Gastrointestinal manifestations of long COVID: A systematic review and meta-analysis

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Abstract

Background: Prolonged symptoms after COVID-19 are an important concern due to the large numbers affected by the pandemic.

Objectives: To ascertain the frequency of gastrointestinal (GI) manifestations as part of long GI COVID.

Design: A systematic review and meta-analysis of studies reporting GI manifestations in long COVID was performed.

Data Sources and Methods: Electronic databases (Medline, Scopus, Embase, Cochrane Central Register of Controlled Trials, and Web of Science) were searched till 21 December 2021 to identify studies reporting frequency of GI symptoms in long COVID. We included studies reporting overall GI manifestations or individual GI symptoms as part of long COVID. We excluded pediatric studies and those not providing relevant information. We calculated the pooled frequency of various symptoms in all patients with COVID-19 and also in those with long COVID using the inverse variance approach. All analysis was done using R version 4.1.1 using packages ‘meta’ and ‘metafor’.

Results: A total of 50 studies were included. The frequencies of GI symptoms were 0.12 (95% confidence interval [CI], 0.06–0.22, $I^2 = 99\%$) and 0.22 (95% CI, 0.10–0.41, $I^2 = 97\%$) in patients with COVID-19 and those with long COVID, respectively. The frequencies of abdominal pain, nausea/vomiting, loss of appetite, and loss of taste were 0.14 (95% CI, 0.04–0.38, $I^2 = 96\%$), 0.06 (95% CI, 0.03–0.11, $I^2 = 98\%$), 0.20 (95% CI, 0.08–0.43, $I^2 = 98\%$), and 0.17 (95% CI, 0.10–0.27, $I^2 = 95\%$), respectively, after COVID-19. The frequencies of diarrhea, dyspepsia, and irritable bowel syndrome were 0.10 (95% CI, 0.04–0.23, $I^2 = 98\%$), 0.20 (95% CI, 0.06–0.50, $I^2 = 97\%$), and 0.17 (95% CI, 0.06–0.37, $I^2 = 96\%$), respectively.

Conclusion: GI symptoms in patients were seen in 12% after COVID-19 and 22% as part of long COVID. Loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain were the five most common GI symptoms of long COVID. Significant heterogeneity and small number of studies for some of the analyses are limitations of the systematic review.

Keywords: abdominal pain, diarrhea, gastrointestinal symptoms, long COVID haulers, nausea, post-COVID syndrome, SARS-CoV-2, vomiting

Introduction

COVID-19 has brought forth a multitude of challenges to the health-care systems globally. Apart from the significant morbidity and mortality associated with COVID-19 during the initial phase, there is a growing recognition and concern about the long-term consequences of COVID-19. Described variously as ‘long COVID’, ‘post-COVID syndrome’, ‘COVID-19 sequelae’, and ‘long haulers’, these symptoms are associated with fatigue, dyspnea, gastrointestinal symptoms, cognitive impairment, and depression. Among these, gastrointestinal symptoms such as abdominal pain, nausea, and diarrhea are particularly common, affecting up to 40% of infected individuals.
COVID,’ ‘long-haul COVID’, and so on, the condition is not clearly characterized regarding the time of onset and the clinical manifestations.\(^1\) The WHO defines it as a constellation of symptoms which occur 3 months after COVID-19 and last for 2 months or more and do not have an alternative explanation.\(^2\) Centers for Disease Control and Prevention (CDC) has described this condition to occur even after 4 weeks of COVID-19.\(^3\) Typically the occurrence of fatigue, breathlessness, and cognitive dysfunction is considered the major manifestation of COVID-19 but the WHO definition also allows for gastrointestinal (GI) issues like diarrhea, constipation, acid reflux, abdominal pain, and altered smell/taste as a part of post-COVID-19 symptoms. The WHO definition is based on Delphi consensus while the CDC’s definition is based on input from a panel of provider and researcher experts.

GI and hepatic manifestations of acute COVID-19 are well recognized.\(^4,5\) The distribution of angiotensin converting enzyme 2 (ACE-2) receptors in the GI tract, systemic effects of the disease, and use of a multitude of the drugs are believed to result in these manifestations.\(^6\)

On the contrary, the GI manifestations of long COVID are not as well recognized. Certain GI symptoms including abdominal pain and diarrhea have been reported with long-COVID syndrome. However, there is a lack of a systematic analysis of the GI manifestations of long COVID and the implications for the patients, health-care workers, and institutions are unclear. It is also unclear as to how these manifestations may vary with respect to various definitions in vogue. These manifestations are, as of now, not included in the standard definition of long COVID. Since these manifestations are likely to affect the quality of life and may result in work-related absences, it is important to characterize the manifestations and their frequency. Therefore, we conducted a systematic review to assess the GI manifestation of ‘long COVID’ and the frequency of these manifestations.

**Methods**

**Search strategy**

The present systematic review and meta-analysis was conducted in accordance with the guidance provided by the PRISMA statement.\(^7\) We searched various electronic databases including Medline, Embase, Cochrane Central Register of Controlled Trials, Scopus, Science Citation Index Expanded, and Emerging Sources Citation Index from inception till 20 December 2021. The keywords used for the search were (‘Covid-19 OR SARS-CoV-2 OR coronavirus disease 2019’) AND (‘long covid OR postcovid OR long haul OR sequelae OR persistent symptoms’). Filters for human studies were applied to all database searches except for Cochrane Central Register of Controlled Trials. Results were limited to English language publications. The detailed search strategy is shown in Supplemental Appendix A. The results obtained from all the databases were combined and duplicate studies were removed. Two reviewers (RT and AC) separately screened the title and abstract to select any studies reporting on data about the GI manifestations or liver dysfunction. The studies selected for full-text screen were seen by two authors (SK and VS) for data extraction.

**Inclusion criteria**

We included studies reporting on frequencies of GI or hepatic manifestations as part of post-COVID/long-COVID syndrome in the adult population. We excluded (1) studies if the number of patients were less than 10, (2) studies reporting the frequency of long COVID in pediatric population as most studies on pediatric population also included multisystem inflammatory syndrome as post-COVID sequelae, (3) studies that report only the multisystem inflammatory syndrome, (4) studies that are non-English, and (5) studies that only report the frequency of changes in taste and smell sensation as part of long-COVID syndrome. We also excluded studies that did not report the relevant outcome data.

**Definitions**

WHO defines long COVID as post-COVID-19 condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.\(^2\)

NICE/CDC describe ‘Post-COVID Condition’ as an umbrella term for the wide range of physical and mental health consequences experienced by
some patients who are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection. Supplemental Table 1 depicts the similarities and differences between the two definitions.

**Data extraction**

Data were extracted from the included studies by two reviewers (RT and AC) and any disagreement was resolved through discussion involving the other two reviewers (SK and VS). Extracted data included publication details (author and year), place and duration of study, total number of COVID patients, total number of long-COVID patients, total number of long COVID with GI symptoms, and their characteristics including age, gender, comorbidity severity of acute SARS-CoV-2 infection, and frequencies of various GI manifestation (nausea, vomiting, diarrhea, constipation, abdominal pain, loss of appetite, loss of taste, irritable bowel syndrome, dyspepsia). We also extracted the data on mean follow-up time, follow-up mode, term used to refer to long-term effects, total patients with resolution of symptoms, and average time to resolution of symptoms. We also extracted the data reporting the frequency of long COVID with respect to the underlying severity of COVID.

**Results**

**Study selection**

Of the 5804 records identified after database search, 2065 were duplicates. Of the 3739 titles which underwent initial screening, 3602 were removed for various reasons and eventually 137 articles underwent full-text screening. A total of 50 studies were included in the final analysis. Full PRISMA flowchart of study selection is depicted in Figure 1. Table 1 shows the details of the included studies with the study design, type of population, symptoms, duration, and the information provided. Supplemental Table 2 shows the excluded studies with reasons of exclusion.

**Frequency of GI long COVID**

The overall frequency of GI symptoms was reported in 14 studies involving 296,487 patients. The frequency of overall GI symptoms in patients with COVID-19 was 0.12 [95% confidence interval (CI), 0.06–0.22, \( I^2 = 99\% \)] (Figure 2). The frequency of GI symptoms in patients with long COVID was 0.22 (95% CI, 0.10–0.41, \( I^2 = 97\% \)) (Figure 2).

The frequency of GI long-COVID symptoms in patients with severe COVID-19 was 0.13 (95% CI, 0.04–0.34, \( F=99\% \)) (five studies, 19,067 patients) (Supplemental Figure 1). The frequency was 0.14 (95% CI, 0.05–0.34, \( F=98\% \)) in studies reporting mixed disease severity (severe as well as non-severe disease) (Supplemental Figure 1). Similarly, the frequency of GI manifestations in
patients having long COVID after severe COVID infection was 0.20 (95% CI, 0.12–0.32, $I^2 = 71\%$) (Supplemental Figure 2). The frequency of long GI COVID in patients having long COVID after mixed severe disease was 0.21 (95% CI, 0.05–0.56, $F = 97\%$) (Supplemental Figure 2).

We also assessed the frequency of GI manifestations as per the different definitions of long COVID. The frequency of GI manifestations in patients with COVID-19 as per WHO definition was 0.18 (95% CI, 0.08–0.36, $F = 99\%$) (Supplemental Figure 3). The frequency of GI manifestations in patients with long COVID as per WHO definition was 0.28 (95% CI, 0.15–0.46, $F = 97\%$) (Supplemental Figure 3). The frequency of GI manifestations in patients with COVID-19 as per NICE/CDC definition was 0.14 (95% CI, 0.06–0.28, $F = 99\%$) (Supplemental Figure 4). The frequency of GI manifestations in patients with long COVID as per NICE/CDC definition was 0.26 (95% CI, 0.11–0.50, $F = 96\%$) (Supplemental Figure 4).

**Clinical manifestations of long COVID**

The frequency of abdominal pain as a part of long GI COVID was 0.07 (95% CI, 0.04–0.12, $F = 98\%$) in patients with COVID-19 infection while it was 0.14 (95% CI, 0.04–0.38, $F = 96\%$) in patients having long COVID (Figure 3). The frequency of nausea/
vomiting as a part of long GI COVID was 0.06 (95% CI, 0.03–0.11, $I^2 = 98\%$) in patients with COVID-19 infection while it was 0.06 (95% CI, 0.01–0.21, $I^2 = 96\%$) in patients having long COV ID 13,18,19,23,30,38,40,43,50,53,60,61 (Figure 3). The frequency of loss of appetite as a part of long GI COVID was 0.09 (95% CI, 0.03–0.23, $I^2 = 99\%$) in patients with COVID-19 infection while it was 0.20 (95% CI, 0.08–0.43, $I^2 = 98\%$) in patients having long COVID 15,16,22,29,33,36,37,39,40,54,57,61,62 (Figure 3). The frequency of constipation as a part of long GI COVID was 0.09 (95% CI, 0.03–0.23, $I^2 = 99\%$) in patients with COVID-19 infection while it was 0.20 (95% CI, 0.08–0.43, $I^2 = 98\%$) in patients having long COVID 15,16,22,29,33,36,37,39,40,54,57,61,62 (Figure 3). The frequency of loss of taste as a part of long GI COVID was 0.10 (95% CI, 0.05–0.19, $I^2 = 97\%$) in patients with COVID-19 infection while it was 0.17 (95% CI, 0.10–0.27, $I^2 = 95\%$) in patients having long COVID 37–40,44,47,50,54,56,57,61,62 (Figure 3). The frequency of diarrhea as a part of long GI COVID was 0.05 (95% CI, 0.03–0.10, $I^2 = 99\%$) in patients with COVID-19 infection while it was 0.10 (95% CI, 0.04–0.23, $I^2 = 98\%$) in patients having long COVID 13–19,24,25,28,34–38,40,41,43,44,46,50,53,56,57,60,61,62 (Figure 3).

The frequency of constipation as a part of long GI COVID was 0.19 (95% CI, 0.05–0.55, $I^2 = 98\%$) in patients with COVID-19 infection (Figure 4). There was only one study reporting frequency of constipation in patients with long COVID.18,25,43,52 The frequency of dyspepsia as a GI manifestation of long COVID-19 was reported by three studies (910 patients of COVID-19).29,31,59 The frequency of dyspepsia after long COVID was 0.20 (95% CI, 0.06–0.50, $I^2 = 97\%$)29,52 (Figure 4). Only two studies reported frequency of dyspepsia in long COVID. Four studies (756 patients) reported the frequency of irritable bowel syndrome (IBS) after COVID-19 infection.18,25,46,59 The pooled rate of IBS after COVID-19 was 0.17 (95% CI, 0.06–0.37, $I^2 = 96\%$) (Figure 4). Only one study reported the frequency of IBS among patients with long COVID.18 Only a few studies reported GI symptoms at multiple time points during the follow-up (Supplemental Table 3).

A single study reported about 12 patients (11 males) showing cholangiopathic changes as delayed manifestation in patients who had recovered from severe COVID.26 This was characterized by both biochemical abnormality (elevated alkaline phosphatase) and radiological abnormality (changes in Magnetic resonance cholangiopancreatography). Another report suggested the presence of gastroparesis in 12 patients as confirmed by a positive gastric-emptying study done for suggestive symptoms.21

**Heterogeneity**

Since there was significant heterogeneity in overall estimates of GI manifestations in long COVID. We performed multiple subgroup analysis. Based on the duration of follow-up (<3 months, >3 months), there were no significant differences in frequency of GI symptoms between these two groups. The frequency of GI symptoms in studies reporting a follow-up of less than 3 months was 0.11 (95% CI, 0.02–0.38, $I^2 = 98\%$) while for studies with more than 3 months of follow-up it was 0.12 (95% CI, 0.06–0.22, $I^2 = 100\%$)13,14,27,28,39,40,42,45,48,49,51,55,59,60 (Supplemental Figure 5). Subgroup analysis on the basis of mode of follow-up suggested a slightly higher frequency of symptoms with telephonic follow-up [0.14 (95% CI, 0.06–0.31, $I^2 = 98\%$)] as compared to in person follow-up [0.04 (95% CI, 0.01–0.19, $I^2 = 98\%$)]13,14,27,28,39,40,42,45,48,49,51,55,59,60 (Supplemental Figure 6). The frequency of GI symptoms in America was 0.12 (95% CI, 0.03–0.36, $I^2 = 99\%$), in Europe was 0.07 (95% CI, 0.03–0.17, $I^2 = 97\%$) whereas only two studies reported frequencies from Asia and one from Africa (Supplemental Figure 7).13,14,27,28,39,40,42,45,48,49,51,55,59,60 On the basis of study type, the frequency of GI symptoms was 0.08 (95% CI, 0.02–0.26, $I^2 = 100\%$) for retrospective studies while it was 0.12 (95% CI, 0.06–0.24, $I^2 = 97\%$) for prospective studies 13,14,27,28,39,40,42,45,48,49,51,55,59,60 (Supplemental Figure 8).

**Risk of bias analysis**

Few studies had concern regarding description of the selected sample with lack of clear details. Most of the studies had included appropriate statistical analysis and appropriate methods of assessment of GI symptoms as well as long COVID (Supplemental Table 4). Few studies did not clearly report the demographic information at the presenting site. On the contrary, almost all studies reported an appropriate sample frame to address the target population. As the Joanna Briggs Institute guidance suggests against using a score cutoff for quality assessment, we also did not score the studies. The visual impression of the funnel plots (Supplemental Figures 9 and 10) and the Egger test did not suggest any publication bias. The $t$ statistic for the overall COVID analysis and long-COVID analysis was $-0.78$ ($p = 0.45210$ and $-1.05$ ($p = 0.3230$).
| Authors                  | Year | Type               | Country         | Included patients | Total number of patients | Total number of patients with GI symptoms | Individual GI symptoms |
|--------------------------|------|--------------------|-----------------|-------------------|--------------------------|------------------------------------------|------------------------|
| Adame et al.             | 2021 | Abstract           | USA             | All               | Total: 101/long COVID 25 | 21                                       | 21 21 21 – – – – – – – |
| Akinci Ozyurek et al.    | 2021 | Retrospective      | Turkey          | All               | Total 315/long COVID 229 | 1                                        | 1 – – – – – – – – – – – |
| Anaya et al.             | 2021 | Cross-sectional    | Colombia        | All               | Total 100/long COVID 65  | –                                        | 46 24 – – – – – – – – – |
| Areekal et al.           | 2021 | Cross-sectional    | India           | Hospitalized      | Total 335/long COVID 221 | –                                        | 6 – – – – – – – – – – – |
| Augustin et al.          | 2021 | Prospective        | Germany         | Non-hospitalized  | Total 353/long COVID 123 | –                                        | 4 – – – – – – – – – – – |
| Blackett et al.          | 2021 | Retrospective      | USA             | Hospitalized      | Total 147/long –         | –                                        | 6 11 6 10 – – – – – – – |
| Blair et al.             | 2021 | Retrospective      | USA             | All               | Total 166/long COVID 118 | –                                        | 4 2 3 – – – – – – – – – |
| Buttery et al.           | 2021 | Cross-sectional    | UK              | All               | Total 1865/long COVID –  | –                                        | – – – – – – – – – – – |
| Calogero et al.          | 2021 | Abstract           | USA             | All               | Total 12,224/long COVID –| –                                        | – – – – – – – – – – – |
| Carrillo-Garcia et al.   | 2021 | Retrospective      | Spain           | Hospitalized      | Total 165/long COVID 109 | –                                        | – – – – – – – – – – – |
| Chevinsky et al.         | 2021 | Retrospective      | USA             | Non-hospitalized  | Total 74,446/long COVID 44,489 | –                                      | – 667 401 – – – – – – – |
| Chopra et al.            | 2021 | Retrospective      | India           | Non-hospitalized  | Total 57/long COVID 25   | –                                        | – 1 – – – – – – – – – |
| Dennis et al.            | 2021 | Prospective        | UK              | All               | Total 201/long COVID –   | –                                        | 118 – – 108 – – – – – |
| Faruqui et al.           | 2021 | Retrospective      | USA             | Hospitalized      | Total 205/long COVID –   | –                                        | – – – – – – – – – – – |
| Faycal et al.            | 2021 | Prospective        | France          | Non-hospitalized  | Total 429/long COVID 175 | 12/175                                  | – – – – – – – – – – – |
| Fernández-de-Las-Peñas et al. | 2021 | Prospective        | Spain           | Hospitalized      | Total 1969/long COVID 1232 | 133                                     | 49 – – – – – – – – – – – |
| Galal et al.             | 2021 | Cross-sectional    | Egypt           | Hospitalized      | Total 430/long COVID 370 | –                                        | – – – – – – – – – – – |
| Galván-Tejada et al.     | 2020 | Retrospective      | Mexico          | All               | Total 141/long COVID –   | –                                        | – – – 22 – – – – – – – |
| Ghoshal et al.           | 2021 | Prospective        | Bangladesh and India | Hospitalized      | Total 280/long COVID –   | –                                        | – – – – – – – – – – – |
| Gold et al.              | 2021 | Prospective        | Greece          | All               | Total 185/Long 56        | –                                        | – 7 – – – – – – – – – |
| Authors Year Type Country Included patients | Total number of patients | Total number of patients with GI symptoms | Individual GI symptoms | Age and sex | Follow-up time | Mode of follow-up | Term used |
|--------------------------------------------|--------------------------|------------------------------------------|------------------------|-------------|----------------|-----------------|-----------|
| Adame et al. 13 2021 Abstract USA All Total: 101/long COVID 25 | 21 21 21 21 – – – – – –/F 20 | 60 days | In person | Long hauler |
| Akinci Ozyurek et al. 14 2021 Retrospective Turkey All Total 315/long COVID 229 | 1 – – – – – – – – – – –/F 158 | 4 weeks | Telephone | Post-COVID syndrome |
| Anaya et al. 15 2021 Cross-sectional Colombia All Total 100/long COVID 65 | – 46 24 – – – – – – Median 49 years/F 53 | Median 219 days | Survey | Post-COVID manifestation |
| Areekal et al. 16 2021 Cross-sectional India Hospitalized Total 335/long COVID 221 | – 6 – – – – – – – – – – –/F 161 | 4 weeks | Telephone | Post-COVID syndrome |
| Augustin et al. 17 2021 Prospective Germany Non-hospitalized Total 353/long COVID 123 | – 4 – – – – – – – – – – –/– 7 months | In person | -COVID syndrome |
| Blackett et al. 18 2021 Retrospective USA Hospitalized Total 147/long – | – 6 11 6 10 – – – – – –/72 | Median 106 days | In person | Post-COVID syndrome |
| Blair et al. 19 2021 Retrospective USA All Total 166/long COVID 118 | – 4 2 3 – – – – – – –/– | 4 weeks | Telephone | Chronic COVID 19 syndrome |
| Buttery et al. 20 2021 Cross-sectional UK All Total 1865/long COVID – | – – – – – – – – – – –/1440 | 12 weeks | Web based | Long COVID |
| Calogero et al. 21 2021 Abstract USA All Total 12,224/long COVID – | – – – – – – – – – – –/– | Chart review | Symptoms after COVID-19 |
| Carrillo-Garcia et al. 22 2021 Retrospective Spain Hospitalized Total 165/long COVID 109 | – – – – – – – – – – –/– | 3 months | Telephone | Sequelae of COVID |
| Chevinsky et al. 23 2021 Retrospective USA Non-hospitalized Total 74,446/long COVID 44,489 | – – 667 401 – – – – – – – 31–120 days | Review | Post-COVID syndrome |
| Chopra et al. 24 2021 Retrospective India Non-hospitalized Total 57/long COVID 25 | – 1 – – – – – – – – – – –/– | 30 days | Telephone | Long COVID |
| Dennis et al. 25 2021 Prospective UK All Total 201/long COVID – | – 118 – – 108 – – – – – – Mean 44/142 | 4 weeks | In person | Post-COVID syndrome |
| Faruqui et al. 26 2021 Retrospective USA Hospitalized Total 2047/long COVID – | – – – – – – – – – – –/– | Mean 58 years/– 118 days | Chart review | Late complication |
| Faycal et al. 27 2021 Prospective France Non-hospitalized Total 429/long COVID 175 | 12/175 – – – – – – – – – – –/311 | Median 41.6 years/F 311 | 30 days | Telephone | Persistent symptoms |
| Fernández-de-Las-Peñas et al. 28 2021 Prospective Spain Hospitalized Total 1969/long COVID 1232 | 133 49 – – – – – – – – – – Mean 61 years/F 915 | Mean 8.4 months/F 915 | Telephone | Post-COVID syndrome |
| Galal et al. 29 2021 Cross-sectional Egypt Hospitalized Total 430/long COVID 370 | – – 157 – – – – – – – – Mean 37.4 years/F 176 days | In person | Post-COVID symptoms |
| Galván-Tejada et al. 30 2020 Retrospective Mexico All Total 141/long COVID – | – – 22 – – – – – – – – Mean 36 days | Telephone | Persistent symptoms |
| Ghoshal et al. 31 2021 Prospective Bangladesh and India Hospitalized Total 280/long COVID – | 15 – – – – – – – – – 16 –/– | Mean 34.9 years/F 1 month | In person | Postinfectious symptoms |
| Gold et al. 32 2021 Prospective Greece All Total 185/Long 56 | – – 7 – – – – – – – –/– | Mean 37.4 years/F 274 | In person | Post-COVID symptoms |

(Continued)
| Authors               | Year  | Type             | Country    | Included patients | Total number of patients | Total number of patients with GI symptoms | Individual GI symptoms |
|----------------------|-------|------------------|------------|-------------------|--------------------------|--------------------------------------------|------------------------|
| Hossain et al.      | 2021  | Prospective      | Bangladesh | All               | Total 2198/long COVID 356 | –                                          | –                      |
| Islam et al.        | 2021  | Cross-sectional  | Bangladesh | All               | Total 1002/long COVID 200 | –                                          | 127                    |
| Nayagam et al.      | 2021  | Retrospective    | UK         | Hospitalized      | Total 564/long COVID –    | –                                          | –                      |
| Jones et al.        | 2021  | Retrospective    | UK         | All               | Total 3151/long COVID 310 | –                                          | 196                    |
| Kararsslan et al.   | 2021  | Prospective      | Turkey     | Hospitalized      | Total 300/long COVID 216  | –                                          | 4                      |
| Klein et al.        | 2021  | Prospective      | Israel     | Mild              | Total 103/long COVID 47   | –                                          | 1                      |
| Kozak et al.        | 2021  | Retrospective    | Canada     | All               | Total 223/long COVID 62   | 19                                         | –                      |
| Leth et al.         | 2021  | Prospective      | Denmark    | Hospitalized      | Total 49/long COVID 47    | 15                                         | 4                      |
| Liang et al.        | 2020  | Prospective      | China      | Hospitalized      | Total 76/long COVID –     | –                                          | 20                     |
| Lombardo et al.     | 2021  | Prospective      | Italy      | All               | Total 303/long COVID 244  | 35                                         | –                      |
| Marasco et al.      | 2021  | Prospective      | Multi-center| Hospitalized      | Total 489/long COVID –    | –                                          | 37                     |
| Messin et al.       | 2021  | Retrospective    | France     | All               | Total 74/long COVID 53    | –                                          | 3                      |
| Mohamed-Hussein et al. | 2021 | Cross-sectional  | Egypt      | All               | Total 262/long COVID 157  | 123                                        | –                      |
| Noviello et al.     | 2021  | Prospective      | Italy      | All               | Total 164/long COVID –    | –                                          | 29                     |
| Rank et al.         | 2021  | Prospective      | Germany    | Mild              | Total 83/long COVID 51    | –                                          | –                      |
| Rizvi et al.        | 2021  | Retrospective    | USA        | Hospitalized      | Total 17,462/long COVID – | 404                                        | 214                    |
| Saigal et al.       | 2021  | Prospective      | UK         | Hospitalized      | Total 643/long COVID –    | 54                                         | –                      |
| Scherlinger et al.  | 2021  | Prospective      | France     | All               | Total 755/long COVID 30   | 9                                          | –                      |
| Shang et al.        | 2021  | Prospective      | China      | Severe            | Total 796/long COVID 441  | 87                                         | –                      |
| Shoosangtrewijit et al. | 2021 | Prospective      | Thailand   | Hospitalized      | Total 87/long COVID 87    | 11                                         | –                      |
| Authors | Year | Type | Country | Included | Total number of patients | Total number of patients with GI symptoms | Age and sex | Follow-up time | Mode of follow-up | Term used |
|---------|------|------|---------|----------|--------------------------|------------------------------------------|------------|---------------|-----------------|------------|
| Hossain et al. | 2021 | Prospective | Bangladesh | All | Total | 2198/long COVID | 356 | Mean 38.7 years/F | 607 | 12 weeks | Long COVID |
| Islam et al. | 2021 | Cross-sectional | Bangladesh | All | Total | 1002/long COVID | 200 | Mean 34.7 years/F | 401 | 30 days | Survey | Long COVID |
| Nayagam et al. | 2021 | Retrospective | UK | Hospitalized | Total | 564/long COVID | – | Mean 67.7 years/F | 258 | 60 days | In person | Persistent symptoms |
| Jones et al. | 2021 | Retrospective | UK | All | Total | 3151/long COVID | 310 | Mean 52.1 year/F | 224 | 4 weeks | Online survey | Long COVID |
| Karaarslan et al. | 2021 | Prospective | Turkey | Hospitalized | Total | 300/long COVID | 216 | Mean 53 year/F | 121 | – | Long COVID |
| Klein et al. | 2021 | Prospective | Israel | Mild | Total | 103/long COVID | 47 | Mean 35 years/F | 39 | – | Telephone | Long-lasting effect |
| Kozak et al. | 2021 | Retrospective | Canada | All | Total | 223/long COVID | 62 | Mean 67.7 years/F | 38 | 90 days | In person | Persistent symptoms |
| Leth et al. | 2021 | Prospective | Denmark | Hospitalized | Total | 49/long COVID | 47 | Mean 58 years/F | 28 | 1 month | Telephone | Persistent symptoms |
| Liang et al. | 2020 | Prospective | China | Hospitalized | Total | 76/long COVID | – | Mean 41.3 years/F | 55 | 6 months | Questionnaires | Persistent symptoms |
| Lombardo et al. | 2021 | Prospective | Italy | All | Total | 303/long COVID | 244 | Median 53 years/F | 165 | Median 12.2 months | Phone | Long-term complication |
| Marasco et al. | 2021 | Prospective | Multi-center | Hospitalized | Total | 489/long COVID | – | Median 58 years/F | 67 | Median 30 days | Questionnaires | Persistent symptoms |
| Messin et al. | 2021 | Retrospective | France | All | Total | 74/long COVID | 53 | Mean 54.7 years/F | 30 | 6 months | Telephone | Persistent symptoms |
| Mohamed-Hussein et al. | 2021 | Cross-sectional | Egypt | All | Total | 262/long COVID | 157 | Mean 33 years/F | 62 | Mean 123 weeks | Questionnaires | Persistent symptoms |
| Noviello et al. | 2021 | Prospective | Italy | All | Total | 164/long COVID | – | Mean 44.1 years/F | 66 | Median 4.8 months | Web based | Persistent symptoms |
| Rank et al. | 2021 | Prospective | Germany | Mild | Total | 83/long COVID | 51 | Mean 50.6 years/F | 18 | 6 months | Questionnaires | Persistent symptoms |
| Rizvi et al. | 2021 | Retrospective | USA | Hospitalized | Total | 17,462/long COVID | 404 | Mean 66 years/F | 336 | – | Questionnaires | GI sequelae |
| Saigal et al. | 2021 | Prospective | UK | Hospitalized | Total | 643/long COVID | – | Mean 62.3 years/F | 245 | Median 65 days | Virtual | Long COVID |
| Scherlinger et al. | 2021 | Prospective | France | All | Total | –/long COVID | 30 | Median 40 years/F | 18 | Median 152 days | Phone | Persistent symptoms |
| Shang et al. | 2021 | Prospective | China | Severe | Total | 796/long COVID | 441 | Median 6 months | 184 | – | Postinfectious FGID | Sequelae of COVID |
| Shoosanglertwijit et al. | 2021 | Prospective | Thailand | Hospitalized | Total | –/long COVID | 87 | Median 6 months | 2 | –/– | Telephone | Postinfectious FGID | (Continued)
Table 1 (Continued)

| Authors            | Year | Type       | Country | Included patients | Total number of patients | Total number of patients with GI symptoms | Individual GI symptoms |
|--------------------|------|------------|---------|-------------------|--------------------------|------------------------------------------|------------------------|
| Salmon-Ceron et al. | 2021 | Prospective | France  | All               | Total –/long COVID 70     | 17                                       | 12                     |
| Suárez-Robles et al. | 2020 | Prospective | France  | Hospitalized     | Total –/long COVID 134    | –                                       | –                      |
| Taquet et al.      | 2021 | Retrospective | UK      | All               | Total 273,618/long COVID 155,962 | 42,630                                  | –                      |
| Tiwari et al.       | 2021 | Cross-sectional | Nepal  | Non-critical     | Total 132/long COVID 66   | –                                       | 1                      |
| Tosato et al.       | 2021 | Cross-sectional | Italy   | Hospitalized     | Total 165/long COVID 137  | –                                       | 32                     |
| Vayner et al.       | 2021 | Abstract    | USA     | All               | Total 90/long COVID –     | –                                       | –                      |
| Vélez et al.        | 2021 | Retrospective | USA     | All               | Total 200/long COVID –    | 79                                      | –                      |
| Weng et al.         | 2021 | Prospective | China   | Hospitalized     | Total 117/long COVID –    | 52                                      | 17                     |
| Zhang et al.        | 2021 | Retrospective | China   | All               | Total 2433/long COVID 1095 | –                                       | 18                     |
| Zhou et al.         | 2021 | Prospective | China   | HCW               | Total 15/long COVID 12    | –                                       | 3                      |

F, females; GI, gastrointestinal; HCW, health-care workers; IBS, irritable bowel syndrome; LOA, loss of appetite; LOT, loss of taste.

Discussion

While the clinical manifestations of acute COVID-19 are in the form of a systemic disease with pulmonary and extrapulmonary manifestations, the long-COVID syndrome has largely been described to have systemic, neuropsychiatric, pulmonary, and cardiac manifestations.\(^{63}\) In fact, initially the manifestations of long COVID including brain fog were met with a denial but now the syndrome is well recognized thanks to advocacy by the patients.\(^{64-66}\) However, the understanding of the entire spectrum of manifestations of long COVID is evolving. Multiple reports have ascribed various GI manifestations to long COVID; however, a systematic assessment of the GI manifestations and frequency has not been previously reported. In this systematic review of 50 studies, we found that loss of taste, loss of appetite, abdominal pain, nausea and vomiting, and diarrhea were encountered in a subset of patients while constipation was one of the most common manifestations. Overall, GI symptoms as part of long COVID occurred in around 12% of patients with acute COVID-19. Further, a significant number of patients developed dyspepsia and irritable bowel syndrome as sequelae to COVID-19. These findings would suggest that GI symptoms are an important accompaniment of long COVID. Our analysis suggests that the GI manifestations of long COVID are not related to severity of underlying COVID-19 and could occur in those with mild initial disease.

The mechanisms behind the GI manifestations occurring as a part of post-COVID syndrome are
| Authors Year Type Country Included | Age and sex | Follow-up time | Mode of follow-up | Term used |
|-----------------------------------|-------------|----------------|-------------------|-----------|
| patients                          |             |                |                   |           |
| patients                          |             |                |                   |           |
| Total number of patients          |             |                |                   |           |
| Included                          |             |                |                   |           |
| patients                          |             |                |                   |           |
| Total number of patients          |             |                |                   |           |
| (with GI symptoms)                |             |                |                   |           |
| Individual GI symptoms            |             |                |                   |           |
| IBS                               |             |                |                   |           |
| LOA                               |             |                |                   |           |
| LOT                               |             |                |                   |           |
| Cholangiopathy                    |             |                |                   |           |
| Gastroparesis                     |             |                |                   |           |
| Dyspepsia                         |             |                |                   |           |
| Median 45 years/F 55              | 2 months    | In person      | Prolonged COVID symptoms |
| 58.53 years/F 72                  | 3 months    | Telephone      | Residual symptoms |
| 46.3 years/ F152157               | 6 months    | –              | Long COVID         |
| 36 years/F 28                     | 2 months    | Telephone or in person | Persistent symptoms |
| 73 years/F 53                     | 25–109 days | –              | Persistent symptoms |
| 49.5 years/–                      | 1 months    | Telephone      | Residual symptoms |
| 46 years/F 60                     | 6 months    | Telephone      | Post-COVID syndrome |
| –/–                              | 90 days     | Telephone      | Long-term sequelae |
| Median 60 years/ F 1228           | 1 year      | Telephone      | Postinfectious symptoms |
| Median 29 years/F 12              | 3 months    | In person      | Persistent symptoms |

not completely understood. The manifestations during acute COVID-19 are believed to be related to the increased expression of ACE-2 expression on the small bowel mucosa which may result in intestinal infection by the virus. Prolonged shedding of virions from the GI tract is recognized and could be responsible for some of the GI manifestations of long COVID.67 Interestingly, presence of coronavirus-like particles has been reported long back in patients with tropical sprue and the diarrhea was explained by enterocyte damage caused by the virus.68 It would be worthwhile to evaluate whether patients with diarrhea and IBS-like presentation after COVID-19 have enterocyte damage resulting from SARS-CoV-2 infection. Postinfectious IBS is a well-recognized condition and the occurrence of IBS after COVID-19 may also be similar to this variant of IBS.69

Gut microbiome profile might also have a role in long-term complications of COVID-19. The susceptibility of the microbiota to viral antigens as well as pro-inflammatory cytokines might have a crucial role in long GI manifestations. Patients with post-COVID-19 syndrome were found to have increased levels of *Ruminococcus gnavus* and *Bacteroides vulgatus* and decreased levels of *Faecalibacterium prausnitzii*.70 The same study also showed gut dysbiosis to have a role in neuropsychiatric as well as respiratory symptoms of post-acute COVID syndrome. However, it is unclear if the changes in gut microbiota play a role in causation of GI manifestations of long COVID. Also, the role of manipulation of gut microbiota profile in prevention or management of post-COVID GI manifestations is unclear.
The strengths of the study include we compiled all the data available on prevalence and symptomatology of GI long COVID for guiding clinicians in the pandemic. This would help define the contours of this new entity. We also compared the long-term outcomes after severe COVID-19 as compared to non-severe disease. There are certain limitations to the study. First, most of the included studies were retrospective. Second, the impact of various strains of SARS-CoV-2 on long COVID could not be analyzed as there were no strain-specific studies. Third, the symptoms were mainly subjective in patients with COVID-19 infection on follow-up. Further, a quantitative analysis could not be done for some symptoms (like constipation) because of the small number of reports. Also, most of the analyses demonstrated significant heterogeneity and although the subgroup analyses were performed, the heterogeneity was still significant.

**Conclusion**

In the present systematic review, GI symptoms as part of long COVID were seen in 12% of patients

Figure 3. Forest plots depicting the pooled frequencies of various GI symptoms (abdominal pain, diarrhea, nausea/vomiting, loss of appetite, loss of taste) in COVID 19 and long COVID, GI, gastrointestinal.

with acute COVID and 22% of long COVID. Loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain were the five most common GI symptoms of long COVID. The odds of having GI manifestations of long COVID among patients with severe versus non-severe disease were not statistically different. Future studies should look at the societal impact, prevention, and treatment of long COVID including the GI manifestations.
Figure 4. Forest plots depicting the pooled frequencies of various GI manifestations (constipation, dyspepsia, and irritable bowel syndrome) in COVID 19 and long COVID. GI, gastrointestinal.
Declarations

Ethics approval and consent to participate
Not applicable because this is a systematic review of already published literature and no patients were recruited for this work.

Consent for publication
Not applicable.

Author contribution[s]
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Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data used for the systematic review is from previously published works and is publicly available.

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Supplemental material
Supplemental material for this article is available online.

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