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Journal
European Journal of Clinical Investigation, 53(8)

ISSN
0014-2972

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Publication Date
2023-08-01

DOI
10.1111/eci.13989

Received: 11 January 2023 | Accepted: 21 March 2023

DOI: 10.1111/eci.13989

RESEARCH LETTER

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The definition of long COVID used in interventional studies

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Abstract

Introduction: There has been little consensus for a specific definition of long COVID, though several organizations have created varying ones. We sought to examine the definition of long COVID used in ongoing clinical trials.

Methods: We searched 'long COVID' and related terms on both PubMed and clinicaltrials.gov for randomized studies that either included patients with long COVID or had a persistent or long-term COVID-related outcome and abstracted long COVID definition components.

Results: Of the 92 studies, a laboratory-only confirmed diagnosis of COVID-19 was stipulated in 54.3% ($n=50$) studies. We found eight different time durations specified for how long symptoms needed to have occurred, ranging from 4 to 52 weeks, with 12 weeks being the most common (34.8%; $n=32$). 35.9% ($n=33$) did not specify a time duration. There were 57 different symptoms specified in total, with a median of one symptom identified per study (range 0–32). 8.7% of trials adhered to NICE or WHO definitions.

Conclusion: Standardized definitions of long COVID should be applied in studies assessing this condition to unify and harmonize research on this topic.

KEYWORDS

long COVID, COVID long-haulers, persistent COVID, randomized studies

1 | INTRODUCTION

Following the emergence of Sars-CoV-2, long COVID or post-acute sequelae of COVID-19 has gained increasing attention in both the media and scientific publications.[1] A PubMed search of all articles for 'long COVID' (as of 13 December 2022) shows 4089 articles in 2020, 8965 articles in 2021 and 9843 articles in 2022. There has been little consensus of the specific definition of long COVID, though the World Health Organization (WHO) and National Institute for Health and Care Excellence (NICE) have both created somewhat differing definitions.[2,3] Defining long COVID is limited by an ever growing list of possible symptoms, unknown temporality of symptoms, and allusivity in formal diagnosis.[4,5] The American College of Cardiology has provided a consensus definition of post-COVID-19 syndrome, which includes a new, returning, or persistence of symptoms, such as fatigue, shortness of breath, palpitations and chest pain, among others, beyond 4 weeks of SARS-CoV-2, lasting for at least 3 months, and not explained by any other illness.[6] An earlier scoping review evaluated long COVID definitions used in registered clinical trials, but information on definitions used was reported in general terms.[7] We sought to examine the definition of long COVID used in ongoing clinical trials. Because randomized clinical trials rely on a specific definition for outcomes and inclusion/exclusion criteria for interventional and control groups, we focused our analysis on randomized interventional trials.

2 | METHODS

We searched "long covid" OR "long hauler" OR "persistent covid" OR "post-acute sequelae SARS-CoV-2 infection" OR "post COVID syndrome" AND "randomized" on PubMed (through 31 August 2022). We also searched the condition 'long COVID' on clinicaltrials.gov, restricting to interventional studies (same dates). We included randomized interventional studies that either included patients with long or persistent COVID or had outcome related to persistent or long COVID.

We abstracted data on components of the definition of long COVID, such as symptoms, duration of symptoms, if symptoms needed to occur or worsen after acute COVID infection, if there could be any other explanation(s) for the symptom, number of symptoms needed to meet study definition of long COVID, how COVID was initially diagnosed (laboratory, clinical or self-diagnosed), and questionnaires used to define long COVID, including the World Health Organization and National Institute for Health and Care Excellence.

We grouped COVID diagnosis as laboratory (any type of laboratory testing), clinical (physician/investigatory assessed symptoms), laboratory and clinical, self-report, or any combination. If a COVID-specific questionnaire was used, we counted all symptoms listed in the questionnaire. We tabulated frequencies and percentages for long COVID definition components in R statistical software (version 4.2.0). We did not obtain institutional review board approval because we used publicly available, non-identifiable data.

3 | RESULTS

Our search resulted in 92 studies on PubMed and 137 on clinicaltrials.gov. Of those, 18 PubMed articles and 79 randomized studies on clinicaltrials.gov met our inclusion criteria. We removed 5 clinicaltrials.gov reports because they were duplicates of PubMed studies, leaving us with 92 studies.

A laboratory-only confirmed diagnosis of COVID-19 was stipulated in 54.3% ($n=50$) studies. There were eight different time durations specified for how long symptoms needed to have occurred, ranging from 4–52 weeks, with 12 weeks being the most common (34.8%; $n=32$). 35.9% ($n=33$) did not specify a time duration for how long symptoms needed to have occurred. 40.2% ($n=37$) did not provide any specifics on long-COVID symptoms; 20.7% ($n=19$) specified that symptoms needed to have occurred or worsened since COVID-19 infection, and 12.0% ($n=11$) stipulated that symptoms could not be explained by another reason (Figure 1, Table 1).

The minimum number of symptoms was not specified in 88.0% ($n=81$) of studies, and 28.3% ($n=26$) used a recognized symptom questionnaire or list to ascertain

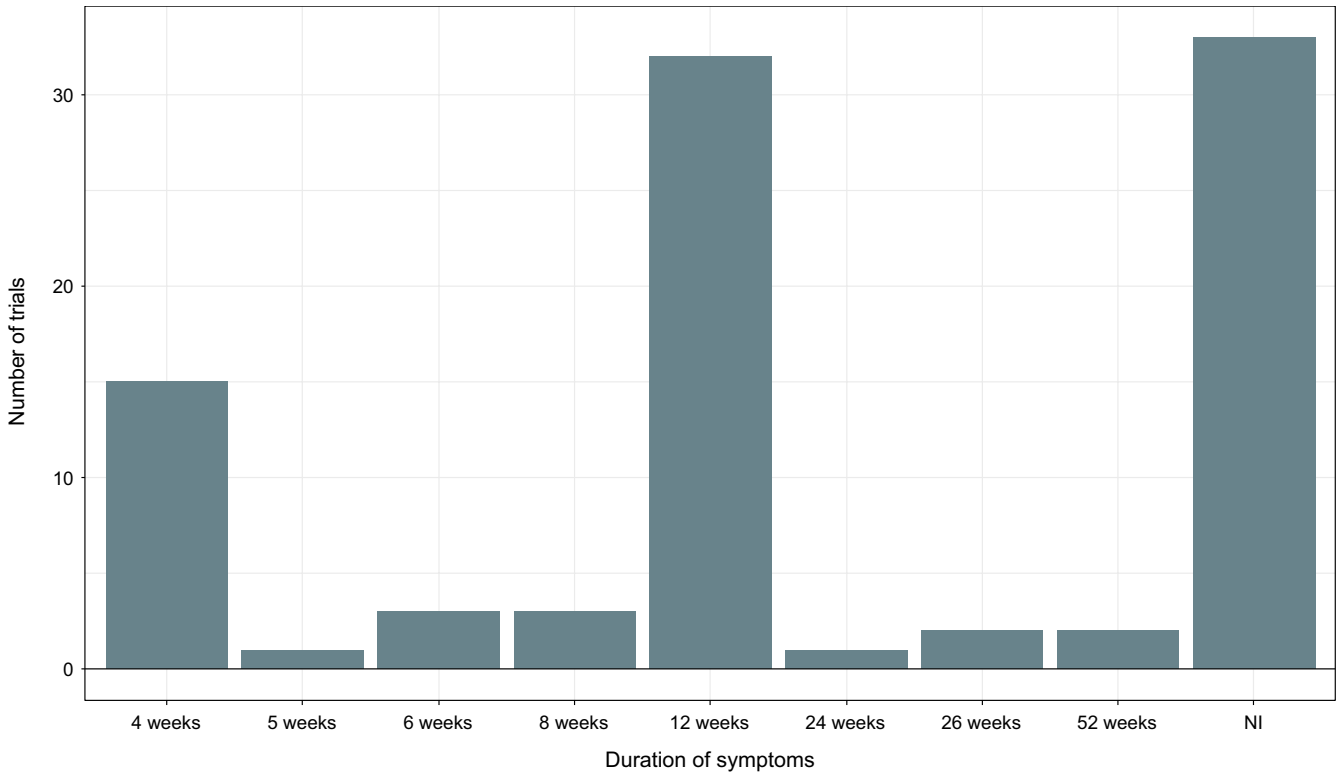

FIGURE 1 Duration of symptoms in long COVID definitions in interventional studies.

TABLE 1 Presence of long COVID definition components in interventional studies ($N = 92$ for all studies/trials; $N = 69$ for studies/trials with laboratory and/or clinical confirmed COVID-19 infection; and $N = 18$ for trials with publications).

	All trials/studies *N* (%)	Trials/studies with laboratory and/or clinical confirmed COVID-19 infection *N* (%)	Published studies *N* (%)
COVID-19 infection determination			
Laboratory only	50 (54.3)	50 (72.5)	9 (50.0)
Laboratory and/or clinical	19 (20.7)	19 (27.5)	4 (22.2)
Any, including self-diagnosis	5 (5.4)	0	1 (5.6)
Data not available	18 (19.6)	0	4 (22.2)
Time			
4 weeks	15 (16.3)	12 (17.4)	5 (27.8)
5 weeks	1 (1.1)	1 (1.4)	1 (5.6)
6 weeks	3 (3.3)	3 (4.3)	0
8 weeks	3 (3.3)	2 (2.9)	0
12 weeks	32 (34.8)	28 (40.6)	4 (22.2)
24 weeks	1 (1.1)	1 (1.4)	0
26 weeks	2 (2.2)	2 (2.9)	2 (11.1)
52 weeks	2 (2.2)	0	1 (5.6)
Data not available	33 (35.9)	20 (29.0)	5 (27.8)
General definition (no specifics of symptoms)	37 (40.2)	26 (37.7)	8 (44.4)
Symptoms only present or worsened after COVID	19 (20.7)	17 (24.6)	6 (33.3)
Symptoms could not be explained by another reason	11 (12.0)	9 (13.0)	3 (16.7)
Minimum number of symptoms to meet definition			
1	7 (7.6)	6 (8.7)	2 (11.1)
2	2 (2.2)	2 (2.9)	0
3	2 (2.2)	2 (2.9)	1 (5.6)
Undefined	81 (88.0)	59 (85.5)	15 (83.3)
Used a questionnaire	26 (28.3)	21 (30.4)	6 (33.3)
Most commonly used questionnaires			
Post-COVID-19 functional status (PCFS)	6 (6.5)	3 (4.3)	0
National Institute for Health and Care Excellence (NICE)	4 (4.3)	3 (4.3)	2 (11.1)
Modified Medical Research Council Dyspnoea Scale (mMRC)	4 (4.3)	4 (5.8)	2 (11.1)
World Health Organization (WHO)	4 (4.3)	4 (5.8)	0
Functional Status Scale (FSS)	4 (4.3)	3 (4.3)	0
Vaccination status reported or inferred	10 (10.9)	7 (10.1)	3 (16.7)
Symptoms[a]			
Fatigue	36 (39.1)	32 (46.4)	8 (44.4)
Shortness of breath	25 (27.2)	21 (30.4)	7 (38.9)
Cognitive impairment	22 (23.9)	19 (27.5)	5 (27.8)
Joint/muscular pain	22 (23.9)	19 (27.5)	5 (27.8)
Cough	20 (21.7)	19 (27.5)	4 (22.2)
Loss of smell/taste	20 (21.7)	17 (24.6)	7 (38.9)

(Continues)

TABLE 1 (Continued)

	All trials/studies *N* (%)	Trials/studies with laboratory and/or clinical confirmed COVID-19 infection *N* (%)	Published studies *N* (%)
Chest pain	17 (18.5)	16 (23.2)	3 (16.7)
Headache	16 (17.4)	15 (21.7)	4 (22.2)
Depression	16 (17.4)	14 (20.3)	5 (27.8)
Anxiety	16 (17.4)	14 (20.3)	5 (27.8)
Post-exertional malaise	15 (16.3)	13 (18.8)	0
Palpitations	15 (16.3)	13 (18.8)	3 (16.7)
Insomnia	15 (16.3)	13 (18.8)	3 (16.7)
Dizziness	15 (16.3)	14 (20.3)	3 (16.7)
Fever	14 (15.2)	12 (17.4)	4 (22.2)
Memory deficit	13 (14.1)	11 (15.9)	3 (16.7)
Paresthesia	12 (13.0)	10 (14.5)	3 (16.7)
Diarrhoea	11 (12.0)	9 (13.0)	4 (22.2)
Tinnitus	11 (12.0)	9 (13.0)	2 (11.1)
Vertigo	10 (10.9)	9 (13.0)	3 (16.7)
Vision changes	9 (9.8)	8 (11.6)	2 (11.1)
Respiratory discharge	9 (9.8)	7 (10.1)	3 (16.7)
Weakness	9 (9.8)	7 (10.1)	0
Nausea	8 (8.7)	7 (10.1)	2 (11.1)
Rash	8 (8.7)	6 (8.7)	3 (16.7)
Sore throat	8 (8.7)	7 (10.1)	2 (11.1)
Difficulty concentrating	7 (7.6)	5 (7.2)	2 (11.1)
Anorexia/loss of appetite	6 (6.5)	5 (7.2)	2 (11.1)
Abdominal pain	6 (6.5)	6 (8.7)	1 (5.6)
Post-traumatic stress disorder	6 (6.5)	4 (5.8)	3 (16.7)
Delirium	5 (5.4)	3 (4.3)	2 (11.1)
Balance/gait issues	5 (5.4)	3 (4.3)	2 (11.1)

[a]Symptoms that were listed 5 or fewer times in the total analytic sample: respiratory issues, menstrual issues, constipation, neuralgia, allergies, acid reflux, functional impairment, difficulty swallowing, attention difficulties and symptoms have gotten worse, incontinence, mobility issues, personal care issues, difficulty muti-tasking, changes/difficulty in speech, sweating, wheezing, confusion, blood pressure changes, oxygen desaturation, chills, irritability, vomiting, earache, abdominal distension and sleep disturbances.

symptoms. There were 57 different symptoms specified in total, with a median of 1 symptom identified per study (range 0–32). The most common symptoms were fatigue (39.1%; $n=36$), shortness of breath (27.2%; $n=25$), cognitive impairment (23.9%; $n=22$), joint/muscular pain (23.9% $n=22$) and cough (21.7%; $n=20$). 8.7% of trials adhered to NICE or WHO definitions.

4 | DISCUSSION

We found the definition of long COVID used in scientific studies has tremendous heterogeneity, with little consensus on the symptoms included, the number of symptoms, or their duration. Objective documentation of COVID-19 infection was lacking in approximately half of studies, and most studies did not stipulate that symptoms had to be new or exacerbated after a COVID-19 infection, or that symptoms should not be attributed to a condition other than COVID. Some of this heterogeneity stems from studies being implemented prior to developed definitions.

There is a great need to develop a standardized definition of long COVID, not only from a scientific standpoint, but also from a societal standpoint. Using a more liberal definition of long COVID, the condition is estimated to cost society $3.7 trillion dollars, which includes costs related to medical spending, quality of life and reduced earnings.[8] However, this estimate was calculated from data of long COVID observational studies that used poorly identified controls. Thus, the number is

likely overestimated because of diagnosis misclassification. A recent retrospective analysis by the US Centers for Disease Control and Prevention (CDC) reported that 1 in 5 patients who have had COVID experience symptoms of long COVID.[9] The agency leverages electronic health—and does not use a comparable control arm, does not assess for resolution of the infection, and provides a 12 month window for a symptom to arise. Whether this estimate is compatible with the experience of most Americans is unknown, and some doctors doubt this estimate.[10]

Because of this uncertainty, standardized definitions should be developed by reputable organizations with skills to critically evaluate study bias. Moreover, definitions should be based on studies that include control groups that are comparable to cases except for having had COVID.[11]

The definition of long COVID should at a minimum specify a confirmed diagnosis of COVID-19, stipulate that symptoms had not been present prior to COVID-19 infection, and rule out pre-existing or concomitant conditions that could be causing symptoms thought to be due to long COVID. Moreover, because more severe infections of any type require longer recovery, the definition should also stipulate a duration of symptoms that is at least commensurate with the severity of initial COVID-19 infection.

It would also be important to separate post-intensive care syndrome from that of long COVID.[12] It is expected that patients with serious conditions requiring critical care, including for the treatment of COVID, will have a longer recovery and experience a greater number of associated lingering symptoms or sequelae. As such, it is important to separate the effects of intensive treatment for a critical condition from persisting symptoms of a less serious infection.

Limitations include definitions coming from clinicaltrials.gov, where the final trial design has yet to be set, and inconsistency in the names of symptoms. Using common themes in long COVID consensus definitions as a starting point, standardized definitions of long COVID should be applied in studies assessing this condition to unify and harmonize research on this topic.

AUTHOR CONTRIBUTIONS

VP and AH conceptualized study design; AH and TO reviewed and abstracted data; VP reviewed and confirmed abstracted data; AH wrote first draft of manuscript; and all authors reviewed and revised subsequent and finalized draft of manuscript.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

Vinay Prasad's Disclosures. (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape, and MedPage (Honoraria) Grand Rounds/lectures from universities, medical centres, non-profits, and professional societies. (Consulting) UnitedHealthcare and OptumRX. (Other) Plenary Session podcast has Patreon backers, YouTube and Substack. All other authors have no financial nor non-financial conflicts of interest to report.

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How to cite this article: Haslam A, Olivier T, Prasad V. The definition of long COVID used in interventional studies. *Eur J Clin Invest*. 2023;00:e013989. doi:10.1111/eci.13989