

Acute gastrointestinal and post-acute COVID-19 gastrointestinal syndrome assessment on the Gastrointestinal Symptom Rating Scale scoring system: A questionnaire-based survey

Sunita Singh¹, Niraj K. Srivastava², Rahul Yadav², Saurabh Paul³,
Shefali Gupta⁴, Sankalp⁵, Priyanshi Dixit⁶

¹Department of Paediatric Surgery, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, ²Department of General Surgery, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, ³Department of Community and Family Medicine, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, ⁴Department of Microbiology, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, ⁵Department of Cardiothoracic Surgery, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, ⁶Nursing Tutor, Vardhman Mahaveer Nursing Medical College, New Delhi, India

ABSTRACT

Background: Post-acute coronavirus disease 2019 (COVID-19) syndrome (PACS) is the persistence of sequel of acute SARS-COV-2 infection. Persistent/acquired gastrointestinal symptoms (GI-PACS) include loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility, dyspepsia, and irritable bowel syndrome. The study aimed to assess the short- and long-term GI-PACS syndrome on the GRS scale. **Methods:** A cross-sectional, retrospective record analysis and telephonic questionnaire-based survey were conducted at a tertiary referral center in northern India. The data incorporated patients treated from April 2021 to March 2023. Exclusion criteria were neurological disorders, dementia, inability to understand Hindi/English languages, and psychiatric problems. All patients who met the inclusion criteria were telephonically called from November 2023 to January 2024. **Results:** The study population was 350 recovered patients from SARS-COV-19 illness. Forty-three responses were removed during data cleaning and removal of duplication. The data analysis of 307 participants (ICU admissions=92, non-ICU admissions=123, and outdoor treatment =92) was done. The proportion of patients not having any GI symptoms, having at least one GI symptom, and having more than one GI symptom before SARS-COV-2 illness was 3%(3/307), 4.9% (15/307), and 3.6% (11/307), respectively. The four major GI symptoms analyzed in the study were vomiting, pain in the abdomen, diarrhea, and constipation. Overall, 13% (40/307) of the study population did not have any major GI symptoms before SARS-COV-2 diseases. During acute SARS-COV-2 illness, 86.97% (267/307) of patients develop new GI symptoms. Post SARS-COV-2 illness, the overall mean GRS score for 15 items was 2.14 ± 0.829 . The acquired GI-PACS was abdominal pain syndrome (mean score $2.5190 \pm SD 0.86650$), constipation syndrome (mean score 2.3844 ± 0.83840), reflux syndrome (mean score 2.2866 ± 1.31889), indigestion syndrome (mean score 1.8591 ± 0.93076), and diarrhea syndrome (mean score 1.8122 ± 0.90899). Overall, fever (95.1%, $P = 0.007$), anosmia (45.0%, $P = 0.042$), cough (80.1%, $P = 0.032$), and hospitalization (30.0%, $P = 0.003$) had a more significant association with one of the major four GI symptoms during the acute phase of SARS-COV-2 illness. Home-isolated patients having loss of appetite (95.4%, $P = 0.0001$) had a significant association with one of the major four GI symptoms during the acute phase

Address for correspondence: Dr. Niraj K. Srivastava,
Type 5, 4A, All India Institute of Medical Sciences, Raebareli,
Uttar Pradesh, India.
E-mail: nirajsri09@gmail.com

Received: 28-04-2024

Revised: 04-08-2024

Accepted: 08-08-2024

Published: 09-12-2024

Access this article online

Quick Response Code:



Website:
<http://journals.lww.com/JFMPC>

DOI:
10.4103/jfmpe.jfmpe_707_24

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How to cite this article: Singh S, Srivastava NK, Yadav R, Paul S, Gupta S, Sankalp, *et al.* Acute gastrointestinal and post-acute COVID-19 gastrointestinal syndrome assessment on the Gastrointestinal Symptom Rating Scale scoring system: A questionnaire-based survey. *J Family Med Prim Care* 2024;13:5787-98.

of SARS-COV-2 illness. Hospitalized patients having fever (80.7%, $P = 0.031$), breathlessness (83.8%, $P = 0.003$), loss of smell (97.0%, $P = 0.001$), and cough (82.7%, $P = 0.048$) had a more significant association with one of the major four GI symptoms during the acute SARS-COV-2 illness. Abdominal pain, reflux, and constipation were considered severe GI symptoms (symptom GSRS score greater than total mean GSRS score). Diarrhea and indigestion were considered mild symptoms (symptom GSRS score was less than the total mean GSRS score). The GI symptoms during acute SARS-COV-2 illness recovered in 66.1% (203/307) patients within 3 months. The respondents taking medicines for more than 1 year following SARS-COV-2 illness were 19.2%. 12.0% (37/307) of respondents suffered from persistent GI symptoms on a mean follow-up of 20.1 ± 0.82 months. **Conclusion:** Long-term COVID-19 syndrome frequently manifested as GI symptoms, whereas most symptoms subsided with time.

Keywords: Corona virus, COVID-19, functional gastrointestinal disorders, GCRS score, irritable bowel syndrome, novel coronavirus, post-acute SARS-COV-2 syndrome (PACS), post-SARS-COV-2 symptoms, SARS-COV-2, SARS novel corona virus disease, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection outbreak in 2019 was declared an International public health emergency by the World Health Organization on March 11, 2020.^[1,2] In addition to the airways and lungs, SARS-COV-2 can multiply in the gastrointestinal (GI) tract, urinary tract, and central nervous system due to the presence of the Angiotensinogen-converting enzyme-2 (ACE-2) receptors in different organs.^[3,4] The ACE-2 receptors are expressed at nearly 100-fold higher levels in GI mucosa than in respiratory organs.^[5,6] SARS-COV-2-associated acute GI symptoms varied from a mild/indolent clinical course to severe symptoms.^[7-9]

Approximately one-third of patients reported chronic symptoms after recovering from the illness from SARS-COV-2, also known as post-acute COVID-19 syndrome (PACS).^[10,11] The exact incidence of PACS is still deficient in the literature.^[11] PACS includes post-traumatic stress disorders, depression, anxiety, and insomnia to acute encephalitis, cardiopulmonary syndromes, fibrosis, hepatobiliary damages, gastrointestinal dysregulation, myocardial infarction, neuromuscular syndromes, neuropsychiatric disorders, pulmonary damage, renal failure, stroke, and vascular endothelial dysregulation.^[12-14]

The most persistent symptoms among PACS were deficits in working memory, attention span, and processing speed due to systematic cytokines binding to ACE2 receptors that damage cerebral blood vessels and intestinal walls. The degradation of the intestinal barrier and increased permeability of the intestine and brain cause harmful toxins produced by the microbiota of the GI tract, or dysbiosis, to pass into the brain, causing damage to neuronal integrity, which presents as cognitive deficits.^[12,15,16]

The persistent/chronic GI symptoms of PACS (GI-PACS) include loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility, dyspepsia, and irritable bowel syndrome.^[10,11,17,18] Post COVID-19 recovery, there is a significant increase in the probability of motility disorders (constipation and diarrhea), esophageal disorders, dysphagia, abdominal pain, and new-onset irritable bowel syndrome.^[18-20]

However, there exists a knowledge gap about the long-term GI symptoms in recovered SARS-COV-2 patients from India. The study aimed to assess the short- and long-term GI symptoms in patients who recovered from SARS-COV-2 patients on the GSRS scale.

Methodology

Study design

A cross-sectional, questionnaire-based survey was conducted at a tertiary referral center in northern India to know the persistent COVID-19-related GI symptoms in recovered patients. Clinical symptom severity correlation was also done by retrospective record analysis of patients discharged from ICU to assess the acute disease severity, medical treatment, and length of ICU stay/ward stay, along with baseline data on presenting symptoms. The patients with persistent symptoms were called by the researcher for further management and treatment of their ignored symptoms to fulfill the unmet needs of the participants. The study was approved by Institutional Ethical Committee, ID 2023-7-EMP-EXP(STS) - 5; Dated 29.10.23.

Inclusion criteria

Patients (aged >18 years) who recovered from SARS-COV-2 were included. The diagnostic criteria were a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swabs. The data records of both admitted and outdoor-treated patients were retrieved from the Hospital Information System.

Exclusion criteria

Patients who suffered from neurological disorders, dementia, inability to understand Hindi/English languages, and psychiatric problems and the patients having preexisting GI symptoms during diagnosis with SARS-COV-2 were excluded.

Sample size and sampling technique

Convenient sampling was used to recruit patients. All patients who met the inclusion criteria were contacted telephonically from November 2023 to January 2024.

Study tools and variables

i. Demographic profile: The demographic profile collected

- was age, gender, marital status, education, and occupation.
- ii. **Comorbidities:** The comorbidities inquired were diabetes mellitus, chronic obstructive pulmonary diseases, hypertension, thyroid disorders, smoking, and drinking status (alcoholic vs nonalcoholic).
 - iii. **Acute COVID-19 Symptoms:** The common presenting symptoms during acute SARS-COV-2 illness inquired were fever, cough, dyspnea, myalgia, fatigue, sputum production, confusion, headache, sore throat, rhinorrhea, chest pain, hemoptysis, abdominal pain, diarrhea, nausea, and vomiting.
 - iv. **Acute GI symptoms:** The GI symptoms during acute SARS-COV-2 illness were anorexia, pain or discomfort in the upper abdomen, ageusia, nausea/vomiting, constipation, blood in stool, and melena/black tarry stool. The four major GI symptoms analyzed during acute SARS-COV-2 illness were vomiting, abdominal pain, diarrhea, and constipation.
 - v. **GSRS Symptoms:** GSRS score was used to assess the post-SARS-COV-2 illness GI symptoms. The persistent/acquired GI symptoms for calculating GSRS score were heartburn, acid reflux, hunger pain, nausea, rumbling in the stomach, bloating, burping, passing gas or flatus, constipation, diarrhea, loose stools, urgent need to evacuate bowel, hard stools, and the sensation of not completely emptying the bowel.^[21,22]
 - vi. **Five domains/subscales of GI symptoms:** GSRS scores were calculated covering five domains called “subscales”. These subscales were reflux syndrome (average of items 2 and 3), abdominal pain (average of items 1, 4, and 5), indigestion syndrome (average of items 6, 7, 8, and 9), constipation syndrome (average of items 10, 13, and 15), and diarrhea syndrome (average of items 11, 12, and 14).^[21,22]
 - vii. **GSRS Score:** The GSRS includes 15 items that address a wide variety of GI symptoms. It has a 7-point response scale to measure a participant’s level of discomfort associated with a given GI symptom, ranging from “No discomfort at all” to “Very severe discomfort.”
The GSRS has a 7-point graded Likert scale, where 1 represents no discomfort at all, 2 represents slight discomfort, 3 represents mild discomfort, 4 represents moderate discomfort, 6 represents severe discomfort, and 7 represents very severe discomfort.
The reliability and validity of the GSRS were well documented in various studies, and norm values for a general population are available. The internal consistency reliability of the GSRS is 0.43–0.87. The test–retest reliability of the GSRS is 0.36–0.75.^[21,22]
 - viii. **Minor and major GI symptoms:** Based on GSRS scoring, the proportion of patients who suffered from GI disturbances was graded as minor (symptom score less than total mean GSRS score for all 15 items) and major (symptom score more than total mean GSRS score for all 15 items).

Data collection

Senior researchers conducted an hour-long training session on data collecting for study assistants (a nursing tutor and a medical

student). All eligible patients were invited to take part in the survey. The interviews were done over the phone.

Statistical analysis

Statistical analysis was done using Microsoft Excel and IBM SPSS Statistics 23.0. Frequencies with percentages and descriptive statistics were used for sociodemographic variables and clinical features. The dependent variable was the GSRS symptoms. All the sociodemographic, clinical, and other relevant variables were considered independent variables for binary logistic regression. The significance of the association between the two variables was assessed using Pearson’s Chi-square test. Binary multivariate logistic regression was used to determine the association between the GSRS syndrome severity category and predictor variables. A *P* value < 0.05 at a confidence interval of 95% was considered statistically significant.

Results

The retrospective data incorporated patients admitted from the second wave of the SARS-COV-2 pandemic in India, April 2021. There were 1568 patients diagnosed with RT-PCR on nasopharyngeal swabs for SARS-COVID-19 from April 2021 to March 2023. The reference population was 990 (390 indoor and 600 outdoor) patients. The sample population, using convenient sampling, was 600. Based on exclusion criteria, 250 patients were excluded. The study population was 350 participants. Forty-three responses were removed during data cleaning and removal of duplications. The data analysis of 307 patients (ICU admissions=92, non-ICU admissions=123, and outdoor treatment=92) was done [Figure 1].

Demography

Female participants were 50.8% (156/307). Healthcare workers and homemakers/unemployed were 26.1% (80/307) and 42.0% (129/307), respectively. The married respondents were 25.7% (79/307). The mean age was 41 ± 0.91 years, and 47.2% (145/307) of respondents were < 30 years old [Table 1]. Healthcare providers were primarily treated in home isolation (85.0%) compared to other professional/ or unemployed workers, and the difference was statistically significant (*P* = 0.001).

Comorbidities

The nonsmoker, nondiabetic, and normotensive patients were (92.8%, 285/307), (80.8%, 248/307), and (69.1% 212/307), respectively. The proportion of patients not suffering from pulmonary diseases, immune disorders, renal disorders, and thyroid disorders at the time of suffering from acute SARS-COV-2 illness was 95.1% (292/307), 94.1% (289/307), 94.1% (304/307%), and 94.1% (274/307), respectively [Table 2].

GI symptoms during acute SARS-COV-2 illness

The proportion of patients without GI symptoms during

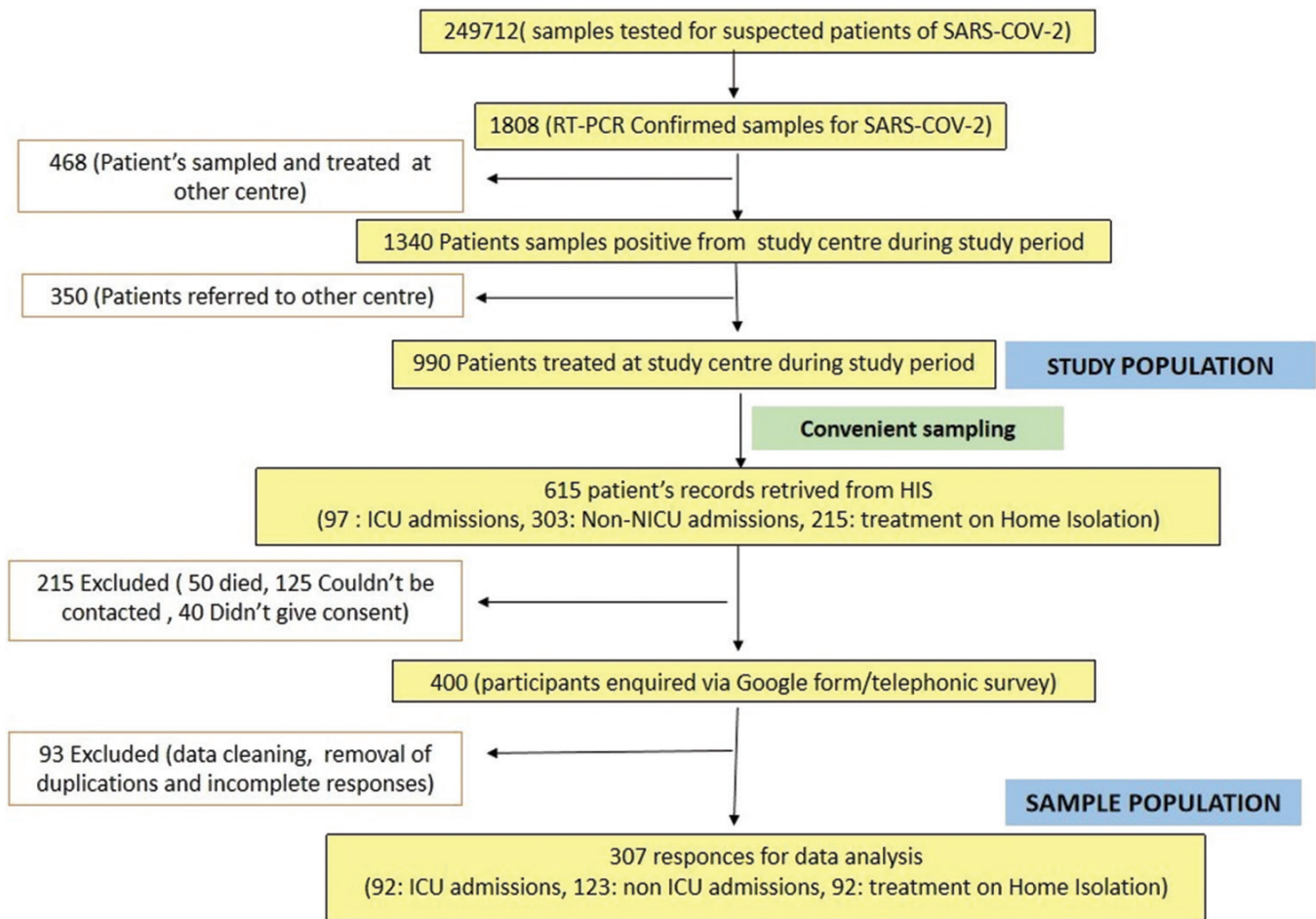


Figure 1: Workflow of the study

SARS-COV-2 illness was 1% (3/307) [Table 3]. The four major GI symptoms analyzed in the study were vomiting, pain in the abdomen, diarrhea, and constipation. Overall, 13% (40/307) of the study population did not have any major GI symptoms before SARS-COV-2 diseases.

Acute SARS-COV-2 illness and GI symptoms

The symptoms during SARS-COV-2 illness were sore throat 301/307 (98.0%), fever 292/307 (95.1%), loss of appetite 255/307 (83.1%), myalgia 227/307 (73.9%), abdominal pain 211/307 (68.7%), ageusia/loss of taste 180/307 (58.6%), breathlessness 155/307 (50.4%), anosmia 138/307 (45.0%), diarrhea 107/307 (34.9%), vomiting 90/307 (35.8%), blood in stool with constipation 93/307 (30.3%), suspected history of melena 72/307 (23.5%), constipation 137/307 (44.6%), and grossly visible blood in stools without constipation 21/307 (6.8%) [Table 4]. The common symptoms during SARS-COV-2 illness among home-isolated patients were fever (94.5%, 87/92), loss of appetite (81.5%, 75/92), cough (79.3%, 73/92), and loss of taste (58.6%, 54/92).

A subgroup of 307 patients who suffered from SARS-COV-2 were hospitalized according to prevailing Indian Council of Medical Research (ICMR) guidelines. Among this subgroup,

92/307 (29.9%) required admission to the ICU. The patients receiving mechanical ventilation, intravenous antibiotics, and intravenous antivirals (Remdisivir) accounted for 53/307 (17.2%), 20/307 (6.51%), and 35/307 (11.4%), respectively. The most common symptoms among ICU patients were fever (95.7%, 88/92), followed by breathlessness (87.0%, 80/92) and cough (81.0%, 75/92).

Persistent/acquired five GI domains

During acute SARS-COV-2 illness, 86.97% (267/307) of patients developed new GI symptoms. Post SARS-COV-2 illness, the mean GSRS score for 15 items for 307 respondents was 2.14 ± 0.829 [Table 5]. The most commonly acquired GI-PACS was abdominal pain syndrome (mean score 2.5190 ± 0.86650), followed by constipation syndrome (mean score 2.3844 ± 0.83840), reflux syndrome (mean score 2.2866 ± 1.31889), indigestion syndrome (mean score 1.8591 ± 0.93076), and diarrhea syndrome (mean score 1.8122 ± 0.90899) [Figure 2].

Major persistent/acquired GI symptoms (GI-PACS)

The major GI symptoms identified were abdominal pain, constipation, and reflux diseases because the mean score of individual symptoms were more than the mean GSRS score of

15 items (symptoms). Diarrhea and indigestion were considered a minor symptom because the mean score of each symptom was lesser than the mean GCRS score for 15 items of minor symptoms (symptoms).

Patients having abdominal pain (73.0%, $P = 0.013$) and diarrhea (39.5%, $P = 0.009$) were significantly more among home isolation patients compared to hospitalized patients. Other GI symptoms do not have any significant association between hospitalization and the home isolation status of the patient [Table 6]. Patients who had a history of abdominal pain (80.0%, $P = 0.011$), vomiting (46.2%, $P = 0.024$), and blood in stool (40.0%, $P = 0.028$) were significantly more among health care providers compared to other professionals.

Table 1: Demographic characteristics (n=307)

Variable	Number (%)
Age (yrs.)	
11-30	145 (47.2)
31-60 y	126 (41.0)
60-100	36 (11.7)
Occupation	
Health care provider	80 (26.1)
Housewife/unemployed	129 (42.0)
Labor	2 (0.7)
Office work or businessman	96 (31.3)
Education	
Illiterate	13 (1.0)
Up to 5 th standard	103 (33.6)
High school and above	124 (40.4)
Graduate and above	77 (25.1)
Gender	
Male	151 (49.2)
Female	156 (50.8)
Smoking status	
i. Present smoker	3
ii. Former smoker	19
iii Nonsmoker	285

Table 2: Comorbid conditions (n=307)

Variable	Number (%)
Hypertension	95 (30.9)
Diabetes mellitus	59 (19.2)
Heart disease	15 (4.9)
Kidney disease	3 (1.0)
Thyroid disorder	33 (10.7)
Immune disorder	18 (5.9)
Respiratory disease	15 (4.9)
GI symptoms before SARS-COV-2 infection	221 (72.0)
i At least one type of GI symptom before SARS-COV-2 infection	75 (24.4)
ii Two or more types of GI symptoms before SARS-COV-2 infection	11 (3.6)
Treatment >12 months (long-term) for GI-Symptoms after SARS-COV-2 illness	59 (19.2)
Treatment for 6 months (short-term) for GI symptoms after SARS-COV-2 illness	45 (14.7)
Anxiety disorders acquired after SARS-COV-2 illness	251 (81.8)

Other GI symptoms do not have any significant association with the occupation of the patients [Table 7].

Overall, fever (95.1%, $P = 0.007$), loss of smell (45.0%, $P = 0.042$), cough (80.1%, $P = 0.032$), and hospitalization (30.0%, $P = 0.003$) with SARS-COV-2 infection had a more significant association with one of the major four GI symptoms during the acute phase of SARS-COV-2 illness among 307 patients.

Patients having a considerable history of loss of appetite (95.4%, $P = 0.0001$) had a significant association with one of the major four GI symptoms during the acute phase of SARS-COV-2 illness among home-isolated patients [Table 8].

Patients having fever (80.7%, $P = 0.031$), breathlessness (83.8%, $P = 0.003$), loss of smell (97.0%, $P = 0.001$), and cough (82.7%, $P = 0.048$) had a more significant association with one of the major four GI symptoms during the acute phase of SARS-COV-2 infection among 92 hospitalized patients [Table 9].

Post-recovery persistent/acquired GI symptoms (GI-PACS)

After recovery from acute SARS-COV-2 illness, 24.4% developed at least one GI symptom, and 3.6% developed two or more GI symptoms. The GI symptoms during acute SARS-COV-2 illness recovered in 66.1% (203/307) within 3 months. The pain in the abdomen and nausea recovered most early (immediately or less than 3 months on recovery), hunger pain retrieved in less than 6 months, and constipation and excess gas persisted for more than 6 months [Table 10]. It takes longer for GI symptoms to subside in patients admitted to the ICU. The degree of acute SARS-COV-2 severity illness could not be significantly predicted by abdominal pain ($P > 0.0001$). The need for medication for GI-PACS was 14.7% (45/307) (short-term outcome). The respondents taking medicines for more than 1 year following

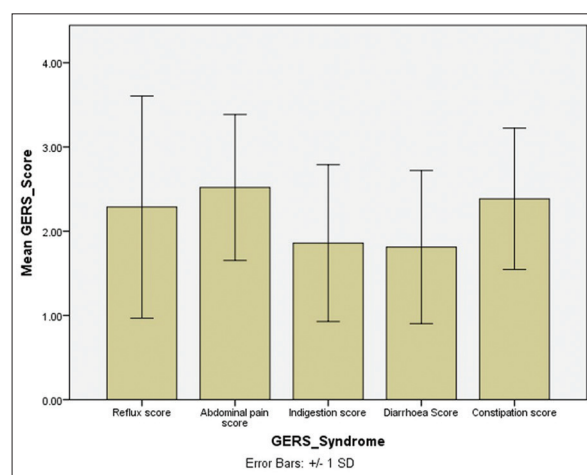


Figure 2: Mean GSRS Score of five dominant/subscales of Gastrointestinal symptoms in recovered patients from SARS-COVID-19 illness

SARS-COV-2 illness was 9.1% (28/307). Only 12.0% (37/307) of respondents suffered from GI-PACS on a mean follow-up of 20.1 ± 0.82 months.

In the binary multivariate logistic regression analysis, the level of multicollinearity was very minimal among all the independent variables as the lowest tolerance value was 0.683, and the variance inflation factor (VIF) was 1.121–1.678. The model was a fit because of a nonsignificant *P* value (*P* = 0.904) using the Hosmer and Lemeshow test. The logistic regression model has explained 45.3% (Cox and Snell R²) and 54.8% (Nagelkerke R²) of the variance of factors related to the severity

of the GERS score and correctly classified 65% of the cases [Table 11]. Participants with age > 60 years, (AOR = 2.406, *P* = 0.049), history of hospitalization (AOR = 3.023, *P* = 0.003), breathlessness (AOR = 2.346, *P* = 0.048), and vomiting (AOR = 1.778, *P* = 0.039) had significantly higher odds of severe GSRS score compared to others. No statistically significant association existed between comorbid conditions, loss of taste (ageusia), loss of appetite, previous GI disorders, or blood in stool with or without constipation with major GI symptoms even after controlling for potential confounders on multivariate analysis. There was no statistically significant association of diarrhea acquired during acute SARS-COV-2 illness with the administration of cephalosporins (*P* = 0.067) and remdisivir (*P* = 0.558). No differences in rates of clinical deterioration were noted between patients with and without GI symptoms when comparing ICU admission, need for mechanical ventilation, or overall mortality.

Table 3: Frequency of different GI symptoms during the acute phase of SARS-COV-2 illness (n=307)

	Number (%)
Number of eight GI symptoms (ageusia, abdominal pain, diarrhea, vomiting, constipation, poor appetite, blood in stool, Melena/black sticky tarry stool) at the time of admission	
No symptoms	3 (1.0%)
One symptom	15 (4.9%)
2 symptoms	46 (15.3%)
3 symptoms	88 (28.7%)
4 symptoms	69 (22.5%)
5 symptoms	5 (16.9%)
6 symptoms	18 (5.9%)
7 symptoms	14 (4.6%)
8 symptoms	1 (0.3%)
Number of 4 major GI symptoms (vomiting, pain in the abdomen, diarrhea, constipation) during acute SARS-COV-2 illness (n=307)	
No symptoms	40 (13.0%)
1 Symptom	82 (26.7%)
2 symptoms	97 (31.6%)
3 symptoms	63 (20.5%)
4 symptoms	25 (8.1%)

Discussion

A developing multisystem illness called long (chronic) COVID-19 syndrome can appear 4 to 12 weeks following an initial SARS-COV-2 infection.^[18] There can be persistent neurological, pulmonary, and gastrointestinal symptoms that impair the quality of life of survivors. There is increased use of pain medications, antidepressants, anxiolytic, antihypertensive, and oral hypoglycemic drugs.^[2,23] There is also evidence of persistent change in laboratory parameters (liver function test/alkaline aminotransferase, etc.).^[14] Long-term COVID-19 syndrome frequently manifests as GI and hepatobiliary symptoms. The GI and hepatobiliary sequelae of prolonged COVID-19 syndrome include dyspepsia, post-COVID-19 cholangiopathy, diarrhea, constipation, loss of taste, lack of appetite, weight loss, and abdominal pain. In the future, long-term COVID-19 is anticipated to place a substantial burden on the healthcare system regarding outpatient treatment and financial expenses.^[18]

Table 4: Overall association of respiratory and constitutional symptoms with major GI symptoms during the acute phase of SARS-COV-2 (n=307)

General symptoms	All patient with SARS-COV-2 illness (n=307) (%)	One of the major four GI symptoms/ acute Constitutional symptoms (%)	Other than four major GI symptoms / acute Constitutional symptoms (%)	<i>P</i>
Fever	292 (95.1)	258/292 (88.4)	34/292 (11.6)	0.007*
Sore throat	301 (98.0%)	200/301 (66.4)	20/301(6.6)	0.112
Loss of appetite	213 (69.4)	188/213 (88.3)	25/213 (11.7)	0.311
Myalgia	227 (73.9)	199/227 (87.7)	28/227 (12.3)	0.543
Loss of smell	138 (45.0)	126/138 (91.3)	12/138 (8.7)	0.042
Cough	246 (80.1)	219/246 (89.0)	27/246 (11.0)	0.032
Blood in stool with constipation	93 (30.3)	82/93 (88.2)	11/93 (11.8)	0.680
Blood in stool without constipation	21 (6.8)	19/21 (90.5)	4/21 (19.0)	0.129
Melena	72 (23.5)	60/72 (83.3)	12/72 (16.7)	0.295
breathlessness	155 (50.4)	128/155 (82.6)	12/155 (7.7)	0.062
Loss of taste	180 (58.6)	161 (89.4)	19 (10.6)	0.125
Hospitalization for SARS-COV-2 illness	92 (30.0)	72 (78.3)	20 (21.7)	0.003
History of GI-symptoms before SARS-COV-2 illness	86 (28.01)	75 (87.2)	11 (12.8)	0.938

*Fisher exact tests

Table 5: GSRS score and with standard deviation for five major GSRS domains/subscales

	Reflux score	Abdominal Pain score	Indigestion score	Diarrhea score	Constipation score
<i>n</i>	307	307	307	307	307
Mean	2.2866	2.5190	1.8591	1.8122	2.3844
Std. deviation	1.31889	0.86650	0.93076	0.90899	0.83840

Table 6: Association of GI symptoms and hospital admission or home isolation status during the acute SARS-COV-2 illness (n=307)

Symptoms	Hospital admission (n=215) (%)	Home isolation (n=92) (%)	<i>P</i>
Abdominal pain	54 (58.7)	157 (73.0)	0.013
Diarrhoea	22 (23.9)	85 (39.5)	0.009
Vomiting	27 (29.3)	83 (38.6)	0.121
Constipation	39 (42.4)	98 (45.6)	0.606
Blood in stool	26 (28.3)	67 (31.2)	0.612
Melena	19 (20.7)	53 (24.7)	0.449
Poor appetite	62 (67.4)	151 (70.2)	0.621
Loss of taste	57 (62.0)	123 (57.2)	0.439

Table 7: Association of occupational and acute GI symptoms during acute SARS-COV-2 illness (n=307)

Symptoms	Healthcare workers n (%)	Other profession n (%)	<i>P</i>
Abdominal pain	64 (80.0)	147 (64.8)	0.011
Diarrhea	29 (36.2)	78 (34.4)	0.760
Vomiting	37 (46.2)	73 (32.2)	0.024
Constipation	31 (38.8)	106 (46.7)	0.219
Blood in stool	32 (40.0)	61 (26.9)	0.028
Melena	14 (17.5)	58 (25.6)	0.144
Poor appetite	56 (70.0)	157 (69.2)	0.889
Loss of taste	43 (53.8)	137 (60.4)	0.303

The GI-PACS symptoms are one of the distressing problems, which might be due to persistent viral infections in C2BBel intestinal cells in brush border; autoimmune reaction; increased production of IFN- α , IFN- β , IFN- λ 1, IFN- λ 2, and IFN- λ 3; plasma serotonin levels; and high fecal calprotectin.^[23] The motility-related GI-PACS are also known as postinfectious neuro-immune-related/postinfectious-functional gastrointestinal disorders. These are new-onset irritable bowel syndrome or functional dyspepsia.^[17] The etiology of motility disorders in animal models is demonstrated due to the crosstalk of gut-innervating specialized sensory neurons (nociceptors) with microorganisms and intestinal epithelial cells.^[10] Furthermore, upper and lower GI endoscopic biopsy after 6 months of post-acute SARS-COV-2 showed positive immunostaining that was significantly higher in upper GI biopsies than in lower GI biopsies (37.34% vs 16.87%, $P = 0.002$). However, this immunostaining did not show significant differences related to previous COVID-19 infections, time since the last infection, and severity of GI symptoms.^[20]

A meta-analysis of 15 studies, with a maximum follow-up of 110 days, showed a 12% prevalence of nausea (16%), fatigue (58%), headache (44%), attention disorder (27%), and so on.^[24] The GI symptoms were rated as the most bothersome PACS symptom in 11% of all patients.^[11,25] The most commonly acquired GI symptoms in our study were abdominal pain followed by constipation, reflux diseases, indigestion, and diarrhea.

Various GI symptoms in acute SARS-COV-2 illness ranged from 12% to 20%.^[8,26] Anorexia (39.9% to 50.2%) and diarrhea (2% to 49.5%) were the most commonly described GI symptoms in acute SARS-COV-2 illness.^[22,27-29] Another systematic review suggested diarrhea (7.4%) followed by nausea/or vomiting (4.6%) as the most common acute GI symptom in acute SARS-COV-2 illness.^[26] In our study, loss of appetite (83.1%), abdominal pain (68.7%), and ageusia (58.6%) were the most common acute GI symptoms.

The frequency of acute GI symptoms in our study was greater than in the Blackett *et al.*^[1] study group, whereas diarrhea (34.9% vs 23%), nausea/vomiting (21%), and abdominal pain (6.1%) were common acute GI symptoms during acute SARS-COV-2 illness. The probable cause of diarrhea during acute illness and PACS might be a hyperinflammatory response, altered gut flora, secondary bacterial infections, antiviral agents (favipiravir and remdesivir), antibiotics (cephalosporins, macrolides, and fluoroquinolones), *Clostridioides difficile*-associated enterocolitis, enteral feeding, proton pump inhibitors, and IL-6 and IL-6 receptor inhibitors (tocilizumab, sarilumab, and siltuximab).^[22] The current study did not reveal any statistically significant association between cephalosporins ($P = 0.067$) and remdesivir ($P = 0.558$) with acute GI symptoms.

A few studies suggested that GI symptoms in acute SARS-COV-2 illness might be a warning sign of a more severe condition with a poor prognosis.^[30] Contrarily, other studies suggested that GI symptoms were associated with indolent disease, that is, longer illness duration but lower ICU admission rate and mortality.^[31] The author did not find any significant difference in five major GI symptoms with the severity of the disease ($P = 0.509$). In a multicenter study in the United States, two-thirds (66.6%) of patients hospitalized with SARS-CoV-2 infection presented with at least one GI symptom where the loss of appetite and diarrhea were the most common symptoms, and these patients reported more fatigue, myalgia, and sore throat.^[24] In the current study, 75% of patients presented with at least one GI symptom, and patients having one GI symptom were correlated with fever, cough, and loss of smell.

The authors did not find a significant association of acute GI symptoms in moderate-severe SARS-CoV-2 disease regarding patient demographics, medical history/comorbid conditions, and presenting laboratory parameters. In the current study, medical staff (26.1%) was less susceptible to persistent GI-PACS symptoms, probably younger age, without comorbidities, and

Table 8: Association of respiratory and constitutional symptoms with major GI symptoms during the acute phase of SARS-COV-2 illness among home isolation patients (n=215)

General symptoms	Hospitalized patient (n=215) (%)	One of the major four GI symptoms (n=195)(%)	Other than major GI symptoms (n=20) (%)	P
Fever	204 (94.9)	187/204 (91.7)	17/204 (8.3)	0.07*
Sore throat	210 (97.67)	20/210 (66.4)	12/210	0.254
Loss of appetite	175 (81.4)	167/175 (95.4)	8/175 (4.6)	0.0001*
Myalgia	164 (76.3)	147/164 (89.6)	17/164 (10.4)	0.419*
Loss of smell	105 (48.8)	94/105 (89.5)	11/105 (89.5) (10.5)	0.563
Cough	171 (79.5)	157/171 (91.8)	14/171 (8.2)	0.256*
Blood in stool with constipation	67 (31.2)	64/67 (95.5)	3/67 (4.5)	0.101
Blood in stool without constipation	19 (8.8)	7/19 (36.8)	4/19 (21.1)	0.123
Malena	53 (24.7)	46/53 (86.8)	7 (13.2)	0.280*
Breathlessness	91 (42.32)	75/91 (82.4)	16/91 (17.58)	0.981
Loss of taste	123 (57.2)	115/123 (93.5)	8/123 (6.5)	0.102
Positive history of any GI disorder before SARS-COV-2 illness	66 (30.7)	59/66 (89.4)	7/66 (10.6)	0.661

*Fisher exact test

Table 9: Association of respiratory and constitutional symptoms and laboratory parameters with major GI symptoms among SARS-COV-2-infected hospitalized patients (n=92)

General symptoms	ICU hospitalized patients (n=92) (%)	One of the major four GI symptoms (n=72) (%)	Other than major GI-symptoms (n=20) (%)	P
Fever	88 (95.7)	71 (80.7)	17 (19.3)	0.031*
Loss of appetite	62 (67.4)	51 (82.3)	11 (17.7)	0.181
Myalgia	63 (68.5)	52 (82.5)	11 (17.5)	0.143
Loss of smell	33 (35.9)	32 (97.0)	1 (3.0)	0.001
Cough	75 (81.5)	62 (82.7)	13 (17.3)	0.048*
Blood in stool with constipation	8 (8.6)	18 (69.2)	8 (30.8)	0.188
Blood in stool without constipation	None (6.8)	19/21 (90.4)	4/21	0.234
Malena	19 (20.7)	14 (73.7)	5 (26.3)	0.550*
breathlessness	80 (87.0)	67 (83.8)	13 (16.2)	0.003*
Loss of taste	57 (62.0)	46 (80.7)	11 (19.3)	0.469
History of any GI symptoms before SARS-COV-2	20 (21.7)	16 (80.0)	4 (20.0)	0.831*
Hypertension	16 (17.4)	15 (93.8)	1 (6.2)	0.179*
Diabetes	11 (12.0)	10 (90.9)	1 (9.1)	0.445*
Heart disease	2 (2.2)	2 (100.0)	0 (0)	1.000*
Anxiety disorder	20 (21.7)	14 (70.0)	6 (30.0)	0.361*
Thyroid disorder	14 (15.2)	13 (2.9)	1 (7.1)	0.289*
Immunodisorder	4 (4.3)	4 (100.0)	0 (0)	0.87*
Respiratory disorder	1 (1.1)	1 (100.0)	0 (0)	1.000*
Length of hospital stay (>14 days)	17 (18.5)	13 (76.5)	4 (23.5)	1.000*
Antibiotic administration -yes	53 (57.6)	41 (77.4)	12 (22.6)	0.807
Antiviral administration -yes	20 (21.7)	18 (90.0)	2 (10.0)	0.223*
Steroid administration -yes	42 (43.5)	33 (78.6)	9 (21.4)	1.000*
Proton pump inhibitor -yes	48 (52.1)	39 (81.2)	9 (18.8)	0.468
Hydroxychloroquine administration - yes	3 (3.3)	2 (66.7)	1 (33.3)	0.525*
IL-6 administration -yes	1 (1.1)	1 (100.0)	0 (0.0)	1.000*
Hb% at admission (mean±SD)	67 [#] (72.8)	12.72±1.622	12.71±2.091	0.996**
CRP at admission (mean±SD)	41 [#] (44.6)	8.01±22.001	4.28±2.451	0.638**
TLC at admission (mean±SD)	63 [#] (68.5)	9174.90±4491.236	10205±3351.082	0.459**
D-Dimer at admission (mean±SD)	13 [#] (14.1)	0.74±0.420	0.43±0.115	0.243**
S ferritin at admission (mean±SD)	8 [#] (8.7)	360.14±104.648	427.67±38.786	0.336**
LDH at admission (mean±SD)	46 [#] (50.0)	910.11±351.074	1123.10±239.205	0.079**
ICU admission n (%)	29 [#] (31.5)	21 (72.4)	8 (27.6)	0.724
Oxygen supplementation (%)	61 [#] (6.5)	48 (74.7)	13 (21.3)	0.215*

CRP: C-reactive protein, IL-2: interleukin-2, LDH: Lactate dehydrogenase, ICU: Intensive care unit, TLC: total leucocyte count.*Fisher exact test, **Independent sample Student t-test, #After excluding missing value

early hospital treatment prevented virus colonization time in gastrointestinal mucosa in this group.^[9]

A study suggested acute GI symptoms in SARS-COV-2 illness were not associated with fecal sample viral RNA

Table 10: Persistence of GI symptoms following recovery of acute SARS-COV-2 illness (GI-PACS)

Maximum duration of persistence of GI-PACS	Symptoms (%)
No discomfort once recovered	Nausea (50.8)
1-3 months	Pain abdomen (31.9)
4-6 months	Hunger pain (28.3)
7-9 months	Constipation (8.8)
>9 months	Passage of gas (10.7)

GI-PACS: Persistent gastrointestinal-post-acute COVID-19 syndrome

positivity ($P = 0.45$). Furthermore, disease severity was also not associated with extended duration of fecal sample viral RNA positivity ($P = 0.60$). However, antiviral treatment was positively associated with the presence of viral RNA in fecal samples ($P = 0.025$).^[32] The stool samples tested positive for SARS-CoV-2 RNA from 5 weeks to 1 year after the respiratory samples tested negative.^[33] This suggests prolonged colonization, replication, and shedding of the virus in the GI tract.^[32,34] The lacunae of the current study were neither stool samples nor serum inflammatory markers tested during acute illness.

The GI-PACS persisted 6 months to 1 year after recovery in 10–40% in various series.^[1,12,14] In a cohort of 1783 COVID-19 survivors, 29% of GI-PACS symptoms were present at 6 months of follow-up. These symptoms were diarrhea (10%), constipation (11%), abdominal pain (9%), nausea/or vomiting (7%), and heartburn (16%) (10). In another cohort of 73,435 COVID-19 survivors, motility disorders (including constipation and diarrhea), esophageal disorders, dysphagia, and abdominal pain persisted for more than 6 months, for which increased use of antiemetics, antacids, and antidiarrheal and antihistamine agents has been demonstrated.^[23] In our study, similar to other authors, GI-PACS was significantly higher in patients having moderate-to-severe (hospitalized) disease or vomiting during acute SARS-COV-2 illness compared with asymptomatic/mild disease.^[17] Here, mild, moderate, and severe diseases were categorized based on prevailing ICMR guidelines. Besides, there is a correlation of GI-PACS with age (>60 years) in our study.

The current study has a high frequency of GI-PACS symptoms compared to Chinese literature.^[8] Previously documented tendencies, such as a lack of sex preference, a link to more severe illness, and variations in laboratory test results (increased leukocytes and transaminases), were not observed in the current study.^[7-10] Variations in hospitalization practices between China and the United States regarding SARS-COV-2 and environmental and social/cultural factors (living conditions, daily routines, diet, mode of transmission) and in-patient clinical factors (medical history, body habitus, home medication) may account for these differences.^[8,24]

Post SARS-COV-2 recovery, shedding of coronavirus in stool was observed in 40.5% of patients with confirmed SARS-COV-2 infection.^[26] The mean time of RNA negative conversion was more for anal swabs than for nasopharyngeal swabs, 3 days (ranged 4–77 days) versus 17 days (4–36 days).^[4] In some countries, routine stool sample testing with real-time RT-PCR

is highly recommended after the clearance of viral RNA in a patient's respiratory samples to prevent fecal-oral transmission.^[32] We did not perform long-term stool testing for coronavirus in our study population.

The strength of the study is that it focused on both in-hospital and ambulatory/home-isolation patients, perhaps analyzing less severe disease. The inquiry was done for GI symptoms during both acute SARS-COV-2 illness and follow-up GI symptoms to give a comprehensive analysis of the broad spectrum of GI symptoms and eliminate selection bias.

The limitations of the study were the retrospective design and thus recall bias. There was a lack of validated symptom definitions of various GI symptoms. Sample size calculation and study of GI symptoms during the natural history of the infection and implications were not the primary aims of the study, thereby limiting deeper interpretation of pooled summary estimates. There needed to be more face-to-face contact with respondents and an award to motivate the respondents to give precise answers.

Conclusion

In the future, long-term COVID-19 is anticipated to burden the healthcare system regarding outpatient treatment. New gastrointestinal symptoms were reported by 40% of patients in SARS-COV-2 survivor groups. Breathlessness, vomiting symptoms, age (>60 years), and hospitalization for SARS-COV-2 during the acute phase of SARS-COV-2 illness significantly predict the severity of the GCRS score post-SARS-COV-2 period. Prospective large cohorts are needed to be studied for the long-lasting GI-PACS for generalization.

Abbreviations

ACE2: Angiotensin-converting enzyme 2
 GSRS scale: Gastrointestinal Symptom Rating Scale (GSRS)
 GI: gastrointestinal tract
 GI-PACS: Gastrointestinal symptoms following Post-acute SARS-COV-2 syndrome
 ICMR: Indian Council of Medical Research
 ICU: Intensive Critical Care Unit
 IFN- α : interferon α
 IFN- β : interferon β
 IFN- λ 1: interferon λ 1
 IFN- λ 2: interferon λ 2
 IFN- λ 3: interferon λ 3
 PACS: Post-acute SARS-COV2 syndrome
 RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction
 RNA: Ribonucleotide
 SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

Financial support and sponsorship

Nil.

Table 11: Binary multivariate logistic regression for the association between GSRS Score and sociodemographic, clinical variables among all the patients (n=307)

Variable	B	SE	df	AOR (95%CI)	Significance
Age (yrs.)					
11-30				Reference	
31-60	-0.090	0.284	1	0.914 (0.524-1.593)	0.914
≥60	0.878	0.467	1	2.406 (1.964-6.005)	0.049
Gender					
Male				Reference	
Female	-0.239	0.270	1	0.788 (0.464-1.338)	0.377
Hospital admission status					
Home isolation				Reference	
Hospitalized	1.106	0.361	1	3.023 (1.489-6.135)	0.002
Breathlessness					
No				Reference	
Yes	0.853	0.432	1	2.346 (1.006-5.472)	0.048
Fever					
Yes	-0.579	0.645	1	0.560 (0.158-1.983)	0.369
No				Reference	
Myalgia					
No				Reference	
Yes	0.166	0.311	1	1.181 (0.642-2.170)	0.593
Loss of smell					
No				Reference	
Yes	-0.005	0.280	1	0.995 (0.575-1.722)	0.987
Cough					
No				Reference	
Yes	0.077	0.340	1	1.080 (0.554-2.104)	0.821
Poor Appetite					
No				Reference	
Yes	-0.179	0.312	1	0.836 (0.453-1.542)	0.566
Blood in stool					
No				Reference	
Yes	0.442	0.316	1	1.556 (0.838-2.891)	0.161
Malena					
No				Reference	
Yes	0.053	0.341	1	1.055 (0.541-2.056)	0.876
Any GI disorder before SARS-COV-2					
No				Reference	
Yes	0.415	0.307	1	1.515 (0.830-2764)	0.176
Any Anxiety disorder					
No				Reference	
Yes	-0.22	0.356	1	0.979 (0.487-1.965)	0.951
Abdominal Pain					
No				Reference	
Yes	0.146	0.312	1	1.157 (0.628-2.132)	0.639
Diarrhea					
No	0.339	0.285	1	1.404 (0.803-2.454)	0.233
Yes					
Vomiting					
No				Reference	
Yes	0.575	0.279	1	1.778 (1.028-3.073)	0.039
Constipation					
No				Reference	
Yes	-0.089	0.277	1	0.914 (0.532-1.572)	0.746
Steroid administration					
No				Reference	
Yes	-0.695	0.515	1	0.499 (0.182-1.369)	0.177

GSRS: Gastrointestinal Symptom Rating Scale, SE: standard error, AOR: adjusted odds ratio, CI: Confidence interval

Conflicts of interest

There are no conflicts of interest.

References

- Blackett JW, Li J, Jodorkovsky D, Freedberg DE. Prevalence and risk factors for gastrointestinal symptoms after recovery from COVID-19. *Neurogastroenterol Motil* 2022;34:e14251.
- Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed* 2020;91:157-60.
- Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, *et al.* COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World J Gastroenterol* 2020;26:4579-88.
- Signorini L, Dolci M, Castelnovo N, Crespi L, Incorvaia B, Bagnoli P, *et al.* Longitudinal, virological, and serological assessment of hospitalized COVID-19 patients. *J Neurovirol* 2022;28:113-22.
- Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, *et al.* The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis* 2020;39:1011-9.
- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020;158:1831-3.e3.
- Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, *et al.* Digestive symptoms in COVID-19 patients with mild disease severity: Clinical presentation, stool viral RNA testing, and outcomes. *Am J Gastroenterol* 2020;115:916-23.
- Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, *et al.* Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. *Gastroenterology* 2020;159:81-95.
- Zhou Z, Zhao N, Shu Y, Han S, Chen B, Shu X. Effect of gastrointestinal symptoms in patients with COVID-19. *Gastroenterology* 2020;158:2294-7.
- Meringer H, Mehandru S. Gastrointestinal post-acute COVID-19 syndrome. *Nat Rev Gastroenterol Hepatol* 2022;19:345-6.
- Freedberg DE, Chang L. Gastrointestinal symptoms in COVID-19: The long and the short of it. *Curr Opin Gastroenterol* 2022;38:555-61.
- Plummer AM, Matos YL, Lin HC, Ryman SG, Birg A, Quinn DK, *et al.* Gut-brain pathogenesis of post-acute COVID-19 neurocognitive symptoms. *Front Neurosci* 2023;17:1232480.
- Sherif ZA, Gomez CR, Connors TJ, Henrich TJ, Reeves WB. Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *Elife* 2023;12:222-47.
- Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;594:259-64.
- Fernández-de-Las-Peñas C, Martín-Guerrero JD, Navarro-Pardo E, Torres-Macho J, Guijarro C, Pellicer-Valero OJ. 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.
- Brooks EF, Bhatt AS. The gut microbiome: A missing link in understanding the gastrointestinal manifestations of COVID-19? *Cold Spring Harb Mol Case Stud* 2021;7:a006031. doi: 10.1101/mcs.a006031.
- Liptak P, Duricek M, Rosolanka R, Ziacikova I, Kocan I, Uhrík P, *et al.* Gastrointestinal sequelae months after severe acute respiratory syndrome coronavirus two infections: A prospective, observational study. *Eur J Gastroenterol Hepatol* 2022;34:925-32.
- Rizvi A, Ziv Y, Crawford JM, Trindade AJ. Gastrointestinal and hepatobiliary symptoms and disorders with long (Chronic) COVID infection. *Gastroenterol Clin North Am* 2023;52:139-56.
- Li J, Zhou Y, Ma J, Zhang Q, Shao J, Liang S, *et al.* The long-term health outcomes, pathophysiological mechanisms, and multidisciplinary management of long COVID. *Signal Transduct Target Ther* 2023;8:416.
- Hany M, Sheta E, Talha A, Anwar M, Selima M, Gaballah M, *et al.* Incidence of persistent SARS-CoV-2 gut infection in patients with a history of COVID-19: Insights from endoscopic examination. *Endosc Int Open* 2024;12:E11-22.
- Kulich KR, Madisch A, Pacini F, Piqué JM, Regula J, Van Rensburg CJ, *et al.* Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: A six-country study. *Health Qual Life Outcomes* 2008;6:12.
- Megyeri K, Dernovics Á, Al-Luhaibi ZII, Rosztóczy A. COVID-19-associated diarrhea. *World J Gastroenterol* 2021;27:3208-22.
- Jin B, Singh R, Ha SE, Zogg H, Park PJ, Ro S. Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19. *World J Gastroenterol* 2021;27:2341-52.
- Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, *et al.* Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;92:55-70.
- Yagi K, Asakura T, Terai H, Ohgino K, Masaki K, Namkoong H, *et al.* Clinical features of Japanese patients with gastrointestinal long-COVID symptoms. JGH opens an open-access *J Gastroenterol Hepatol* 2023;7:998-1002.
- Parasa S, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, *et al.* Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: A systematic review and meta-analysis. *JAMA Netw Open* 2020;3:e2011335.
- Leung WK, To K-F, Chan PKS, Chan HLY, Wu AKL, Lee N, *et al.* Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology* 2003;125:1011-7.
- T, Colombel J-F, Patel G. What should gastroenterologists and patients know about COVID-19? *Clin Gastroenterol Hepatol* 2020;18:1409-11.
- Hanzel J, Ma C, Marshall JK, Feagan BG, Jairath V. Managing inflammatory bowel disease during COVID-19: Summary of recommendations from gastrointestinal societies. *Clin Gastroenterol Hepatol* 2020;18:2143-6.
- Roy K, Agarwal S, Banerjee R, Paul MK, Purbey PK. COVID-19 and gut immunomodulation. *World J Gastroenterol* 2021;27:7925-42.
- Nobel YR, Phipps M, Zucker J, Lebowhl B, Wang TC,

- Sobieszczyk ME, *et al.* Gastrointestinal symptoms and coronavirus disease 2019: A case-control study from the United States. *Gastroenterology* 2020;159:373-5.e2.
32. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, *et al.* Prolonged presence of SARS-CoV-2 viral RNA in fecal samples. *Lancet Gastroenterol Hepatol* 2020;5:434-5.
33. Su Q, Lau RI, Liu Q, Chan FKL, Ng SC. Post-acute COVID-19 syndrome and gut dysbiosis linger beyond one year after SARS-CoV-2 clearance. *Gut* 2023;72:1230-2.
34. Troisi J, Venutolo G, Pujolassos Tanyà M, Delli Carri M, Landolfi A, Fasano A. COVID-19, and the gastrointestinal tract: Source of infection or merely a target of the inflammatory process following SARS-CoV-2 infection? *World J Gastroenterol* 2021;27:1406-18.