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Original Article

Persistence of long COVID symptoms in COVID-19 survivors worldwide and its potential pathogenesis - A systematic review and meta-analysis

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Abstract

The study sought to determine the prevalence of persistent long COVID symptoms such as anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss, and hair loss among coronavirus disease 2019 (COVID-19) survivors worldwide and to discuss the potential pathogeneses. Potential studies were searched in three databases (PubMed, Scopus, and Web of Science) as of January 30, 2021. Data on study characteristics, patient characteristics during the follow-up, the number of patients with persistent long COVID symptoms and total COVID-19 survivors were collected according to PRISMA guidelines. To assess the quality of studies, the Newcastle-Ottawa scale was used. The estimated prevalence of each long COVID symptom and the association between COVID-19 severity and the occurrence of prolonged symptoms was assessed, if appropriate. The global prevalence of prolonged anxiety was 15.76% (95%CI: 6.36%, 25.15%). Chest pain persisted in 10.36% (239/3,224) of COVID-19 patients (95%CI: 4.92%, 15.80%). Prolonged depression was found in 24 of 548 COVID-19 survivors with an estimated prevalence of 4.32% (95%CI: 2.62%, 6.03%) and dizziness was presented in 4.83% (118/2,219, 95%CI: 1.50%, 8.16%) after recovery. Hair loss was complained by 527 of 2,251 recovered patients (cumulative prevalence of 24.76%, 95%CI: 19.60%, 29.91%), while weight loss was identified in 37 cases among 452 COVID-19 survivors (8.19%, 95%CI: 5.66%, 10.71%). Prolonged palpitation was experienced by 19.38% (211/1,926) survivors with 95%CI: 2.40%, 41.16%. Sleep difficulty was found in 541 of 2,622 COVID-19 survivors (17.87%, 95%CI: 7.55%, 28.20%). The association between COVID-19 severity and the occurrence of persistent long COVID symptoms was not analyzed due to the lack of data. In conclusion, persistent psychological symptoms are frequently reported among COVID-19 survivors. Follow-up studies with a longer duration and larger population are warranted to assess the extent of prolonged symptoms and the

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Received: May 22, 2021 - Accepted: July 3, 2021 - Published online: August 1, 2021

quality of life of COVID-19 survivors. Despite various potential pathogeneses that have been hypothesized, a definitive mechanism is yet to be addressed. PROSPERO registration: CRD42021247172

Keywords: COVID-19, follow-up study, prolonged symptom, long COVID, systematic review

Introduction

The coronavirus disease 2019 (COVID-19) was declared a global pandemic on March 11th, 2020. The disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused more than 131 million confirmed cases and more than 2.8 million deaths, worldwide [1]. Not only causing socioeconomic disruption [2, 3], COVID-19 has also affected the healthcare system [4-7]. These concerns, along with the risk of discrimination [8] and stigmatization [9, 10] among patients and healthcare workers [11], can lead to psychological problems [12].

A study found that depressed mood (14.9%), anxiety (14.8%), post-traumatic stress disorder (PTSD) (32.2%), insomnia (12.1%), and irritability (12.8%) were frequently reported after severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) infection [13]. This could imply that SARS-CoV-2 infection may have a similar course of persistent long COVID symptoms to SARS or MERS infection following recovery of disease [13]. The global pandemic also has triggered a social discriminatory crisis and stigmatization against suspected, confirmed, and recovered COVID-19 patients [12]. Fear, panic, and misinformation about the transmission of COVID-19 have become reasons why verbal abuse and violent acts have occurred against COVID-19 patients and hospital workers [14]. One study reported that among 4,172 COVID-19 survivors in Wuhan, 615 patients had experienced depression, and 528 patients had anxiety with risk factors such as being female, living alone, had low income and had chronic comorbid disease [15]. In South Korea, a study reported that 10% and 50% of COVID-19 patients developed depression and PTSD, respectively one month after discharge from the hospital [16]. Another study reported that being female was significantly related to depressive emotion and PTSD while being retired and having good social support reduced the risk of psychological distress during the early convalescence of COVID-19 (14-days quarantine after hospital discharge) [17].

Several studies found that palpitations either as cardiovascular sequelae or long COVID disturbance have been reported during COVID-19 follow-up [18-20]. Sleep disturbance was also a concern not only during the follow-up but also since hospitalization with acute COVID-19. Longer hospitalization and higher depression rate were found in COVID-19 patients with poor sleep quality [21]. A study found that, after 38 days post-recovery, insomnia was found in 56.3% (89/158) of COVID-19 survivors [22]. Numerous studies have been conducted to identify the persistent symptoms in COVID-19 survivors, however, a detailed pooled analysis of the long COVID symptoms is scarce. Therefore, this systematic review sought to assess (a) the global estimated prevalence of persistent long COVID symptoms among COVID-19 survivors, including anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss, and hair loss, and (b) the association of COVID-19 severity during initial infection and persistent long COVID symptoms post-recovery.

Methods

Registration and protocol

We conducted a systematic review to estimate the prevalence of persistent long COVID symptoms such as anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss, and hair loss. The study protocol was registered to PROSPERO (CRD42021247172) and no ethical clearance was required. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) in searching the databases and reporting the results (**Supplementary material**) [23].

Eligibility criteria of studies

Observational studies reporting at least one persistent long COVID symptom (anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss, and hair loss) in COVID-19 survivors were considered eligible. All editorials, commentaries, reviews, case reports, and case series with less than 10 patients were excluded. RT-PCR of SARS-CoV-2 RNA from nasal or oropharyngeal swab samples must be used to confirm COVID-19 diagnosis. Diagnosis based on clinical symptoms without nucleic acid testing and suspected cases were excluded. A COVID-19 survivor was defined based on discharge criteria from either WHO or China's National Health Commission [24, 25]. Persistent symptoms were described as symptoms that were presented since hospitalization or during the infection period which prolonged until the patient was discharged.

Information sources and search strategy

Three databases (PubMed, Scopus, and Web of Science) were searched as of January 30th, 2021. The searches were limited to 2019-2021 and only articles written in English were considered eligible. The search strategies were as follows. PubMed ([Title]("SARS-CoV-2" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan virus" OR "novel coronavirus" OR "nCoV" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "2019-nCoV" OR "2019 novel coronavirus" OR "SARS 2") AND ([Title]("prolong*" OR "follow-up" OR "persistent" OR "sequelae" OR "consequen*" OR "prospective" OR "cohort" OR "long-term" OR "follow*" OR "longitudinal"). Web of Science ([Title]("SARS-CoV-2" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan virus" OR "novel coronavirus" OR "nCoV" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "2019-nCoV" OR "2019 novel coronavirus" OR "SARS 2") AND ([Title]("prolong*" OR "follow-up" OR "persistent" OR "sequelae" OR "consequen*" OR "prospective" OR "cohort" OR "long-term" OR "follow*" OR "longitudinal"). Scopus ([Title]("SARS-CoV-2" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan virus" OR "novel coronavirus" OR "nCoV" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "2019-nCoV" OR "2019 novel coronavirus" OR "SARS 2") AND ([Title]("prolong*" OR "follow-up" OR "persistent" OR "sequelae" OR "consequen*" OR "prospective" OR "cohort" OR "long-term" OR "follow*" OR "longitudinal").

Study selection and data extraction

Information for relevant articles was imported to EndNote X9 (Thompson Reuters, Philadelphia, PA, USA) with duplicated references among the three databases removed. Initial screening of titles and abstracts was done to identify eligible articles. Two authors (MF and MI) downloaded and reviewed the full text of potentially eligible articles based on eligibility criteria and the availability of the data. Data from the eligible articles and supplementary materials were extracted and the list of references was retrieved for further relevant studies.

Study characteristics of the eligible articles including author(s), year of study, study site and country, study design, time of follow-ups conducted after discharge, number of COVID-19 patients who were followed, number of COVID-19 patients with prolonged specific long COVID symptom, and severity of the COVID-19 during admission in the hospitals were collected.

Outcomes

There were two main outcomes in this study: (a) global prevalence of persistent long COVID symptoms such as anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss and hair loss in COVID-19 survivors; and (b) associations of COVID-19 severity with the presence of persistent long COVID symptoms. We also discussed the possible mechanisms of persistent long COVID symptoms in COVID-19 survivors.

Risk of bias assessment

The quality of each study was assessed by using the Newcastle-Ottawa scale (NOS) [26]. Nine characteristics of a study were evaluated in NOS, including four items for sample selection, one item for group comparison and three items for the outcome. The scores ranged between 0 to 9 and the quality of the study was classified as low (≤ 4), moderate (5–6), and high (≥7).

Data synthesis and statistical analysis

The estimated prevalence of each persistent long COVID symptoms was calculated as the number of patients who had prolonged symptoms divided by the total number of patients with or without the specific long COVID symptom during the follow-up and expressed as frequency (%) and 95% confidence interval (95%CI). The associations of the COVID-19 severity during infection and the risk of persistent long COVID symptoms were calculated and expressed as odds ratios (ODs) and 95% CI. Forest plots were used to visualize the data.

The heterogeneity of the pooled data was evaluated by the Q-test. Data was analyzed using a random-effects model. The publication bias was assessed by using Egger's test with $p<0.05$ considered as publication bias. Review Manager version 5.3 (the Cochrane Collaboration) was used to analyze the data [27].

Results

Study eligibility results

The search resulted in 4,050 eligible articles, with 2,045 duplicates. The titles and abstracts of the remaining 2,005 references were screened, and 1,244 articles were excluded. Screening of the full-text of 761 studies excluded an additional 747 references for reasons such as being reviews, case series, case reports, initial reports on COVID-19, letter/commentaries, studies on specific groups, recommendations, and studies with insufficient data. The final screening process yielded 14 articles which were included in the meta-analysis (**Figure 1**).

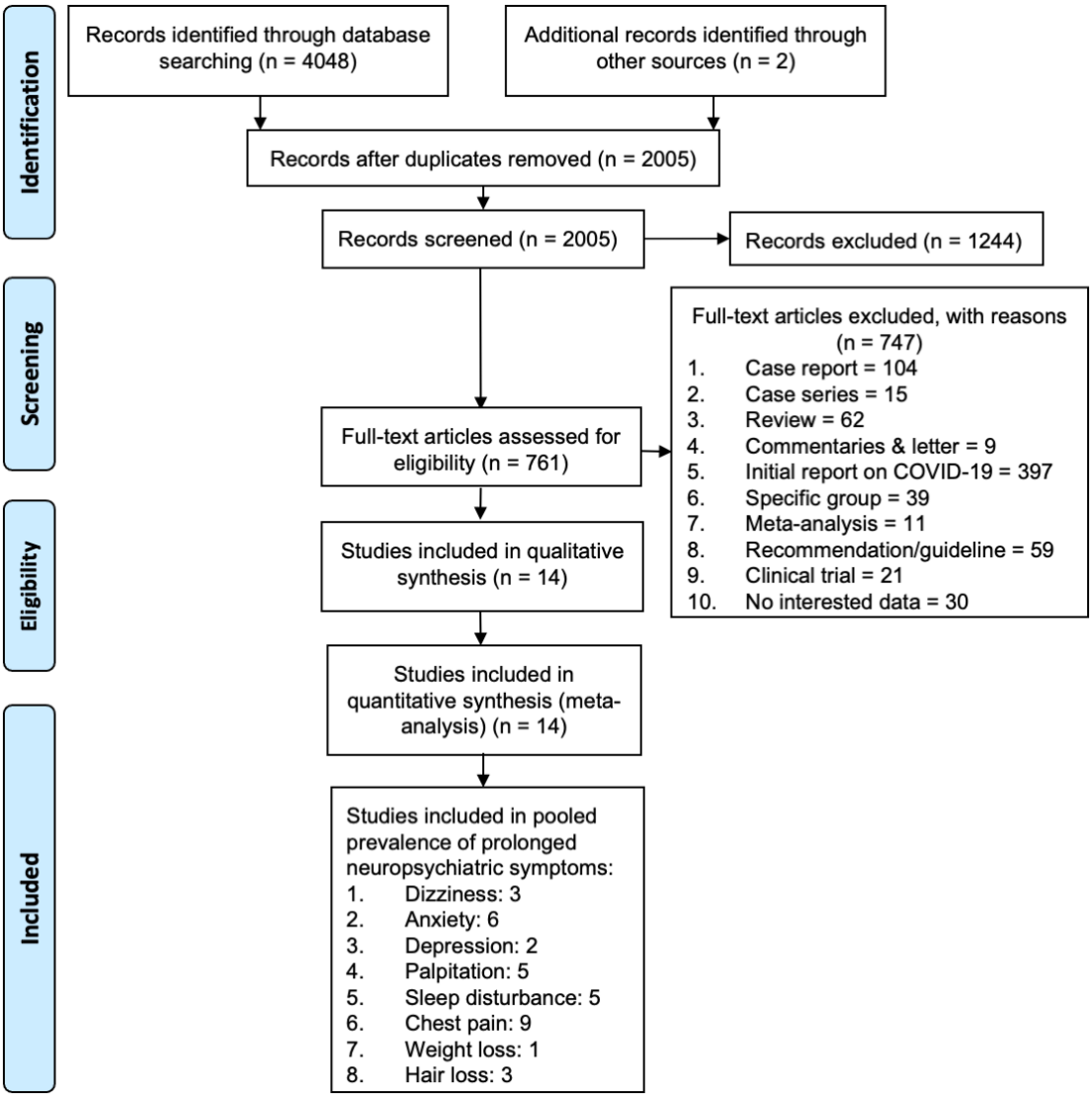

Figure 1. Flowchart of the results of literature search according to PRISMA

Table 1. The prevalence of persistent long COVID symptoms among COVID-19 survivors

Symptom	Year	Study design	Country	Days from discharge to follow-up	Followed up COVID-19			Association between COVID-19 severity and occurrence of symptoms						NOS	Ref
					Prolonged symptom	Total patient	%	Mild-moderate	Total	%	Severe	Total	%		
Dizziness	2021	Cohort	China	153 (146–160)	101	1655	6.10	92	1538	5.98	9	117	7.69	8	[28]
	2020	Cohort	USA	38 (21–49)	3	26	11.54							8	[29]
	2021	Prospective	China	97 (95–102)	14	538	2.60							8	[30]
	Total				118	2219	5.32								
Anxiety	2021	Cohort	China	153 (146–160)	367	1617	22.70	331	1506	21.98	36	111	32.43	8	[28]
	2020	Cohort	USA	38 (21–49)	8	26	30.77							8	[29]
	2021	Retrospective	China	30	20	304	6.58	16	243	6.58	4	61	6.56	7	[31]
	2021	Prospective	China	97 (95–102)	35	538	6.51							8	[30]
	2020	Prospective	China	14	17	337	5.04							7	[32]
	2020	Cohort	Italy	23 (20-29)	55	185	29.73							8	[33]
	Total				502	3007	16.69								
Depression	2021	Prospective	China	97 (95–102)	23	538	4.28							8	[30]
	2020	Prospective	South Korea	25 (13–50)	1	10	10.00							8	[16]
	Total				24	548	4.38								
Palpitation	2021	Cohort	China	153 (146–160)	154	1655	9.31	141	1538	9.17	13	117	11.11	8	[28]
	2020	Cohort	USA	38 (21–49)	6	26	23.08							8	[29]
	2020	Prospective	China	14	3	131	2.29	2	62	3.23	1	69	1.45	7	[34]
	2020	Prospective	China	28	1	38	2.63							7	[35]
	2020	Prospective	China	90	47	76	61.84							8	[36]
	Total				211	1926	10.96								
Sleep difficulties	2021	Cohort	China	153 (146–160)	437	1655	26.40	406	1538	26.40	31	117	26.50	8	[28]
	2020	Cohort	USA	38 (21–49)	7	26	26.92							8	[29]
	2021	Retrospective	China	30	21	304	6.91	12	243	4.94	9	61	14.75	7	[31]
	2020	Prospective	Iran	28	25	452	5.53	21	400	5.25	4	52	7.69	9	[37]
	2020	Cohort	Italy	23 (20-29)	51	185	27.57							8	[33]
	Total				541	2622	20.63								

Symptom	Year	Study design	Country	Days from discharge to follow-up	Followed up COVID-19			Association between COVID-19 severity and occurrence of symptoms						NOS	Ref
					Prolonged symptom	Total patient	%	Mild-moderate	Total	%	Severe	Total	%		
Chest pain	2021	Cohort	China	153 (146–160)	75	1655	4.53	65	1538	4.23	10	117	8.55	8	[28]
	2020	Cohort	USA	38 (21–49)	10	26	38.46							8	[29]
	2020	Retrospective	Iran	91 (±15.5)	9	52	17.31							8	[38]
	2021	Retrospective	China	30	15	304	4.93	7	243	2.88	8	61	13.11	7	[31]
	2020	Prospective	China	14	4	131	3.05	3	62	4.84	1	69	1.45	7	[34]
	2021	Prospective	China	97 (95–102)	66	538	12.27							8	[30]
	2020	Prospective	China	14	28	337	8.31							7	[32]
	2020	Prospective	Italy	60.3 (±13.6)	31	143	21.68							7	[39]
	2020	Prospective	China	28	1	38	2.63							7	[35]
	Total				239	3224	7.41								
Weight loss	2020	prospective	Iran	28	37	452	8.19	31	400	7.75	6	52	11.54	9	[37]
	Total				37	452	8.19								
Hair loss	2021	Cohort	China	153 (146–160)	359	1655	21.69	331	1538	21.52	28	117	23.93	8	[28]
	2021	Prospective	China	97 (95–102)	154	538	28.62							8	[30]
	2020	Prospective	Japan	108 (±23)	14	58	24.14							7	[40]
	Total				527	2251	23.41								

Among the 14 studies, three studies were included in meta-analysis to calculate the prevalence of prolonged dizziness [28-30], six studies for persistent anxiety [28-33], two studies for persistent depression [16, 30], five studies for palpitation [28, 29, 34-36] , five studies for sleep disturbance [28, 29, 31, 33, 37], nine articles for prolonged chest pain [28-32, 34, 35, 38, 39], one study for weight loss [37] and three studies for hair loss [28, 30, 40]. The summary of studies included is presented in **Table 1**.

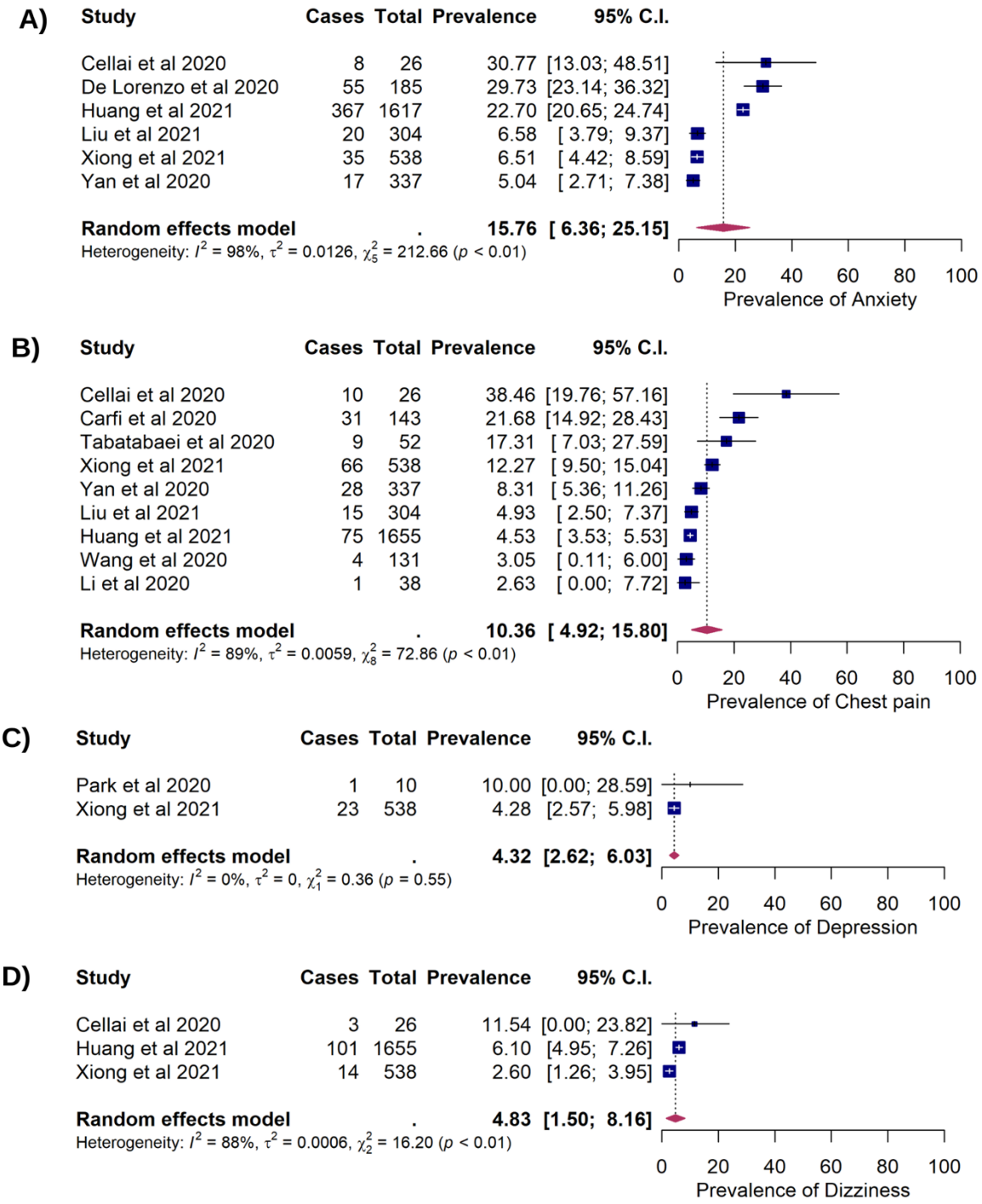

Figure 2. Forest plots showing of the long COVID symptoms in COVID-19 survivors. (A) The prevalence of anxiety (15.76%; 95%CI: 6.36%, 25.15%); p=0.001; pHet <0.001; pEgger=0.085); (B) The prevalence of chest pain (10.36%; 95%CI: 4.92%, 15.80%]; p<0.001; pHet<0.001; pEgger<0.001); (C) The prevalence of depression (4.32%; 95%CI: 2.62%. 6.03%; p<0.001; pHet=0.547; pEgger<0.001); (D) The prevalence of dizziness (4.83%; 95%CI: 1.50%, 8.16%; p=0.004; pHet<0.001; pEgger=0.320).

Prevalence of persistent long COVID symptoms in COVID-19 survivors

Six studies which included 3,007 COVID-19 patients reported prolonged anxiety among 502 patients after recovery, with an estimated prevalence of 15.76% (95%CI: 6.36%, 25.15%). Nine studies reported prolonged chest pain in 239 of 3,224 COVID-19 patients (10.36%, 95%CI:4.92%, 15.80%). Prolonged depression presented in 24 of 548 COVID-19 patients which corresponded to a pooled prevalence of 4.32% (95%CI: 2.62%, 6.03%). The estimated prevalence of persistent dizziness among COVID-19 survivors was 4.83% (118/ 2,219 95%CI: 1.50%, 8.16%) (**Figure 2**). Hair loss was found in three studies consisting of 2,251 COVID-19 survivors, of which 527 patients were reported having the prolonged symptom (cumulative prevalence of 24.76%, 95%CI: 19.60%, 29.91%). Persistent palpitation was reported in 19.38% (211/1,926) survivors with 95%CI: 2.40%, 41.16%. Sleep difficulty was identified in 541 out of 2,622 COVID-19 survivors (17.87%, 95%CI: 7.55%, 28.20%) and weight loss was reported in 8.19% survivors (37/452, 95%CI: 5.66%, 10.71%) (**Figure 3**).

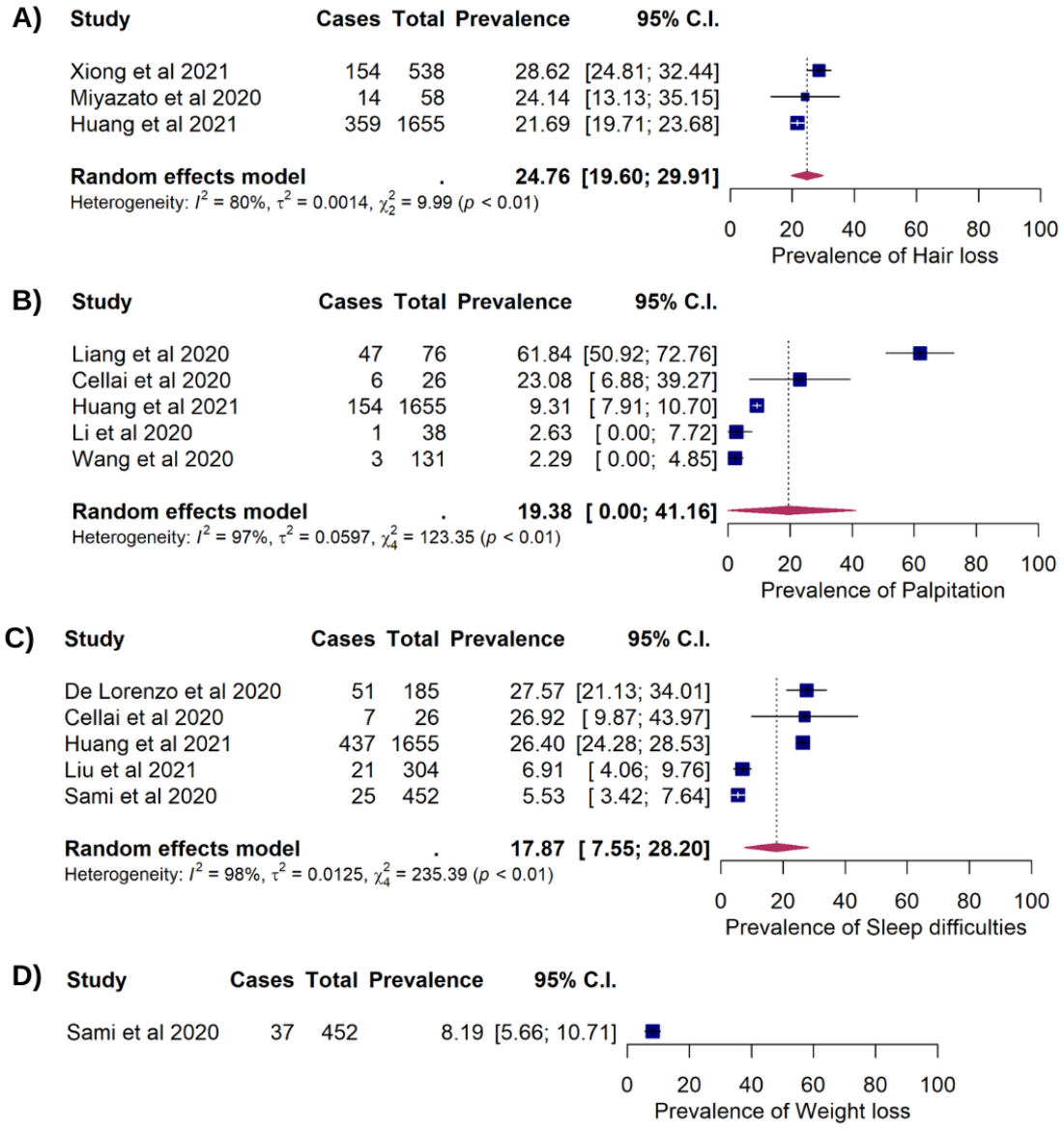

Figure 3. Forest plots showing the long COVID symptoms in COVID-19 survivors (A) The prevalence of hair loss (24.76%; 95%CI: 19.60%, 29.91%; p<0.001; pHet=0.006; pEgger=0.875; (B) The prevalence of palpitation (19.38; 95%CI: 2.40, 41.16; p=0.081; pHet<0.001; pEgger=0.185; (C) The prevalence of sleep difficulties (17.87%; 95%CI: 7.55%, 28.20%); p<0.001; pHet<0.001; pEgger=0.328. (D) The prevalence of weight loss (8.19%; 95%CI: 5.66%, 10.71%).

Association of COVID-19 severity and persistent long COVID symptoms

Due to the scarcity of data relating to persistent long COVID symptoms among mild-moderate and severe COVID-19 patients, the association between COVID-19 severity and the risk of persistent long COVID symptoms was unable to be determined.

Discussion

The COVID-19 outbreak is an ongoing health crisis with concerns about patients' health status that arise not only during the initial infection but also post-recovery. Studies have reported persistent symptoms and prolonged lung function, physical and psychological problems in discharged patients [30, 39, 41-43].

Psychological issues during the COVID-19 pandemic were common due to social isolation, concern about transmitting the disease, and the fear of stigma and discrimination society [44]. Long-term quarantine and loneliness among COVID-19 patients might increase psychological distress, including severe depression and insomnia, leading to suicidal thoughts and behaviour [45]. While psychological distress increased universally among the general population [46, 47], this is apparent only in the initial period of the pandemic before swift recovery to baseline [48], indicating prolonged distress as a specific attribute of long COVID.

The host immune response also plays an important role in cognitive-behavioural changes in COVID-19 infection. High levels of interleukin (IL)-1β, IL-6, IL-4, IL-10, tumor necrosis factor-alpha (TNF-α), chemokine (C-C-motif) ligand 2 (CCL2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon (IFN)-γ suggests a cytokine dysregulation in SARS-CoV-2 infection that might lead to altered neurotransmitter signalling [49]. Cytokine dysregulation, particularly of IL-1β, IL-6, IL-10, IFN-γ and TNF-α are known to be associated with the development and progression of psychological disorders, including depressive mood and anxiety [50-52]. There is evidence of SARS-CoV-2 causing changes in the brain parenchyma and blood vessels [53, 54]. These changes may induce brain inflammation, blood-brain-barrier dysfunction, neurotransmitter impairment and hypothalamic-pituitary adrenal (HPA) axis disruption which might induce neurological manifestation such as brain fog, tinnitus, and poor sleep quality [22].

Weight loss of more than 5% of initial body weight was found among 31% (48/156) hospitalized and 21% (12/57) non-hospitalized COVID-19 patients after recovery in Milan, Italy [55]. Several mechanisms may be involved in weight loss among COVID-19 patients. Vascular leakage combined with endothelial barrier disruption in COVID-19 patients may result in an inflammatory cascade, disrupting tissue homeostasis [56]. The presence of abundant acute phase proteins and cytokines in COVID-19 patients may cause dysregulation of metabolism [57-59], proteolysis [59-61], and the hypothalamus pathway, thereby increasing resting energy expenditure and muscle catabolism [62], that could further cause weight loss [63, 64]. Psychological problems also contribute to decreased food intake, consequently aggravating the COVID-19 patients' malnutrition [65-67]. As a result, these conditions contribute to tissue degeneration [68]. Additionally, appetite loss, fatigue, changes in smell and taste, anosmia, ageusia, and fever all contribute to malnutrition and cachexia [69, 70], which can result in anabolic failure and subsequent weight loss [71].

Chest pain is commonly complained by COVID-19 survivors [72]. Another study reported that chest pain was experienced by 60% of 430 patients on initial infection and 32.6% of 370 patients after COVID-19 recovery [73]. It is crucial to understand whether persistent chest pain in post-COVID-19 is due to musculoskeletal, cardiovascular, or lung lesions. As symptoms on chest are self-defined by the patient, sometimes it is also termed as chest tightness which is related to musculoskeletal symptoms or chest burn as cardiovascular symptoms[74]. Coronary microvascular ischemia has been reported to cause persistent chest pain in patients that have recovered from COVID-19 [75]. Chest discomfort is also attributed to pulmonary lesions, such as lung fibrosis[76], mild pleural effusion and bronchiectasis[77].

Data on hair loss in COVID-19 survivors is still limited and may be associated with androgenetic alopecia in men [78] or telogen effluvium in women [79]. Hair loss in COVID-19 patients could also be explained by vascular leakage caused by stress, as well as endothelial and

epithelial scalp cell death, which could trigger an inflammatory cascade by disrupting homeostasis, such as IL-1 [80, 81]. Inflammatory mediators are cytotoxic to hair cells [82, 83] and high IL-1 level has been linked to hair loss [84, 85].

This study compiled preliminary data on prolonged symptoms of COVID-19, such as anxiety, depression, dizziness, chest pain, sleep difficulty, palpitations, weight loss, and hair loss. Due to the small number of current studies on persistent symptoms of COVID-19, there is no standard data on the onset and duration of persistent symptoms of COVID-19. However, our study presents basic data on the prevalence and the duration of prolonged symptoms of SARS-CoV-2 infection. The low number of articles included in this meta-analysis significantly influenced the findings of our study and due to the lack of data on severity of COVID-19 in these studies, no association between persistent symptoms and the severity of COVID-19 could be determined. Therefore, further studies with larger populations and subgroup analysis are warranted to ascertain these findings, including determining the association between COVID-19 severity and the presence of prolonged symptoms in COVID-19 survivors.

Conclusions

Persistent long COVID symptoms are prevalent in COVID-19 survivors. The result of our study suggested that longer follow-up studies within a larger population are needed. Supportive care is also necessary to ensure a smooth transition back to the community and increasing the quality of life of COVID-19 patients after discharge.

Declarations

Ethics approval

Not required.

Acknowledgments

The authors would like to thank Narra Studio Journal Indonesia for assisting the writing processes.

Conflict of interest

The authors declare that they have no competing interests.

Funding

This study received no external funding.

Supplementary material

PRISMA checklist is available from: https://doi.org/10.6084/m9.figshare.14371784.

How to cite

Fahriani M, Ilmawan M, Fajar JK, *et al.* Persistence of long COVID symptoms in COVID-19 survivors worldwide and its potential pathogenesis - A systematic review and meta-analysis. Narra J 2021; 1(2): e36. http://doi.org/10.52225/narraj.v1i2.36.

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