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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

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AC and RT are equal first authors

SK and VS are both senior authors

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', '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 week 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.[3,8] 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.

Data analysis

The data analysis was done using R version 4.1.1.[9] The packages 'meta' and 'metafor' were used apart from the base package.[10] For calculation of pooled rates, the estimates were logit transformed and combined using the 'inverse variance' approach. The pooled relative risk was estimated using the Mantel–Haenszel method.[11] We performed analyses for frequency of GI manifestations (including individual overall GI long-COVID manifestations and individual symptoms like diarrhea, pain abdomen, dyspepsia, nausea/vomiting, loss of taste, loss of appetite, constipation, and irritable bowel syndrome). Separate analysis was done for GI manifestations of long COVID in the entire subset of COVID-19 and in patients who had long COVID.

Risk of bias assessment

Two investigators made independent assessments of methodological rigor and risk of bias in the included studies. The Joanna Briggs Institute tool for prevalence studies was used to assess the studies that showed the prevalence of GI symptoms.[12] This includes assessment regarding the appropriateness of the included population, and the sampling, description of subjects, and whether the diagnosis of long COVID was assessed appropriately and similarly in all individuals. Publication bias was assessed for the GI manifestations of long COVID in patients with COVID-19 and those with long COVID by using funnel plot and Egger test.

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.[13–62] 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.[13,14,27,28,39,40,42,45,48,49,51,55,59,60] 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 long COVID was reported in 12 studies (158,731 patients).[13,14,27,28,39,40,42,45,51,52,53,55] 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, $I^2 = 99\%$) (five studies, 19,067 pat ients)[40,48,49,51,60] (Supplemental Figure 1). The frequency was 0.14 (95% CI, 0.05–0.34, $I^2 = 98\%$) in studies reporting mixed disease severity (severe as well as non-severe disease)[13,14,39,42,45,55,59] (Supplemental Figure 1). Similarly, the frequency of GI manifestations in

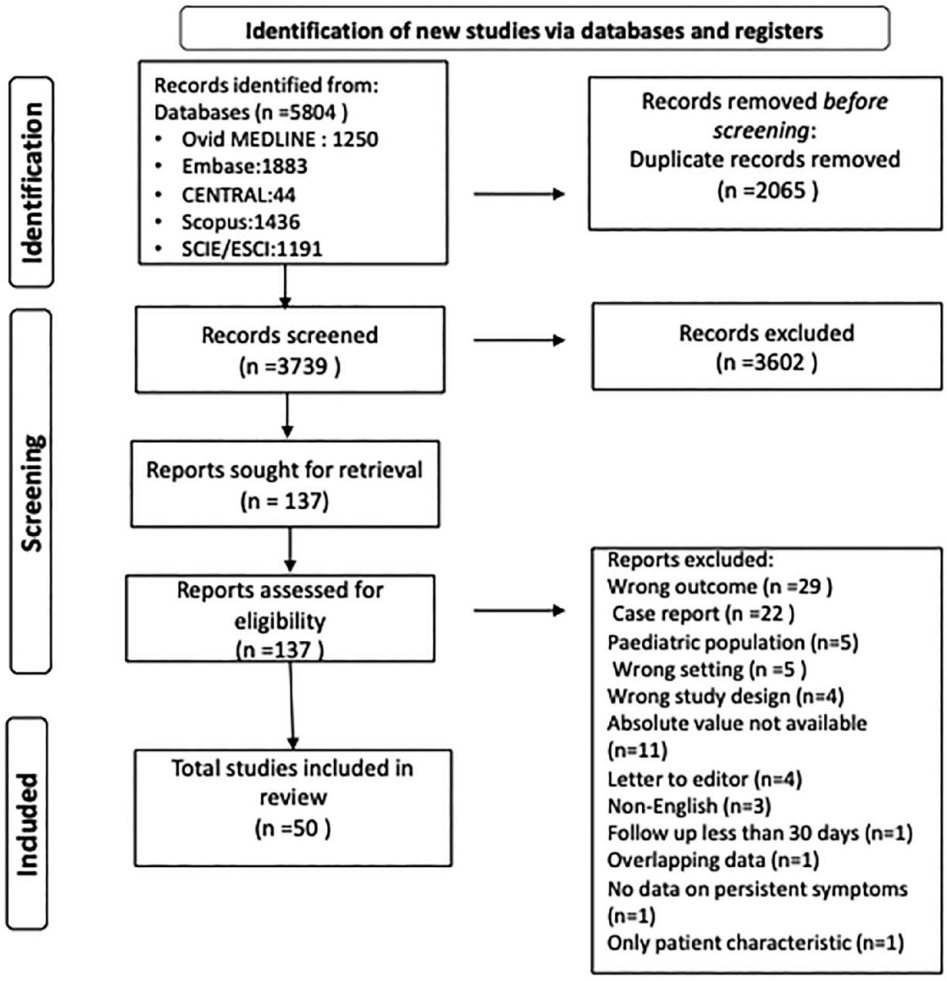

Figure 1. PRISMA flowchart depicting the process of screening and selection of studies.

patients having long COVID after severe COVID infection was 0.20 (95% CI, 0.12–0.32, $I^2 = 71\%$)[40,51,52] (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, $I^2 = 97\%$)[14,39,42,45,53,55] (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, $I^2 = 99\%$)[39,40,42,45,48,51,59,60] (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, $I^2 = 97\%$)[39,40,42,45,51,52,55] (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, $I^2 = 99\%$)[13,14,39,40,42,45,48,49,51,59,60] (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, $I^2 = 96\%$)[13,14,39,40,42,45,51,52,53,55] (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, $I^2 = 98\%$) in patients with COVID-19 infection while it was 0.14 (95% CI, 0.04–0.38, $I^2 = 96\%$) in patients having long COVID[13,15,18,19,23,32,36,38,40,43,52,53,60] (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 COVID[13,18,19,23,30,38,40,43,50,53,58,60,61] (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] 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[37–40,44,47,50,54,56,57,58,61] (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[13–19,24,25,28,34,36–38,40,41,43,44,46,50,53,56,57,60,61,62] (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.[18,31,46,59] 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 ($p = 0.3230$).

Table 1. Table showing the list of included studies with demographic details of included patients.

Authors	Year	Type	Country	Included patients	Total number of patients	Total number of patients with GI symptoms	Individual GI symptoms			
							Diarrhea	Pain	Nausea/ vomiting	Constipation
Adame *et al.*[13]	2021	Abstract	USA	All	Total: 101/ long COVID 25	21	21	21	21	–
Akinci Ozyurek *et al.*[14]	2021	Retrospective	Turkey	All	Total 315/long COVID 229	1	1	–	–	–
Anaya *et al.*[15]	2021	Cross-sectional	Colombia	All	Total 100/long COVID 65	–	46	24	–	–
Areekal *et al.*[16]	2021	Cross-sectional	India	Hospitalized	Total 335/long COVID 221	–	6	–	–	–
Augustin *et al.*[17]	2021	Prospective	Germany	Non-hospitalized	Total 353/long COVID 123	–	4	–	–	–
Blackett *et al.*[18]	2021	Retrospective	USA	Hospitalized	Total 147/ long –	–	6	11	6	10
Blair *et al.*[19]	2021	Retrospective	USA	All	Total 166/long COVID 118	–	4	2	3	–
Buttery *et al.*[20]	2021	Cross-sectional	UK	All	Total 1865/ long COVID –	–	–	–	–	–
Calogero *et al.*[21]	2021	Abstract	USA	All	Total 12,224/ long COVID –	–	–	–	–	–
Carrillo-Garcia *et al.*[22]	2021	Retrospective	Spain	Hospitalized	Total 165/long COVID 109	–	–	–	–	–
Chevinsky *et al.*[23]	2021	Retrospective	USA	Non-hospitalized	Total 74,446/ long COVID 44,489	–	–	667	401	–
Chopra *et al.*[24]	2021	Retrospective	India	Non-hospitalized	Total 57/long COVID 25	–	1	–	–	–
Dennis *et al.*[25]	2021	Prospective	UK	All	Total 201/long COVID –	–	118	–	–	108
Faruqui *et al.*[26]	2021	Retrospective	USA	Hospitalized	Total 2047/ long COVID –	–	–	–	–	–
Faycal *et al.*[27]	2021	Prospective	France	Non hospitalized	Total 429/long COVID 175	12/175	–	–	–	–
Fernández-de-Las-Peñas *et al.*[28]	2021	Prospective	Spain	Hospitalized	Total 1969/ long COVID 1232	133	49	–	–	–
Galal *et al.*[29]	2021	Cross-sectional	Egypt	Hospitalized	Total 430/long COVID 370	–	–	–	–	–
Galván-Tejada *et al.*[30]	2020	Retrospective	Mexico	All	Total 141/long COVID –	–	–	–	22	–
Ghoshal *et al.*[31]	2021	Prospective	Bangladesh and India	Hospitalized	Total 280/long COVID –	–	–	–	–	–
Gold *et al.*[32]	2021	Prospective	Greece	All	Total 185/ Long 56	–	–	7	–	–

IBS	LOA	LOT	Cholangiopathy	Gastroparesis	Dyspepsia	Age and sex	Follow-up time	Mode of follow-up	Term used
–	–	–	–	–	–	–/F 20	60 days	In person	Long hauler
–	–	–	–	–	–	–/F158	4 weeks	In person	Long COVID
–	23	–	–	–	–	Median 49 years/F 53	Median 219 days	Survey	Post-COVID manifestation
–	8	–	–	–	–	–/F 161	4 weeks	Telephone	Post-COVID syndrome
–	–	–	–	–	–	–/–	7 months	In person	-COVID syndrome
44	–	–	–	–	–	–/72	Median 106 days	Web based	Persistent syndrome
–	–	–	–	–	–	–/–	4 weeks	Telephone	Chronic COVID 19 syndrome
–	430	–	–	–	–	–/1440	12 weeks	Web based	Long COVID
–	–	–	–	12	–	–/–	161 days	Chart review	Symptoms after COVID-19
–	55	–	–	–	–	–/–	3 months	Telephone	Sequelae of COVID
–	–	–	–	–	–	–	31–120 days	Review	Post-COVID syndrome
–	–	–	–	–	–	Mean 34.9 years/–	30 days	Telephone	Long COVID
–	–	–	–	–	–	Mean 44/142	4 weeks	In person	Post-COVID syndrome
–	–	–	12	–	–	Mean 58 years/–	118 days	Chart review	Late complication
–	–	–	–	–	–	Median 41.6 years/F 311	30 days	Telephone	Persistent symptoms
–	–	–	–	–	–	Mean 61 years/F 915	8.4 months	Telephone	Post-COVID syndrome
–	157	–	–	–	119	Mean 37.4 years/F 274	Mean 176 days	In person	Post-COVID symptoms
–	–	–	–	–	–	–/–	Mean 36 days	In person	Persistent symptoms
15	–	–	–	–	16	–/–	1 month	In person/ Telephone	Postinfectious symptoms
–	–	–	–	–	–	–/–	1 month	Survey	Long COVID

(Continued)

Table 1. (Continued)

Authors	Year	Type	Country	Included patients	Total number of patients	Total number of patients with GI symptoms	Individual GI symptoms			
							Diarrhea	Pain	Nausea/ vomiting	Constipation
Hossain *et al.*[33]	2021	Prospective	Bangladesh	All	Total 2198/ long COVID 356	–	–	–	–	–
Islam *et al.*[34]	2021	Cross-sectional	Bangladesh	All	Total 1002/ long COVID 200	–	127	–	–	–
Nayagam *et al.*[35]	2021	Retrospective	UK	Hospitalized	Total 564/long COVID –	–	–	–	–	–
Jones *et al.*[36]	2021	Retrospective	UK	All	Total3151/ long COVID 310	–	196	196	–	–
Karaarslan *et al.*[37]	2021	Prospective	Turkey	Hospitalized	Total 300/long COVID 216	–	4	–	–	–
Klein *et al.*[38]	2021	Prospective	Israel	Mild	Total 103/long COVID 47	–	1	1	1	–
Kozak *et al.*[39]	2021	Retrospective	Canada	All	Total 223/long COVID 62	19	–	–	–	–
Leth *et al.*[40]	2021	Prospective	Denmark	Hospitalized	Total 49/long COVID 47	15	4	5	4	–
Liang *et al.*[41]	2020	Prospective	China	Hospitalized	Total 76/long COVID –	–	20	–	–	–
Lombardo *et al.*[42]	2021	Prospective	Italy	All	Total 303/long COVID 244	35	–	–	–	–
Marasco *et al.*[43]	2021	Prospective	Multi-center	Hospitalized	Total 489/long COVID –	–	37	47	41	67
Messin *et al.*[44]	2021	Retrospective	France	All	Total 74/long COVID 53	–	3	–	–	–
Mohamed-Hussein *et al.*[45]	2021	Cross-sectional	Egypt	All	Total 262/long COVID 157	123	–	–	–	–
Noviello *et al.*[46]	2021	Prospective	Italy	All	Total 164/long COVID –	–	29	–	–	–
Rank *et al.*[47]	2021	Prospective	Germany	Mild	Total 83/long COVID 51	–	–	–	–	–
Rizvi *et al.*[48]	2021	Retrospective	USA	Hospitalized	Total 17,462/ long COVID –	404	214	–	–	–
Saigal *et al.*[49]	2021	Prospective	UK	Hospitalized	Total 643/long COVID –	54	–	–	–	–
Scherlinger *et al.*[50]	2021	Prospective	France	All	Total –/long COVID 30	–	9	–	3	–
Shang *et al.*[51]	2021	Prospective	China	Severe	Total 796/long COVID 441	87	–	–	–	–
Shoosanglertwijit *et al.*[52]	2021	Prospective	Thailand	Hospitalized	Total –/long COVID 87	11	–	2	–	4

IBS	LOA	LOT	Cholangiopathy	Gastroparesis	Dyspepsia	Age and sex	Follow-up time	Mode of follow-up	Term used
–	12	–	–	–	–	Mean 38.7 years/F 607	12 weeks	–	Long COVID
–	–	–	–	–	–	Mean 34.7 years/F 401	30 days	Survey	Long COVID
–	–	–	24	–	–	Median 67.7 years/F 258	60 days	In person	Persistent symptoms
–	294	–	–	–	–	Mean 52.1 year/F 224	4 weeks	Online survey	Long COVID
–	31	45	–	–	–	Mean 53 year/F 121	1 month	Telephone	Persistent symptoms
–	–	8	–	–	–	Mean 35 years/F 39	6 months	Telephone	Long-lasting effect
–	3	10	–	–	–	49.1 years/F 38	>90 days	In person	Long COVID
–	2	15	–	–	–	Median 58 years/F 28	Median 128 days	Telephone and in person	Persistent symptoms
–	–	–	–	–	–	41.3 years/F 55	3 months	In person	Persistent symptoms
–	–	–	–	–	–	Median 53 years/F 165	Median 12.2 months	Phone	Long-term complication
–	–	–	–	–	–	50.6 years/F –	30 days	Questionnaires	Persistent symptoms
–	–	8	–	–	–	54.7 years/F30	6 months	Telephone	Persistent symptoms
–	–	–	–	–	–	–	12 weeks	Clinic or phone	Long COVID
43	–	–	–	–	–	Median 44.1 years/F 66	Median 4.8 months	Web based	Persistent symptoms
–	–	18	–	–	–	–	–/–	Questionaries	Long-term symptoms
–	–	–	–	–	–	Median 66 years/F 336	6 months	In person	GI sequelae
–	–	–	–	–	–	62.3 years/F 245	Median 63 days	Virtual	Long COVID
–	–	3	–	–	–	Median 40 years/F 18	Median 152 days	In person	Long COVID
–	–	–	–	–	–	–	6 months	Phone	Sequelae of COVID
–	–	–	–	–	2	–/–	6 months	–	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			
							Diarrhea	Pain	Nausea/ vomiting	Constipation
Salmon-Ceron *et al.*[53]	2021	Prospective	France	All	Total –/long COVID 70	17	12	3	6	–
Suárez-Robles *et al.*[54]	2020	Prospective	France	Hospitalized	Total –/long COVID 134	–	–	–	–	–
Taquet *et al.*[55]	2021	Retrospective	UK	All	Total 273,618/ long COVID 155,962	42,630	–	–	–	–
Tiwari *et al.*[56]	2021	Cross-sectional	Nepal	Non- critical	Total 132/long COVID 66	–	1	–	–	–
Tosato *et al.*[57]	2021	Cross-sectional	Italy	Hospitalized	Total 165/long COVID 137	–	32	–	–	–
Vayner *et al.*[58]	2021	Abstract	USA	All	Total 90/ long COVID -	–	–	–	2	–
Vélez *et al.*[59]	2021	Retrospective	USA	All	Total 200/long COVID –	79	–	–	–	–
Weng *et al.*[60]	2021	Prospective	China	Hospitalized	Total 117/long COVID -	52	17	8	21	–
Zhang *et al.*[61]	2021	Retrospective	China	All	Total 2433/ long COVID 1095	–	18	–	5	–
Zhou *et al.*[62]	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 a 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

IBS	LOA	LOT	Cholangiopathy	Gastroparesis	Dyspepsia	Age and sex	Follow-up time	Mode of follow-up	Term used
–	–	–	–	–	–	Median 45 years/F 55	2 months	In person	Prolonged COVID symptoms
–	36	29	–	–	–	58.53 years/F72	3 months	Telephone	Residual symptoms
–	–	–	–	–	–	46.3 years/ F152157	6 months	–	Long COVID
–	9	1	–	–	–	36 years/F 28	2 months	Telephone or in person	Persistent symptoms
–	63	53	–	–	–	73 years/F 53	25–109 days	–	Persistent symptoms
–	–	10	–	–	–	49.5 years/–	1 months	Telephone	Residual symptoms
21	–	–	–	–	77	46 years/F 60	6 months	Telephone	Post-COVID syndrome
–	28	–	–	–	–	–/–	90 days	Telephone	Long-term sequelae
–	20	35	–	–	–	Median 60 years/ F 1228	1 year	Telephone	Postinfectious symptoms
–	3	–	–	–	–	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.

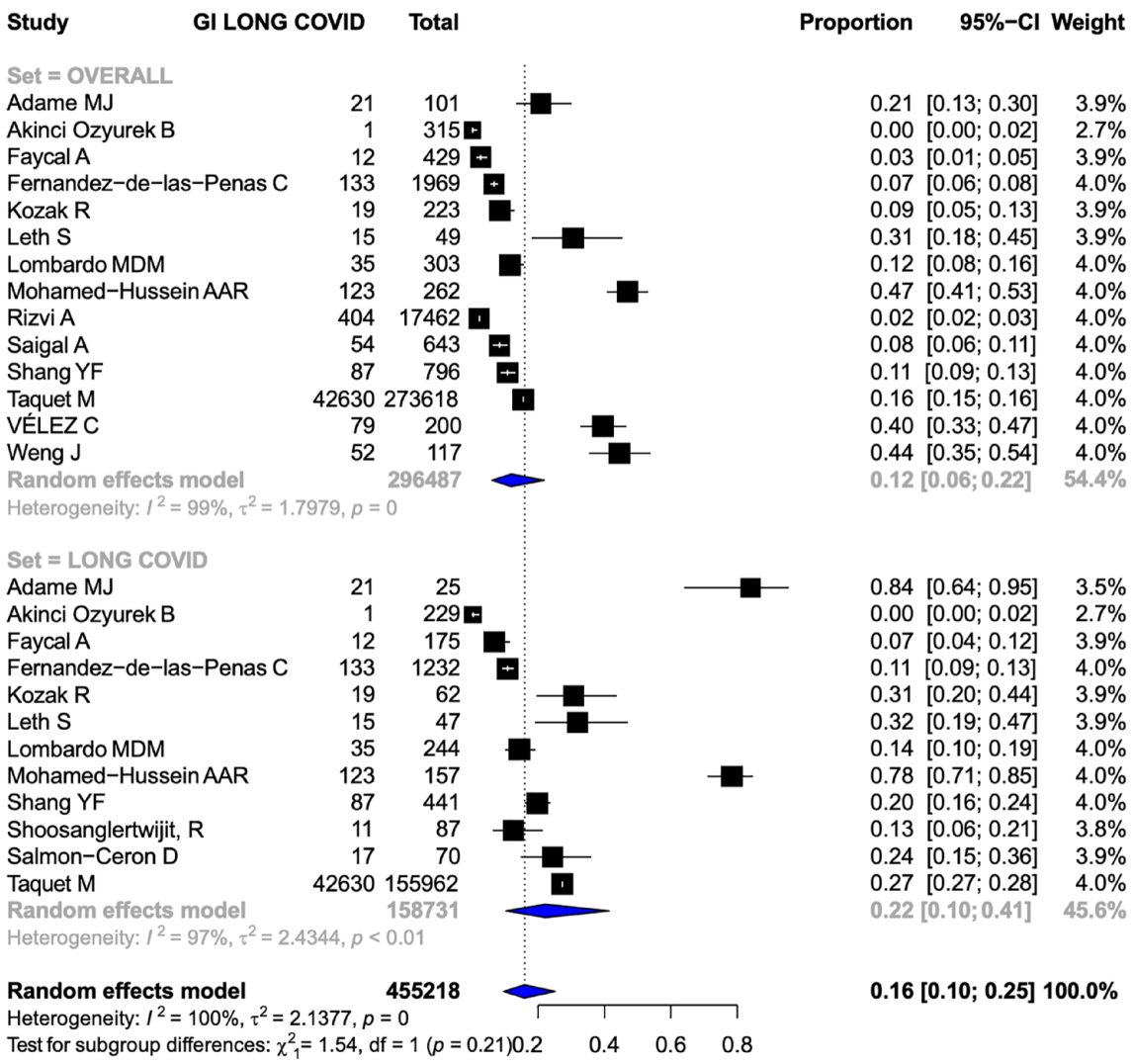

Figure 2. Forest plots showing the pooled frequency of GI manifestations of long COVID in patients with COVID-19 (Upper Forest plot) and patients with long COVID (Lower Forest Plot). GI, gastrointestinal.

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

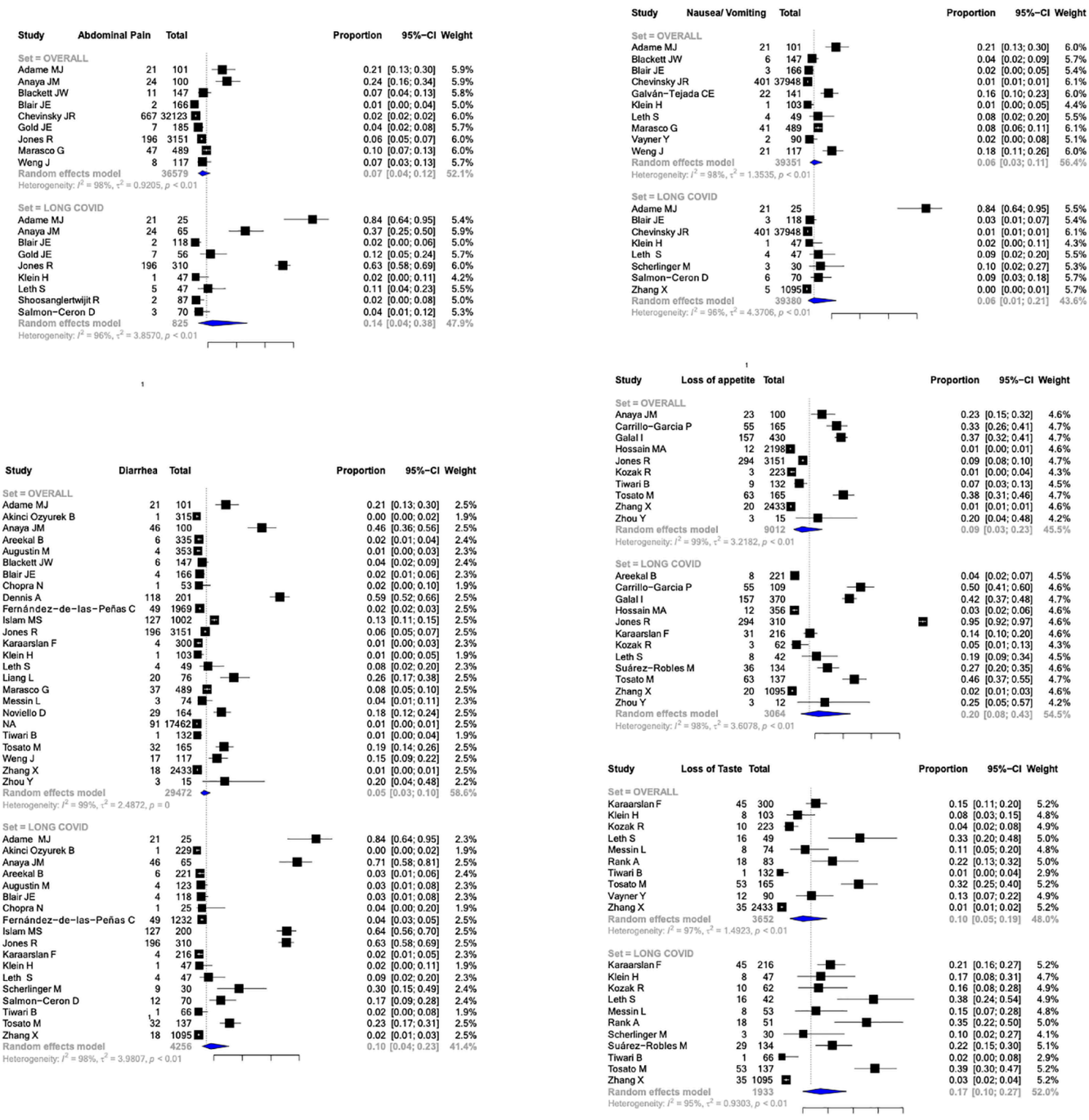

Figure 3. Forest plots depicting the pooled frequencies of various GI symptoms (abdomen pain, diarrhea, nausea/vomiting, loss of appetite, loss of taste) in COVID 19 and long COVID. GI, gastrointestinal.

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.

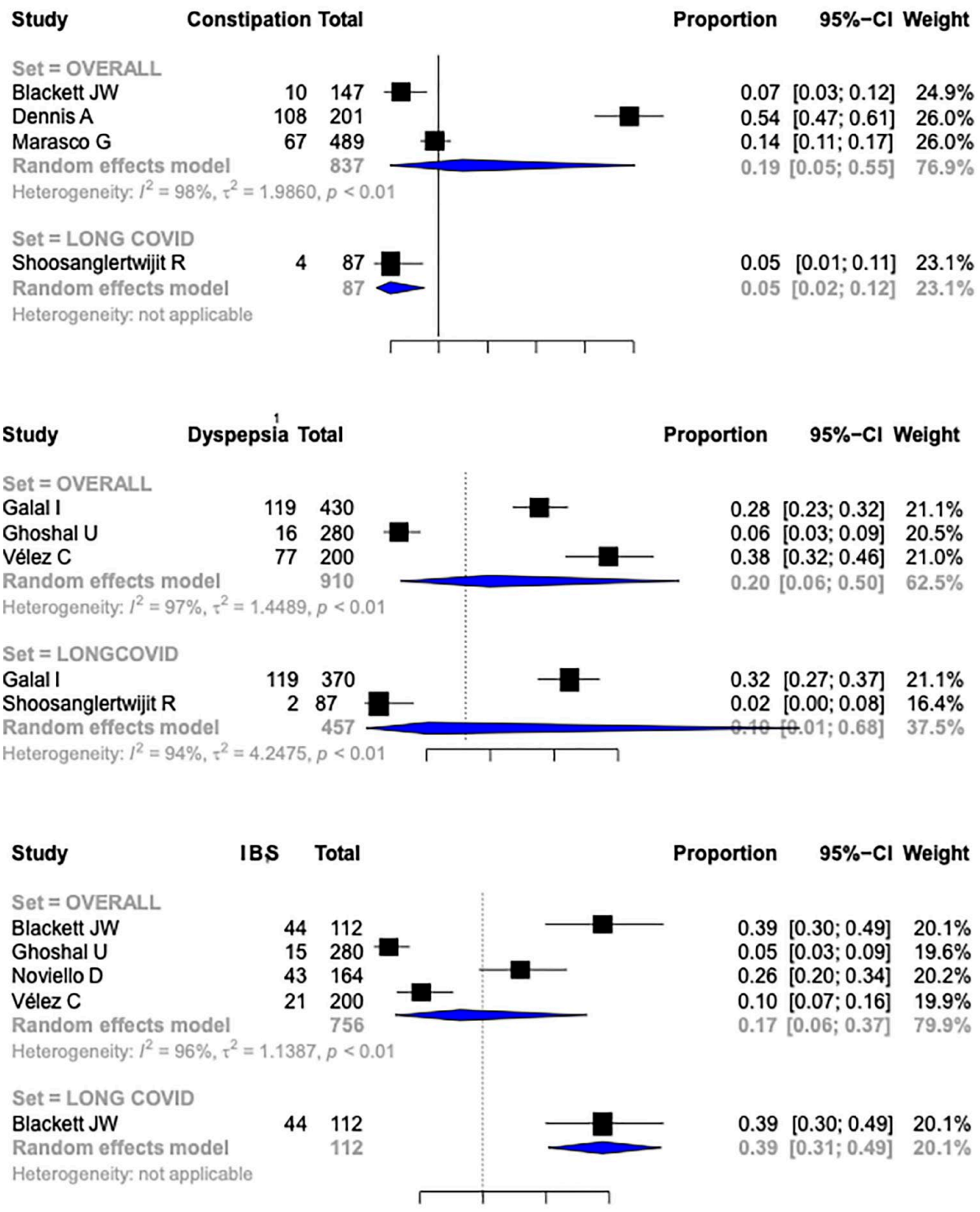

Figure 4. Forest plots depicting the pooled frequencies of various GI manifestations (constipation, dyspepsia, and irritable bowel syndrome) in COVID 19 and long COVID. GI, gastrointestinal.

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)

Arup Choudhury: Data curation; Validation; Writing – original draft.

Raseen Tariq: Data curation; Validation; Writing – original draft.

Anuraag Jena: Validation; Writing – review & editing.

Elissa Kinzelman Vesely: Data curation.

Siddharth Singh: Validation; Writing – review & editing.

Sahil Khanna: Conceptualization; Supervision; Validation; Writing – review & editing.

Vishal Sharma: Conceptualization; formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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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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