evaluated the incidence of these syndromes following viral infection. Additionally, the long-term consequences of COVID-19 infection on the gastrointestinal tract remain unclear due to the limitations of previous studies, including small sample size, limited follow-up, lack of controls and retrospective design.[14–16] Here, we report the results of a prospective, global, multicentre, controlled study assessing the prevalence of PI gastrointestinal symptoms in patients who were hospitalised with COVID-19 compared with a non-COVID hospitalised control group, who were followed-up for 12 months after hospitalisation.

METHODS

Design

This study was promoted by the Department of Medical and Surgical Science at the University of Bologna, Italy and IRCCS S. Orsola in Bologna, Italy, and was endorsed by the European Society of Neurogastroenterology and Motility (ESNM), the United European Gastroenterology (UEG), and the Rome Foundation (RF).The study was carried out in 36 centres in 14 countries: Italy, Bangladesh, Cyprus, Egypt, Israel, India, Macedonia, Malaysia, Romania, the Russian Federation, Serbia, Spain, Sweden and Turkey. Country and centre selection were based on the availability of principal investigators who either were contacted directly or responded to advertisements on UEG, ESNM and RF websites.

Patients

For this study, hospitalised patients with or without COVID-19 were prospectively and consecutively enrolled on hospital admission, and followed up with symptom reassessment at 1, 6 and 12 months. The enrolment timeframe lasted from 1 to 3 months for each centre. All patients were evaluated according to standard clinical practice, and gave their written informed consent. Eligible patients were≥18 and ≤85 years of age, with or without a diagnosis of COVID-19 according to the WHO definition (laboratory-confirmed SARS-CoV-2 infection),[17] with symptoms severe enough to warrant hospital admission, and recruited from May to October 2020. Patients were excluded if they were unable to conform to study protocol (under mechanical ventilation or unable to report data or to sign informed consent), or were diagnosed with concurrent cancer. The control group comprised patients hospitalised for reasons other than COVID-19—including disease/disorders of gastroenterological, traumatic, and surgical pertinence—who were prospectively enrolled within the study timeframe in the internal medicine units of participating centres.

Assessment

Study data were simultaneously collected from each centre using an e-Case report form on the REDCap platform. Descriptive statistics were used to report all demographics, medical history, laboratory and imaging tests, and other clinical data, including the presence of gastrointestinal symptoms according to the Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire at admission and at 1, 6 and 12 months of follow-up. The GSRS is a self-administered questionnaire with a well-documented reliability and validity, and has been developed for the assessment of gastrointestinal symptoms in IBS and peptic ulcer disease, including a recall period of 1 week.[18] On admission, patients were assessed for the presence of COVID-19-related symptoms—including current or previous (1 week before hospitalisation) gastrointestinal symptoms, using the GSRS, which comprises 15 items including common upper and lower gastrointestinal symptoms, graded on a 7-point Likert-like scale.[18] To avoid overestimation of gastrointestinal symptoms, the GSRS was also used to assess the presence of gastrointestinal symptom onset at least 6 months before hospitalisation, and symptomatic patients were excluded from the primary aim analyses. After enrolment, all patients were contacted by telephone and interviewed at 1 month to reassess GSRS and hospitalisation outcomes, and at 6 and 12 months to reassess GSRS and to complete the Hospital Anxiety and Depression Scale (HADS).[19] The HADS is a self-assessment scale useful for detecting states of depression and anxiety in the setting of an hospital medical outpatient clinic.[19] Data from the HADS were scored for depression and anxiety as follows: score 0–7, normal; 8–10, borderline abnormal; and 11–21, abnormal.[19] At the 6 and 12 months assessments, DGBI were diagnosed according to the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults.[20]

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

Endpoints

The primary endpoint of this study was the assessment of long-term post-COVID-19 gastrointestinal symptoms and DGBI. The secondary endpoints included the assessment of predictive factors associated with the development of PI DGBI, if a statistically significant between-group difference was found. Exploratory endpoints included long-term gastrointestinal symptoms, and the development of DGBI and anxiety and depression within the entire study cohort at the 12-month follow-up (2053 patients).

Statistical analysis

Continuous variables were reported as mean and SD, and categorical variables as number and percentage. Primary and secondary aim analyses were conducted after excluding subjects with chronic gastrointestinal symptoms or previous gastrointestinal surgery. Presence of chronic gastrointestinal symptoms was defined as the report of at least one GSRS item of any severity—except borborygmi, flatus and eructation, for which the additional presence of at least one other GSRS item was required due to their common frequency in the general population, with onset reported at least 6 months before hospitalisation. Patients without COVID-19 diagnosis were used as the control group for the primary study outcome. Data recorded at admission and during follow-up evaluations were compared using the χ^2 test, Fisher's test, Student's t-test and Mann-Whitney U test, as appropriate. Significant follow-up data regarding the occurrence of DGBI and anxiety and depression at 12 months were graphically translated using histograms. When significant between-group differences were identified, the data recorded at admission were tested as predictors of gastrointestinal symptoms at 12 months, according to GSRS and/or DGBI occurrence in patients with COVID-19, using logistic regression univariate and multivariate analysis. We calculated the estimated OR and 95% CI, and p values of <0.05 (two tailed) were considered statistically significant. The results obtained from multivariate analysis were translated into graphic form, using a nomogram for logistic regression. All analyses were carried out using STATA statistical software (Stata Corp.).

RESULTS

Patients

From 1 May to 30 October of 2020, a total of 2183 hospitalised patients were consecutively enrolled from the 36 recruiting centres. Of these patients, 130 were excluded: 75 for incomplete or missing questionnaire data, 34 for being unable to conform to the study protocol during follow-up (death), 14 due to cancer, and 7 controls due to COVID-19 diagnosis during follow-up. Of the remaining 2053 patients, 1314 (64%) had a diagnosis of COVID-19. A total of 1170 patients (700 in the COVID-19 population and 470 in the control group) were excluded from the primary and secondary aim analyses due to pre-existing gastrointestinal symptoms and/or surgery (figure 1). Data from 883 subjects without pre-existing gastrointestinal symptoms (614 COVID-19 and 269 controls) were used for baseline evaluations and follow-up for primary and secondary study aims. Follow-up evaluations were completed by 772 patients (548 COVID-19 and 224 controls) at 6 months, and by 623 patients (435 COVID-19 and 188 controls) at 12 months. Table 1 presents the demographics and clinical characteristics of patients included in the study.

Gastrointestinal symptoms after COVID-19 infection

At enrolment, gastrointestinal symptoms occurred more frequently in patients with COVID-19 compared with controls: 106/267 controls (39.7%) versus 364/614 patients with COVID-19 (59.3%), p<0.001. Compared with the control group, patients with COVID-19 reported higher rates of nausea (12.6% vs 28.8%, p<0.001), diarrhoea (9.4%, vs 37.3%, p<0.001), loose stools (7.9% vs 27.2%, p<0.001), and urgency (4.9% vs 15.9%, p=0.001), and a lower rate of hard stools (12.7 vs 7.7%, p=0.038).

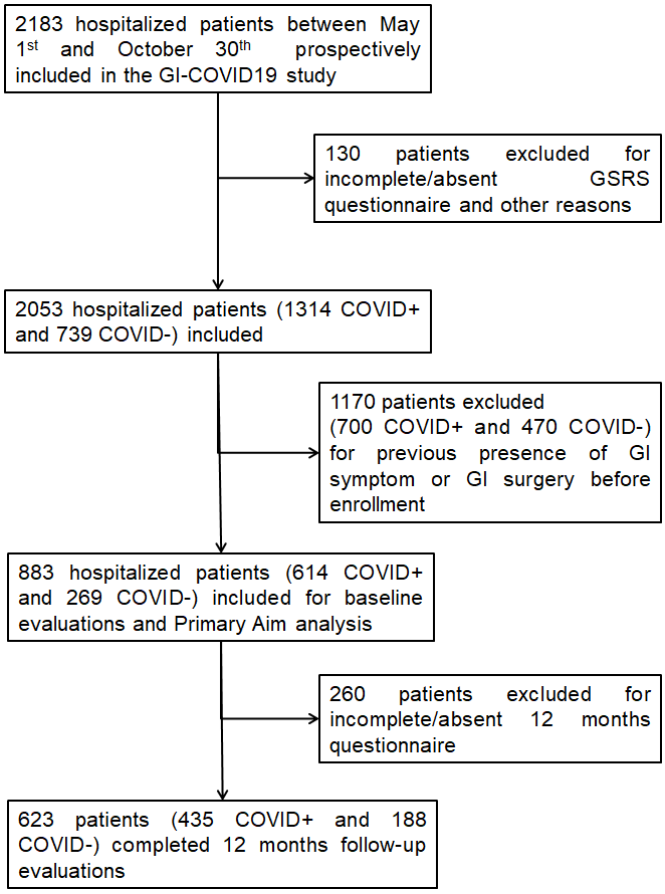


Figure 1 Flow chart of the selection of patients enrolled in the study. GI, gastrointestinal; GSRS, Gastrointestinal Symptoms Rating Scale.

At the 1-month follow-up, compared with controls, patients with COVID-19 showed significantly higher rates of nausea (1.7% vs 8.7%, p=0.015) and acid regurgitation (2.1% vs 8.4%, p=0.006). At the 6-month follow-up, compared with controls, patients with COVID-19 reported lower rates of flatus (19.1% vs 17.6%, p=0.024), constipation (17.1% vs 8.9%, p<0.001) and hard stools (17.2% vs 9.6%, p=0.030). At the 12-month follow-up, compared with controls, patients with COVID-19 reported significantly lower rates of constipation (16% vs 9.6%, p=0.019) and hard stools (17.7% vs 10.9%, p=0.011). We found no other significant between-group differences in GSRS results.

The rates of gastrointestinal symptom intensity scores in the study population at enrolment, and at the 1-month, 6-month and 12 month follow-ups are reported in online supplemental tables 1–4. For the exploratory endpoints, the occurrence of long-term gastrointestinal symptoms at the 12-month follow-up in the entire study cohort (2053 patients) is reported in online supplemental table 5.

Post COVID-19 disorders of gut–brain interaction

There were no significant differences at the 6-month follow-up in the rates of epigastric pain syndrome (0% vs 0.6%, p=0.267),

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

Table 1 Demographics and anamnestic characteristics of patients selected for primary aim analysis in the GI-COVID-19 study

	Controls, **n (%) or Mean±SD n=*269***	COVID-19, **n (%) or Mean±SD n=*614***	**P value**
Age	50.9±18.1	49.9±16.1	0.471
Sex, male	164 (62.1)	364 (59.9)	0.532
BMI	26.8±5.5	27.7±5.3	0.023
Smoker			<0.001
No	125 (47.5)	436 (71.8)	
Current	72 (27.4)	60 (9.9)	
Former	66 (25.1)	111 (18.3)	
Alcohol consumption	58 (22.3)	95 (15.7)	0.018
Physical activity (at least 30 min 3 times/week)	78 (30)	174 (29.9)	0.976
Comorbidities			
Neurological	21 (7.8)	16 (2.6)	<0.001
Cardiovascular	105 (39)	173 (28.2)	0.001
Respiratory	31 (11.5)	40 (6.5)	0.012
Liver	16 (6)	19 (3.1)	0.045
Kidney	20 (7.4)	28 (4.6)	0.083
Diabetes	60 (22.3)	89 (14.5)	0.004
Metabolic other than diabetes	32 (11.9)	58 (9.5)	0.268
Musculoskeletal	8 (3)	16 (2.6)	0.757
Psychiatric	9 (3.4)	6 (1)	0.012
Gynaecological	3 (1.1)	1 (0.2)	0.052
Urological	20 (7.4)	21 (3.4)	0.009
Rheumatological	7 (2.6)	14 (2.3)	0.772
Allergies	13 (4.8)	18 (2.9)	0.158
Autoimmune	11 (4.1)	17 (2.8)	0.303
Neoplastic	11 (4.1)	13 (2.1)	0.097
Psychological	11 (4.1)	8 (1.3)	0.009
Haematological	10 (3.7)	7 (1.1)	0.010
Chronic medication intake with GI effect			
Proton pump inhibitors	68 (25.3)	74 (12.1)	<0.001
Non-steroidal anti-inflammatory drugs	33 (12.3)	33 (5.4)	<0.001
Steroids	13 (4.8)	7 (1.1)	0.001
Metformin	16 (6)	31 (5.1)	0.584
Serotonin selective reuptake inhibitors	9 (3.4)	11 (1.8)	0.153
Antipsychotic	4 (1.5)	3 (0.5)	0.125
Iron	5 (1.9)	5 (0.8)	0.177
Fibrates	1 (0.4)	7 (1.1)	0.267
ACE-I	32 (11.9)	56 (9.1)	0.205
Beta-blockers	45 (16.7)	76 (12.4)	0.084
Angiotensin-2 antagonist	20 (7.4)	56 (9.1)	0.411
Lithium	0	0	–
Carbamazepine	3 (1.1)	1 (0.2)	0.052
Furosemide	25 (9.3)	10 (1.6)	<0.001
5-ASA	3 (1.1)	5 (0.8)	0.664
Rifaximin	3 (1.1)	0	0.009
Opiates	4 (1.5)	2 (0.3)	0.053
Anticholinergics	1 (0.4)	1 (0.2)	0.594
Verapamil	3 (1.1)	3 (0.5)	0.297
Levothyroxine	11 (4.1)	19 (3.1)	0.453
Cholestyramine	1 (0.4)	0	0.131
Monoclonal antibodies	1 (0.4)	0	0.131
Digoxin	0	1 (0.2)	0.508
Dopaminergic agents	1 (0.4)	2 (0.3)	0.914
H2 blockers	3 (1.1)	1 (0.2)	0.052
Benzodiazepines	13 (4.8)	11 (1.8)	0.011
Tricyclic antidepressant	3 (1.1)	2 (0.3)	0.150
Antibiotics in the last 3 months	91 (34.5)	132 (21.5)	<0.001
Probiotics in the last 3 months	28 (10.7)	46 (7.5)	0.125

ACE-I, ACE inhibitor; 5-ASA, acid 5 amino-salicylic; BMI, body mass index; GI, gastrointestinal; n, number; SD, Standard deviation.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

Table 2 DGBI and anxiety and depression occurrence at the 6-month and 12-month follow-ups in patients selected for primary aim analysis of the GI-COVID-19 study

	6-Month follow-up			*12-Month follow-up*		
	Controls n (%) n=*224*	COVID-19 n (%) n=*548*	P value	Controls n (%) n=*188*	COVID-19 n (%) n=*435*	P value
DGBI						
Epigastric pain syndrome	0	3 (0.6)	0.267	2 (1.1)	8 (1.8)	0.480
Postprandial distress syndrome	3 (1.3)	9 (1.6)	0.757	3 (1.6)	17 (3.9)	0.134
Functional dyspepsia	3 (1.3)	11 (2)	0.528	4 (2.1)	16 (3.7)	0.314
Chronic nausea and vomiting syndrome	3 (1.3)	6 (1.1)	0.774	3 (1.6)	2 (0.5)	0.145
Cyclic vomiting syndrome	1 (0.5)	0	0.118	–	–	–
Functional diarrhoea	0	1 (0.2)	0.522	0	1 (0.2)	0.511
Irritable bowel syndrome	2 (0.9)	3 (0.6)	0.587	1 (0.3)	14 (3.2)	0.045
HADS						
Depression			0.014			0.1
Normal	209 (93.3)	471 (86)		176 (93.6)	384 (88.3)	
Borderline abnormal	9 (4)	54 (9.9)		7 (3.7)	36 (8.3)	
Abnormal	6 (2.7)	23 (4.1)		5 (2.7)	15 (3.4)	
Anxiety			0.914			0.088
Normal	196 (90.7)	445 (89.7)		174 (92.5)	390 (89.7)	
Borderline abnormal	12 (5.6)	31 (6.3)		12 (6.4)	25 (5.8)	
Abnormal	8 (3.7)	20 (4)		2 (1.1)	20 (4.5)	

DGBI, disorders of gut–brain interaction; HADS, Hospital Anxiety and Depression Scale; n, number.

post-prandial distress syndrome (1.3% vs 1.6%, p=0.757), functional dyspepsia (1.3% vs 2%, p=0.528), IBS (1.3% vs 1.6%, p=0.587) and functional diarrhoea (0% vs 0.2%, p=0.522) in controls compared with COVID-19, respectively (table 2).

At the 12-month follow-up, compared with controls, patients with COVID-19 reported significantly higher rates of IBS (0.5% vs 3.2%, p=0.045) (figure 2). The only control patient who developed IBS reported IBS with diarrhoea (IBS-D). On the other hand, among the 14 patients with COVID-19 who developed IBS, 4 (28.6%) reported IBS with constipation, 7 (50%) IBS-D, 1 (7.1%) IBS with mixed bowel habits, and 2 (14.3%) IBS undefined subtype. Patients with COVID-19 also reported higher rates of other DGBI at 12 months; however, no other significant differences were found (table 2).

Post COVID-19 anxiety and depression

Compared with controls, patients with COVID-19 showed a significantly higher rate of depression, according to the HADS, at the 6-month follow-up: borderline abnormal, 4% versus 9.9% and abnormal, 2.7% versus 4.2% (p=0.014). A similar trend was observed for anxiety, according to the HADS, at the 12-month follow-up, although this difference was not significant (figure 3). With regards to the exploratory endpoints, the development of DGBI and anxiety and depression within the entire study cohort (2053 patients) is reported in online supplemental table 6.

Factors associated with post-COVID-19 DGBI

Baseline rates of antibiotic intake in the previous 3 months, cough, dyspnoea, headache and antibiotic intake during hospitalisation were significantly higher in patients who would develop post-COVID IBS (online supplemental table 7). All demographic, anamnestic and clinical data assessed at baseline (including comorbidities, chronic medication intake, and gastrointestinal symptoms significantly associated with COVID-19,

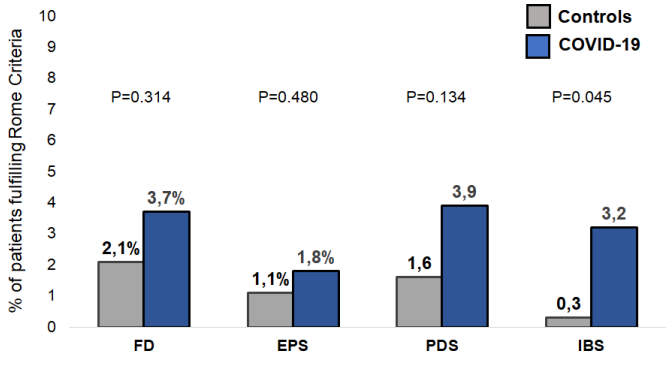


Figure 2 Disorders of gut–brain interaction diagnosis (DGBI) at the 12-month follow-up in controls and patients with COVID-19 diagnosis. EPS, epigastric pain syndrome; FD, functional dyspepsia; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome.

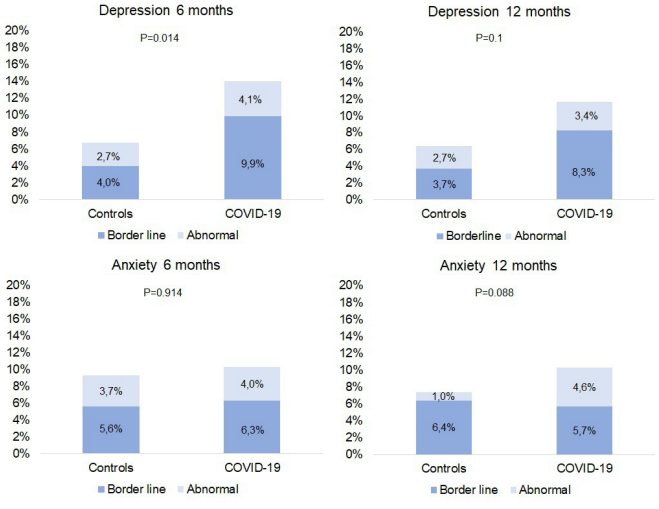


Figure 3 Hospital Anxiety and Depression Scale (HADS) at 6 and 12 months among controls and patients with COVID-19 diagnosis.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

Table 3 Univariate and multivariate logistic regression for identifying factors associated with irritable bowel syndrome occurrence at 12 months follow-up in patients with COVID-19 of the study group selected for primary aim analysis

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Comorbidities				
Liver diseases	4.845 (0.989 to 23.734)	0.052		
Allergies	6.212 (1.239 to 31.149)	0.026	10.024 (1.766 to 56.891)	0.009
Chronic medication intake				
Proton pump inhibitors	4.030 (1.300 to 12.499)	0.016	4.816 (1.447 to 16.025)	0.010
Antibiotic intake in the previous 3 months	3.158 (1.081 to 9.220)	0.035		
Clinical course				
Cough	4.935 (1.091 to 22.321)	0.038		
Dyspnoea	4.167 (1.369 to 12.680)	0.012	4.157 (1.336 to 12.934)	0.014
In-hospital antibiotic administration	3.945 (0.871 to 17.851)	0.075		
Anxiety according to HADS at 6 months	2.081 (0.996 to 4.347)	0.051		

CI, Confidence Interval; HADS, Hospital Anxiety and Depression Scale; OR, Odd Ratio; p, p value.

according to GSRS), as well as data from the HADS at the 6-month follow-up, were tested in univariate analysis as independent predictors of IBS diagnosis in both the entire study cohort selected for primary aim evaluations as post-hoc analysis (online supplemental table 9), and in patients with COVID-19 at the 12-month follow-up. The post-hoc analysis carried out in the entire study cohort found that predictive factors for IBS occurrence were COVID-19 diagnosis (OR 10.686), history of allergies (OR 7.642), and chronic intake of proton pump inhibitors (PPI; OR 5.439). As for the group of patients with COVID-19, the univariate analysis revealed the following as predictive factors for IBS: history of comorbidities, such as liver diseases and allergies; chronic intake of PPI; antibiotic intake within the 3 months prior to hospital admission; presence of cough and dyspnoea at enrollment; in-hospital antibiotic administration; and the presence of anxiety, according to HADS at the 6-month follow-up (table 3). In subsequent multivariate analysis, only three variables remained significant: history of allergies (OR, 10.024; 95% CI 1.766 to 56.891; p=0.009), chronic intake of PPI (OR, 4.816; 95% CI 1.447 to 16.025; p=0.010), and dyspnoea (OR, 4.157; 95% CI 1.336 to 12.934; p=0.014). Figure 4 presents a nomogram assessing the individual risk factors associated with IBS diagnosis at 12 months.

DISCUSSION

Long-term follow-up of the GI-COVID study provides evidence that most gastrointestinal symptoms declined after hospitalisation for SARS-CoV-2 infection. In fact, compared with controls, patients with COVID-19 showed a lower prevalence of constipation and hard stools at the 12-month follow-up. Additionally, at the 12-month follow-up, patients with COVID-19 showed a significantly higher prevalence of IBS compared with control patients. IBS risk was increased among patients with history of allergies, chronic intake of PPI and dyspnoea at hospitalisation. Patients with COVID-19 also showed higher levels of depression and anxiety at 6 and 12 months after hospitalisation.

Several previous studies have assessed the development of long-term gastrointestinal symptoms and DGBI after COVID-19. However, these studies have been limited by biases, including small sample size,[14 15 21] retrospective[14 15] or cross-sectional design,[21] single-centre setting,[14 21] and use of historic outpatient[16] control group comparators. Moreover, they have suffered from limited follow-up assessment, at most up to 6 months,[14–16] have not used the standardised Rome IV questionnaires,[14 16] have not adjusted analyses for the presence of gastrointestinal symptom or DGBI before the acute bout of SARS-CoV-2 infection,[14 15 21] or have not assessed the influence of other variables with gastrointestinal effects.[16] As a matter of fact, without adjusting results for the abovementioned variables, we found no significant differences in DGBI occurrence in our exploratory endpoint analysis.

The GI-COVID study[2] included a large prospective multicentre controlled cohort of hospitalised patients with COVID-19 diagnosis, compared with a control population of hospitalised patients without COVID-19 who were enrolled at the same time as the study cases. Patients were followed up until 12 months after hospitalisation, and the results were adjusted for the presence of previous gastrointestinal symptoms, abdominal surgery, chronic gastrointestinal diseases and medication intake. The groups did not differ in GSRS domains at 6 and 12 months, except that the patients with COVID-19 had lower rates of constipation and hard stools compared with control patients. These data are in contrast with previous reports. A small monocentric study found

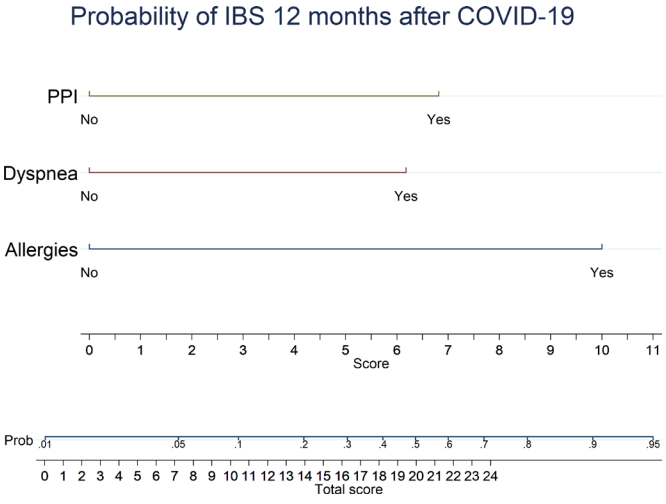


Figure 4 Nomogram reporting a probability score for irritable bowel syndrome (IBS) development at 12 months after COVID-19 Infection. Each predictor is assigned a score on each axis; the sum of all points for all predictors is computed and denoted as the total score up to 24, associated with a probability of about 75% for developing IBS. PPI, proton pump inhibitors.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

more frequent loose stools among COVID-19 survivors at 6 months compared with controls, and no difference in the rate of constipation.[14] On the other hand, other large retrospective matched-controlled studies have reported an increased rate of constipation in patients with COVID-19,[22 23] together with an increased use of laxatives.[22]

Compared with controls, we found a higher rate of IBS (3.2%) in the COVID-19 group. Interestingly, this rate of IBS is lower than those previously reported among patients with COVID-19, which have ranged from 5.3% according to Rome III criteria at 6 months,[16] up to 15.9% according to Rome IV criteria.[21] These discrepancies may be partly explained by our rigorous patient selection, which may have lowered the occurrence rates in our cohort. However, our post-COVID-19 IBS rate is in line with data from a recent meta-analysis that reported an IBS rate of 6.4% after viral infections.[24]

No previous data are available regarding predictors of post-COVID-19 IBS. We found that predictive factors for post-COVID-19 IBS occurrence were consistent with previous findings in IBS.[13] Our data indicated an association of post-COVID-19 IBS with history of allergies, which is in line with previous evidence,[25 26] and with the evidence of immune dysregulation and loss of mucosal homeostasis in patients with IBS.[27–29] We also found an association between baseline dyspnoea and post-COVID-19 IBS. A previous large retrospective cohort study[30] also reported that dyspnoea at hospital admission was associated with post-COVID-19 IBS, and suggested that the severity of the acute infection and systemic symptoms may be involved in the development of chronic intestinal symptoms.

Our present results also showed that patients with COVID-19 reporting chronic use of PPIs were at risk for IBS development. PPIs can contribute to alterations of gut microbiota,[31 32] and PPI use during COVID-19 increases the risk of infection and worsens outcomes.[33] Changes in gut microbiota have been implicated in the pathogenesis of gastrointestinal symptoms[2] during the acute phase of COVID-19,[31] as well as in the development of long-lasting post-COVID-19 gastrointestinal symptoms.[34 35] patients with COVID-19 have exhibited reduced microbial diversity, higher levels of *Ruminococcus gnavus* and *Bacteroides vulgatus*, lower levels of *Faecalibacterium prausnitzii*, and heavily reduced levels of butyrate-producing bacteria, including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii*.[34]

While a number of pathophysiological mechanisms may be involved in the development of gastrointestinal symptoms during acute SARS-CoV-2 infection,[11] the mechanisms underlying the persistence of symptoms after SARS-CoV-2 eradication remain unknown. Besides gut microbiota modifications, evidence suggests the involvement of gut dysmotility, increased intestinal permeability and modifications of enteroendocrine cell function and serotonin metabolism.[13]

The biological plausibility of COVID-19 leading to the development of de novo IBS is based on evidence that SARS-CoV-2 can infect the gastrointestinal tract, in particular the ileum and colon according to the distribution of ACE2 receptors,[11] and that outbreaks of viral gastroenteritis evoke IBS development.[36] Indeed, SARS-CoV-2 nucleic acids have been found in the small bowel of COVID-19 survivors up to 6 months after the acute infection, together with persistent immune activation.[37] Other studies have also found persistent aberrant immunological activation several months after an initial SARS-CoV-2 infection,[38 39] with enrichment of the cytotoxic T-cell pool in patients with long-term gastrointestinal symptoms.[35] Therefore, it is possible to speculate that long-term SARS-CoV-2 antigen persistence in the small bowel leads to persistent immune activation and inflammation, and thus to post-COVID-19 gastrointestinal symptoms. This persistent and delayed immune activity may partly explain the delayed peak of post-COVID-19 IBS occurrence at 12 months, as highlighted herein, which differs from other PI-IBS that occur soon after the acute bout of infection.[13]

Our study has several limitations. First, the outcomes may have been influenced by a number of other factors not included in our analysis. Moreover, the prevalence of outcomes may have been affected by the length of follow-up, which was limited to 1 year after acute infection and by the use of the GSRS for the assessment of the presence of gastrointestinal symptoms before hospitalisation to adjust our results, thus introducing a recall bias. Second, the exclusion of subjects with any previous gastrointestinal symptoms reduced the sample size, which may have lowered our ability to detect significant increases of DGBI or psychological factors in the COVID-19 vs control populations, for a possible type II error. In addition, at each study time-point we reported about 15% of random drop-outs, but this may have not influenced the assessment of our endpoints according to the baseline GSRS with the exception of eructation, loose stool and borborygmi, for which less severely affected patients were more likely to drop-out (online supplemental table 11). Third, we included a control group of hospitalised patients for reasons other than gastrointestinal disease and/or surgery, which reported more comorbidities and medication intake at baseline compared with patients with COVID-19, thus possibly reducing the power of our results. We recorded a very low number of IBS diagnoses, similar to in other reports.[16] Therefore, our multivariate model for the evaluation of predictive factors for IBS occurrence in COVID-19 suffered an overfitting variable bias. However, we tried to partially overcome this limitation by selecting variables according to pathophysiological plausibility. In addition, for hospital access restrictions due to the COVID-19 pandemic, patients were interviewed telephonically at follow-up although questionnaire used should have been self-administred, thus possibly introducing a questionnaire bias. Finally, we conducted our study only including hospitalised patients from certain countries (about 60% from Italy and Turkey); therefore, our data may not be generalisable to outpatients and the global population.

In conclusion, COVID-19 is associated with a modest increased risk of long-term gastrointestinal symptoms and IBS. Given the high prevalence of COVID-19 at the global level, an increase in new-onset disorders of gut–brain interaction should be expected due to COVID-19, especially after hospitalisation for this disease. Future studies are needed to improve our understanding of the mechanisms underlying symptom development in these patients, and to identify novel therapeutic strategies to prevent and treat these conditions.

Author affiliations
[1]Azienda Ospedaliero-Universitaria di Bologna IRCCS, Bologna, Emilia-Romagna, Italy
[2]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[3]Medical-Surgical Department of Clinical Sciences and Translational Medicine, University Sapienza Rome, Rome, Italy
[4]Loginov Moscow Clinical Scientific Center, Moscow, Russian Federation
[5]Tver State Medical University, Tver, Russian Federation
[6]Medicine and Dentistry, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia
[7]Gastroenterology, Grigore T Popa University of Medicine and Pharmacy Faculty of Medicine, Iasi, Romania

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

[8]Department of Infectious Diseases, 'Grigore T Popa' University of Medicine and Pharmacy, Iasi, Romania
[9]Gastroenterology Unit, University of Bologna, Imola, Italy
[10]Internal Medicine Department, Zagazig University, Zagazig, Egypt
[11]Gastroenterology Unit, University of Brescia, Brescia, Italy
[12]Department of New Technologies and Translational Research in Medicine and Surgery, University of Pisa, Pisa, Italy
[13]Department of Gastroenterology, Sheikh Russel National Gastroliver Institute and Hospital, Dhaka, Bangladesh
[14]Gastroenterology Department, Hospital Universitario Parc Tauli, Sabadell, Cataluña, Spain
[15]Digestive System Research Unit, Hospital General Vall D'Hebron, Barcelona, Spain
[16]Ege University School of Medicine, Izmir, Turkey
[17]Division of Gastroenterology, Acibadem University, Altunizade Acibadem Hospital, Istanbul, Turkey
[18]Department of Infectious Diseases, Ege University, Izmir, Turkey
[19]Division of Gastroenterology, University of Health Sciences, Keciören Education and Research Hospital, Keciören, Turkey
[20]Division of Gastroenterology, Eskisehir City Hospital, Eskisehir, Turkey
[21]Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Division of Gastroenterology, Turkey
[22]Division of Gastroenterology, Kocaeli University, Kocaeli, Turkey
[23]Division of Gastroenterology, Adiyaman Education and Research Hospital, Adiyaman, Turkey
[24]Division of Gastroenterology, University of Health Sciences, Diyabakır Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey
[25]Division of Gastroenterology, Dokuz Eylül University, Izmir, Turkey
[26]Division of Gastroenterology, İstanbul Aydın University Florya Liv Hospital, Istanbul, Turkey
[27]Division of Gastroenterology, Darıca Farabi Education and Research Hospital, Kocaeli, Turkey
[28]Department of Infectious Diseases, İstanbul Aydın University Florya Liv Hospital, Istanbul, Turkey
[29]Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia, Beograd, Beograd, Serbia
[30]Clinic of Gastroenterohepatology, Skopje, Macedonia (the former Yugoslav Republic of)
[31]Research Division, Assuta Medical Center, Tel Aviv, Tel Aviv, Israel
[32]2nd Medical Department of Internal Medicine, University of Medicine and Pharmacy, Cluj-Napoca, Romania
[33]Division of Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy
[34]Department of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[35]Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[36]Medsi Clinical Hospital, Moscow, Russian Federation
[37]Division of Gastroenterology, University of Modena and Reggio Emilia, Modena, Italy
[38]CIBERehd, University Hospital Germans Trias i Pujol, Barcelona, Spain
[39]Gastroenterology, L.Sacco University Hospital, Milan, Italy
[40]Department of Translational Medicine, University of Ferrara, Ferrara, Italy
[41]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milano, Italy
[42]Division of Internal Medicine "A. Murri", Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro", Bari, Italy
[43]First Department of Internal Medicine, Università degli Studi di Pavia Facoltà di Medicina e Chirurgia, PV, Lombardia, Italy
[44]Geriatric Clinic Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy
[45]Department of Life and Health Sciences, Cyprus University of Nicosia, Nicosia, Cyprus
[46]School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia

Twitter Giovanni Marasco @giomara89, Berat Ebik @BeratEbik and Yeong Yeh Lee @justntweet

Acknowledgements We thank the European Society of Neurogastroenterology and Motility, the United European Gastroenterology, and the Rome Foundation for supporting this study.

Collaborators Alessio Piacentini, Mariam Shengelia, Valeriy Vechorko, Carla Cardamone, Claudia Agabiti Rosei, Andrea Pancetti, Francesco Rettura, Marc Pedrosa, Adoración Nieto, Claudia Barber, Alejandro Henao, Caterina Campoli, Dragana Mijac, Milos Korac, Uros Karic, Aleksandar Markovic, Ana Najdeski, Dafina Nikolova, Marija Dimzova, Orly Lior, Nadav Shinhar, Ori Perelmutter, Yehuda Ringel, Cristina Marica Sabo, Ana Chis, Gregorio Bonucchi, Giacomo Pietro Ismaele Caio, Caterina Ghirardi, Beatrice Marziani, Barbara Rizzello, Ariadna Aguilar, Domenica Maria Di Paolo, Leonilde Bonfrate, Giovanni Marconi, Michele Di Stefano, Sara Tagliaferri, Juan Enrique Naves, Andrea Galli, Gabriele Dragoni, Laurentiu Nedelcu, Milena Stevanovic, Ance Volkanovska Nikolovska, Antonio Capogreco, Alessio Aghemo, Paula Antonia Mauloni, Sara Del Vecchio, Luca Rotondo, Federica Capuani, Davide Montanari, Francesco Palombo, Clara Paone, Giada Mastel, Claudia Fontana, Lara Bellacosa, Rosanna F. Cogliandro.

Contributors GB, GMarasco, CC, and VS designed the study; all authors collected data for the study; GMarasco carried out statistical analysis; GMarasco, GB, and CC validated and interpretated data; GB, GMarasco, CC, and VS drafted the manuscript; and all authors critically revised, approved, and agree on all aspects of the final version of the manuscript. GB is the guarantor of the article.

Funding GB's contribution to this research was partly supported by funding from Fondazione Cassa di Risparmio in Bologna, the Italian Ministry of Education, University and Research; and Fondazione del Monte di Bologna e Ravenna and European Grant H2020, DISCOvERIE, SC1-BHC-01-2019

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by IRCCS Policlinico S. Orsola Ethical Committee - Coordinating center approval: 399/2020/Oss/AOUBo. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available on reasonable request. All figures have associated raw data. The additional data that support the findings of this study are available from the corresponding author by request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for personal use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs
Pietro Fusaroli http://orcid.org/0000-0002-4397-9314
Javier Santos http://orcid.org/0000-0002-4798-5033
Jessica Sjölund http://orcid.org/0000-0002-3946-0480
Uday C Ghoshal http://orcid.org/0000-0003-0221-8495
Giovanni Maconi http://orcid.org/0000-0003-0810-4026
Roberto De Giorgio http://orcid.org/0000-0003-0867-5873
Silvio Danese http://orcid.org/0000-0001-9867-8861
Antonio Di Sabatino http://orcid.org/0000-0002-0302-8645
Yeong Yeh Lee http://orcid.org/0000-0002-6486-7717
Vincenzo Stanghellini http://orcid.org/0000-0003-0559-4875
Giovanni Barbara http://orcid.org/0000-0001-9745-0726

REFERENCES

1 WHO Coronavirus (COVID-19) Dashboard. Who coronavirus (COVID-19) Dashboard with vaccination data. Available: https://covid19.who.int/ [Accessed 26 Feb 2022].
2 Marasco G, Cremon C, Barbaro MR, *et al*. Prevalence of gastrointestinal symptoms in severe acute respiratory syndrome coronavirus 2 infection: results of the prospective controlled multinational GI-COVID-19 study. *Am J Gastroenterol* 2022;117:147–57.
3 Goyal P, Choi JJ, Pinheiro LC, *et al*. Clinical characteristics of Covid-19 in New York City. *N Engl J Med* 2020;382:2372–4.
4 Jackson LA, Anderson EJ, Rouphael NG, *et al*. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* 2020;383:1920–31.
5 Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603–15.
6 Mlcochova P, Kemp SA, Dhar MS, *et al*. SARS-CoV-2 B.1.617.2 delta variant replication and immune evasion. *Nature* 2021;599:114–9.
7 Hui KPY, Ho JCW, Cheung M-C, *et al*. SARS-CoV-2 omicron variant replication in human bronchus and lung ex vivo. *Nature* 2022;603:715–20.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.

8 Crook H, Raza S, Nowell J, *et al*. Long covid-mechanisms, risk factors, and management. *BMJ* 2021;374:n1648.
9 Nalbandian A, Sehgal K, Gupta A, *et al*. Post-Acute COVID-19 syndrome. *Nat Med* 2021;27:601–15.
10 Groff D, Sun A, Ssentongo AE, *et al*. Short-Term and long-term rates of Postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open* 2021;4:e2128568.
11 Marasco G, Lenti MV, Cremon C, *et al*. Implications of SARS-CoV-2 infection for neurogastroenterology. *Neurogastroenterol Motil* 2021;33:e14104.
12 Schmulson M, Ghoshal UC, Barbara G. Managing the inevitable surge of Post–COVID-19 functional gastrointestinal disorders. *Am J Gastroenterol* 2021;116:4–7.
13 Barbara G, Grover M, Bercik P, *et al*. Rome Foundation working team report on Post-Infection irritable bowel syndrome. *Gastroenterology* 2019;156:46–58.
14 Noviello D, Costantino A, Muscatello A, *et al*. Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: a controlled cohort study. *Neurogastroenterol Motil* 2022;34:e14187.
15 Yusuf F, Fahriani M, Mamada SS, *et al*. Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis. *F1000Res* 2021;10:301.
16 Ghoshal UC, Ghoshal U, Rahman MM, *et al*. Post-infection functional gastrointestinal disorders following coronavirus disease-19: a case-control study. *J Gastroenterol Hepatol* 2022;37:489–98.
17 Diagnostic testing for SARS-CoV-2. Available: https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2 [Accessed 02 Mar 2021].
18 Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988;33:129–34.
19 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
20 Palsson OS, Whitehead WE, van Tilburg MAL, *et al*. Rome IV diagnostic questionnaires and tables for Investigators and clinicians. *Gastroenterology* 2016;150:1481–91.
21 Ebrahim Nakhli R, Shanker A, Sarosiek I, *et al*. Gastrointestinal symptoms and the severity of COVID-19: disorders of gut-brain interaction are an outcome. *Neurogastroenterol Motil* 2022;34:e14368.
22 Al-Aly Z, Xie Y, Bowe B. High-Dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;594:259–64.
23 Blackett JW, Wainberg M, Elkind MSV, *et al*. Potential long coronavirus disease 2019 gastrointestinal symptoms 6 months after coronavirus infection are associated with mental health symptoms. *Gastroenterology* 2022;162:648–50.
24 Klem F, Wadhwa A, Prokop LJ, *et al*. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. *Gastroenterology* 2017;152:1042–54.
25 Koloski N, Jones M, Walker MM, *et al*. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel syndrome, independent of psychological distress. *Aliment Pharmacol Ther* 2019;49:546–55.
26 Burns G, Carroll G, Mathe A, *et al*. Evidence for local and systemic immune activation in functional dyspepsia and the irritable bowel syndrome: a systematic review. *Am J Gastroenterol* 2019;114:429–36.
27 Barbara G, Stanghellini V, De Giorgio R, *et al*. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126:693–702.
28 Barbara G, Wang B, Stanghellini V, *et al*. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007;132:26–37.
29 Robles A, Perez Ingles D, Myneedu K, *et al*. Mast cells are increased in the small intestinal mucosa of patients with irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil* 2019;31:e13718.
30 Fernández-de-Las-Peñas C, Martín-Guerrero JD, Navarro-Pardo E, *et al*. Exploring the recovery curve for gastrointestinal symptoms from the acute COVID-19 phase to long-term post-COVID: the LONG-COVID-EXP-CM multicenter study. *J Med Virol* 2022;94:2925–7.
31 Zuo T, Zhang F, Lui GCY, *et al*. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology* 2020;159:944–55.
32 Gu S, Chen Y, Wu Z, *et al*. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. *Clin Infect Dis* 2020;71:2669–78.
33 Li G-F, An X-X, Yu Y, *et al*. Do proton pump inhibitors influence SARS-CoV-2 related outcomes? A meta-analysis. *Gut* 2021;70:1806–8.
34 Liu Q, Mak JWY, Su Q, *et al*. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut* 2022;71:544–52.
35 Su Y, Yuan D, Chen DG, *et al*. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022;185:881–95.
36 Porter CK, Faix DJ, Shiau D, *et al*. Postinfectious gastrointestinal disorders following norovirus outbreaks. *Clin Infect Dis* 2012;55:915–22.
37 Gaebler C, Wang Z, Lorenzi JCC, *et al*. Evolution of antibody immunity to SARS-CoV-2. *Nature* 2021;591:639–44.
38 Phetsouphanh C, Darley DR, Wilson DB, *et al*. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022;23:210–6.
39 Sun J, Xiao J, Sun R, *et al*. Prolonged persistence of SARS-CoV-2 RNA in body fluids. *Emerg Infect Dis* 2020;26:1834–8.

Gut: first published as 10.1136/gutjnl-2022-328483 on 9 December 2022. Downloaded from http://gut.bmj.com/ on March 3, 2023 at Kocaeli Universitesi. Protected by copyright.