SARS-CoV-2 post-acute sequelae in previously hospitalised patients: systematic literature review and meta-analysis

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PASC is a complex, multisystem condition with multiple clinical phenotypes and prolonged duration. Further research is needed to better define the duration of PASC and determine the impact of factors such as disease severity, vaccination and treatments. https://bit.ly/3Ks39Vx

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Abstract

Background Many individuals hospitalised with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection experience post-acute sequelae of SARS-CoV-2 infection (PASC), sometimes referred to as "long COVID". Our objective was to conduct a systematic literature review and meta-analysis to identify PASC-associated symptoms in previously hospitalised patients and determine the frequency and temporal nature of PASC.

Methods Searches of MEDLINE, Embase, Cochrane Library (2019–2021), World Health Organization International Clinical Trials Registry Platform and reference lists were performed from November to December 2021. Articles were assessed by two reviewers against eligibility criteria and a risk of bias tool. Symptom data were synthesised by random effects meta-analyses.

Results Of 6942 records, 52 studies with at least 100 patients were analysed; ∼70% were Europe-based studies. Most data were from the first wave of the pandemic. PASC symptoms were analysed from 28 days after hospital discharge. At 1–4 months post-acute SARS-CoV-2 infection, the most frequent individual symptoms were fatigue (29.3% (95% CI 20.1–40.6%)) and dyspnoea (19.6% (95% CI 12.8–28.7%)). Many patients experienced at least one symptom at 4–8 months (73.1% (95% CI 44.2–90.3%)) and 8–12 months (75.0% (95% CI 56.4–87.4%)).

Conclusions A wide spectrum of persistent PASC-associated symptoms were reported over the 1-year follow-up period in a significant proportion of participants. Further research is needed to better define PASC duration and determine whether factors such as disease severity, vaccination and treatments have an impact on PASC.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can result in severe acute illness and hospitalisation, and although the early phase of the pandemic was associated with high mortality, the majority of individuals survive. However, a significant proportion of survivors have ongoing symptoms after the initial infectious period and experience a prolonged recovery to their baseline health [1–3], often described as "post-acute sequelae of SARS-CoV-2 infection" (PASC) or "long COVID" [2].

A high volume of research, including primary studies and systematic literature reviews (SLRs), has been published on PASC. The variety of symptoms, temporal nature and frequency of PASC are yet to be

comprehensively characterised and no consistent definition of PASC has been determined, although proposed definitions include the presence of symptoms from 4 weeks to 3 months after initial SARS-CoV-2 infection [2–5]. Due to inconsistency in the definition of PASC and the design and conduct of studies, the reported prevalence of PASC and its particular symptoms have dramatically varied [6]. As a result, much prior research is subject to challenges or limitations. Owing to the rapid pace of evidence generation for SARS-CoV-2 infection, many literature reviews, especially early in the pandemic, included preprint literature, which may have increased the risk of inclusion of lower quality data [7–11]. In our search of the literature, few previous SLRs examined outcomes at multiple time-points and therefore have been unable to quantify the changing symptom profile of PASC. Furthermore, relatively few literature reviews have included meta-analyses to synthesise outcome data.

To address this knowledge gap, our SLR and meta-analysis aimed to determine the nature and prevalence at multiple time-points of specific classes of PASC in individuals hospitalised for SARS-CoV-2 infection and to contribute knowledge that may help inform a definition of PASC for use in future analytical work.

Methods

The SLR was performed in accordance with a prespecified protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022306931) on 27 January 2022.

Identification of studies

Studies published from 2019 onwards were identified through electronic database searches conducted on 16 November 2021, in MEDLINE (including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print), Embase and Cochrane Library. The bibliographies of relevant SLRs and (network) meta-analyses identified through the electronic database searches were individually reviewed to identify additional studies of relevance. The World Health Organization International Clinical Trials Registry Platform was also searched, on 3 December 2021. Additional grey literature, such as congresses and preprint articles, were not searched due to the recency of the COVID-19 pandemic and a decision to prioritise peer-reviewed literature. Lists of the search terms used in each source are presented in the supplementary material.

Study selection

Each abstract and full text was reviewed against predefined eligibility criteria, developed using the Population, Intervention, Comparison and Outcomes (PICO) framework. In line with accepted practice, each title and abstract was reviewed against the eligibility criteria by one reviewer [12]. A second independent reviewer provided input in cases of uncertainty, and independently reviewed 10% of the excluded articles and all included articles.

Each full-text article was then reviewed by two independent reviewers, with disagreements resolved by discussion until consensus was met. If necessary, a third independent reviewer made the final decision. Studies were required to have an objective of investigating PASC and include patients aged $\geqslant$12 years experiencing long-term effects of SARS-CoV-2 infection. Interventional and observational studies were included, while case reports and non-peer-reviewed literature were excluded. Specific criteria were imposed on the study population to increase the reliability of results and reduce heterogeneity. The population was restricted to patients who had been hospitalised for SARS-CoV-2 infection. This ensured that only studies in populations with a definite, confirmed diagnosis of SARS-CoV-2 infection were included, rather than self-diagnosed patients. The required minimum duration of follow-up was 28 days (4 weeks) after SARS-CoV-2 infection diagnosis. Studies that reported outcomes before patients had been discharged from the hospital were excluded based on the clinical definitions used by the Centers for Disease Control and Prevention (CDC) guidelines and the 2021 National Institute for Health and Care Excellence (NICE) rapid guideline (NG188) [3, 13].

In a protocol amendment, due to a large volume of identified evidence, only studies that reported on clinical symptoms associated with PASC were carried through to data extraction. Studies with sample sizes of at least 100 patients were prioritised to improve the precision of outcome estimates.

Data extraction, quality assessment and prioritisation for quantitative synthesis

Data extractions and quality assessments were performed in line with guidelines from the University of York Centre for Reviews and Dissemination by a single individual, with a second individual independently verifying all extracted information (and arbitration by a third individual if necessary) [14]. Top-line information on the included studies was first extracted into a prespecified evidence compendium. Following this, only studies that clearly reported the method of SARS-CoV-2 infection diagnosis were

prioritised for quantitative synthesis *via* a meta-analysis. Subsequently, detailed extractions were conducted to capture information on study characteristics, patient characteristics and PASC symptoms.

Feasibility assessment and meta-analysis

A feasibility assessment was undertaken to assess the suitability of the identified studies for meta-analysis. This consisted of an assessment of the heterogeneity, reported symptoms and follow-up time-points of the included studies. Random effects meta-analyses were conducted to synthesise estimates of the frequency of each symptom reported across studies and pooled estimates were obtained for each symptom at each specific time-point. The estimates generated in the meta-analysis represent the average percentage of patients experiencing the symptoms, while the ranges of symptom frequency (supplementary table S1) provide an indication as to the extent of variation in the percentage of patients experiencing each symptom.

The meta-analyses were run using the metaprop function from the meta package (version 5.1-1) in R software (version 4.1.2) [15]. The metafor package (version 3.4-0) was used to perform a generalised linear mixed model logistic regression [16]. The corresponding 95% confidence intervals were estimated using the Clopper–Pearson method. A 0.5 zero-cell correction was applied in the case of studies reporting zero patients experiencing a specific symptom. Where possible, data from the full study population were used. Where necessary, additional data were digitised from plots and calculations were performed (*e.g.* pooling of study subgroups). Plots were identified in a systematic manner across all studies and digitised using DigitizeIt software [17]; values obtained *via* digitisation were checked for quality by an independent reviewer. The approaches used in the feasibility assessment and meta-analysis were validated by clinician feedback.

The time-points at which PASC was reported were grouped into three periods for the meta-analysis based on the spread of reported follow-up time-points: $\geqslant$1 to <4, $\geqslant$4 to <8 and $\geqslant$8 to <12 months (figure 1a). The selected lower bound for the first time period was chosen to align with the CDC and NICE definitions of PASC [3, 13].

Funnel plots were created and Egger's tests were performed to assess publication bias across individual symptoms. In the funnel plots, the standard error of each study was plotted against the size of the study's treatment effect in the meta-analysis. Egger's test (a linear regression of the treatment effect estimates on their standard errors weighted by their inverse variance) evaluated potential publication bias *via* funnel plot asymmetry.

Results

Identified studies

After the removal of duplicates, 4373 records were identified through electronic database searches. After the exclusion of 3840 irrelevant records based on title and abstract, 533 full texts were screened. Following this, 200 records were considered relevant for inclusion in the SLR on the basis that they aimed to characterise an aspect of long-term SARS-CoV-2 infection. An additional 55 records were included from bibliography searches, resulting in 255 total records that met an aspect of the initial PICO criteria. After prioritisation of studies that reported a relevant clinical outcome, had at least 100 patients and reported a clear method for diagnosis of SARS-CoV-2, 60 publications on 52 unique studies were included in the quantitative analysis (figure 2).

Study and patient characteristics

Study characteristics varied across the 52 studies (table 1). The majority of studies were prospective cohorts (n=34) and almost all (n=43) used convenience sampling to recruit participants. Almost all studies (n=43) enrolled patients during the first 4 months of 2020, coinciding with the first wave of the pandemic. Study sites spanned Asia, Europe and North America.

Coronavirus disease 2019 (COVID-19) severity and oxygen status were poorly reported but varied across study populations (figure 3). Of the 13 studies that reported disease severity, seven included only severe cases while four included a mix of mild, moderate and severe cases, based on individual study definitions of severity. Of the 29 studies reporting oxygen status, approximately half (n=14) included patients on supplemental oxygen, although all studies reported mechanical ventilation.

The percentage of intensive care unit (ICU) admissions and the duration of hospitalisation were reported by 34 and 30 studies, respectively (figure 3). ICU admissions ranged from 1.5% to 48.5%, while average duration of hospitalisation (reported by studies as either median or mean) ranged from 5 to 23 days. Reported follow-up time-points ranged from 1 to 12 months.

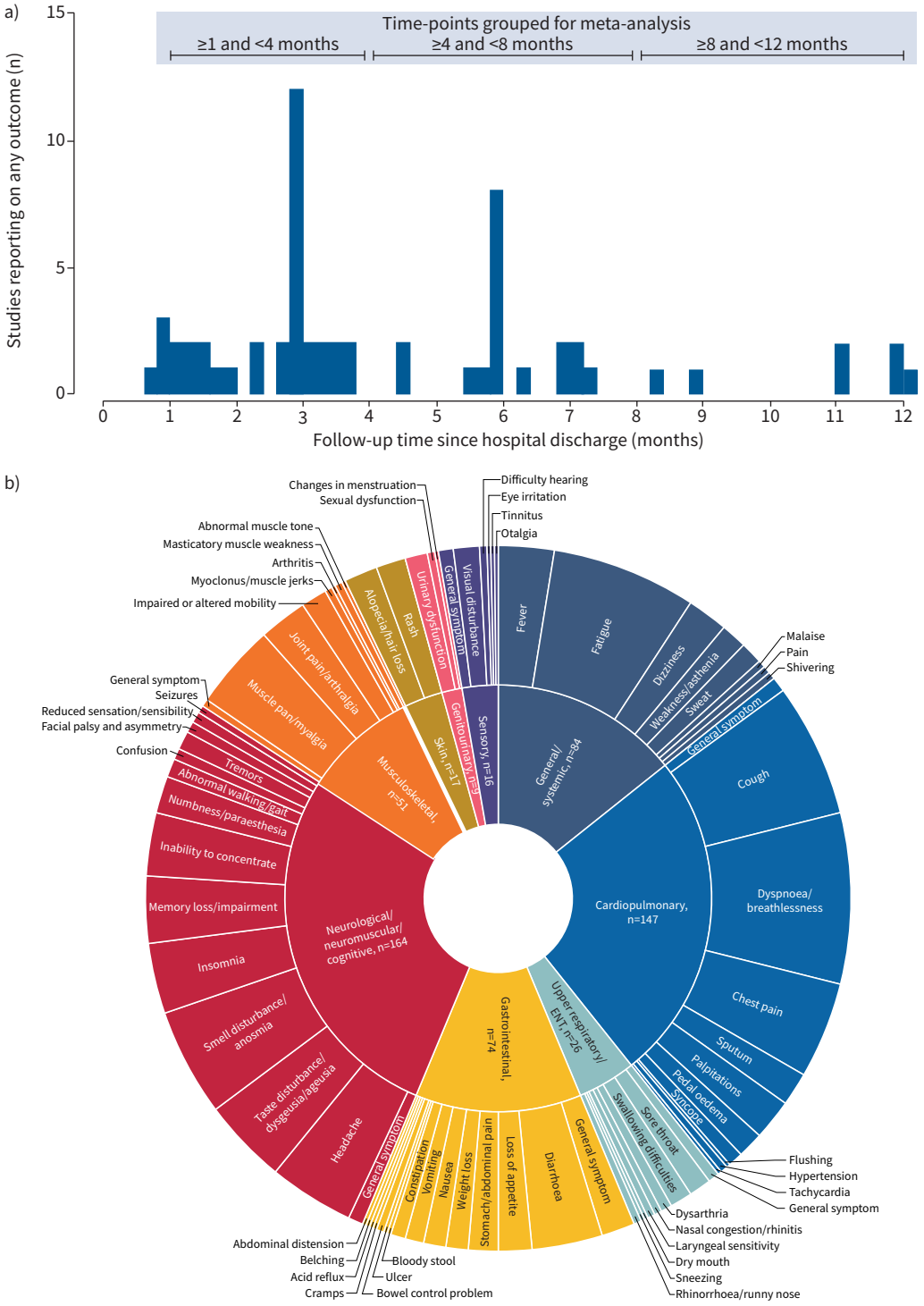

FIGURE 1 a) Histogram summarising frequency of reporting of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) outcomes in extracted studies. Studies that reported on more than one follow-up time-point are included in the plot at each time-point they reported on. b) Sunburst plot summarising frequency of reporting of PASC outcomes in extracted studies. The sunburst plot summarises the frequency of reporting of PASC symptoms across the extracted studies, with the inner ring divided by symptom category and the outer ring reporting all symptoms within each category. The size of each section in both the inner and the outer ring reflects the number of primary publications that reported each symptom. The starburst plot does not contain any information on combined symptoms or the percentage of patients experiencing at least one symptom. COVID-19: coronavirus disease 2019; ENT: ear–nose–throat.

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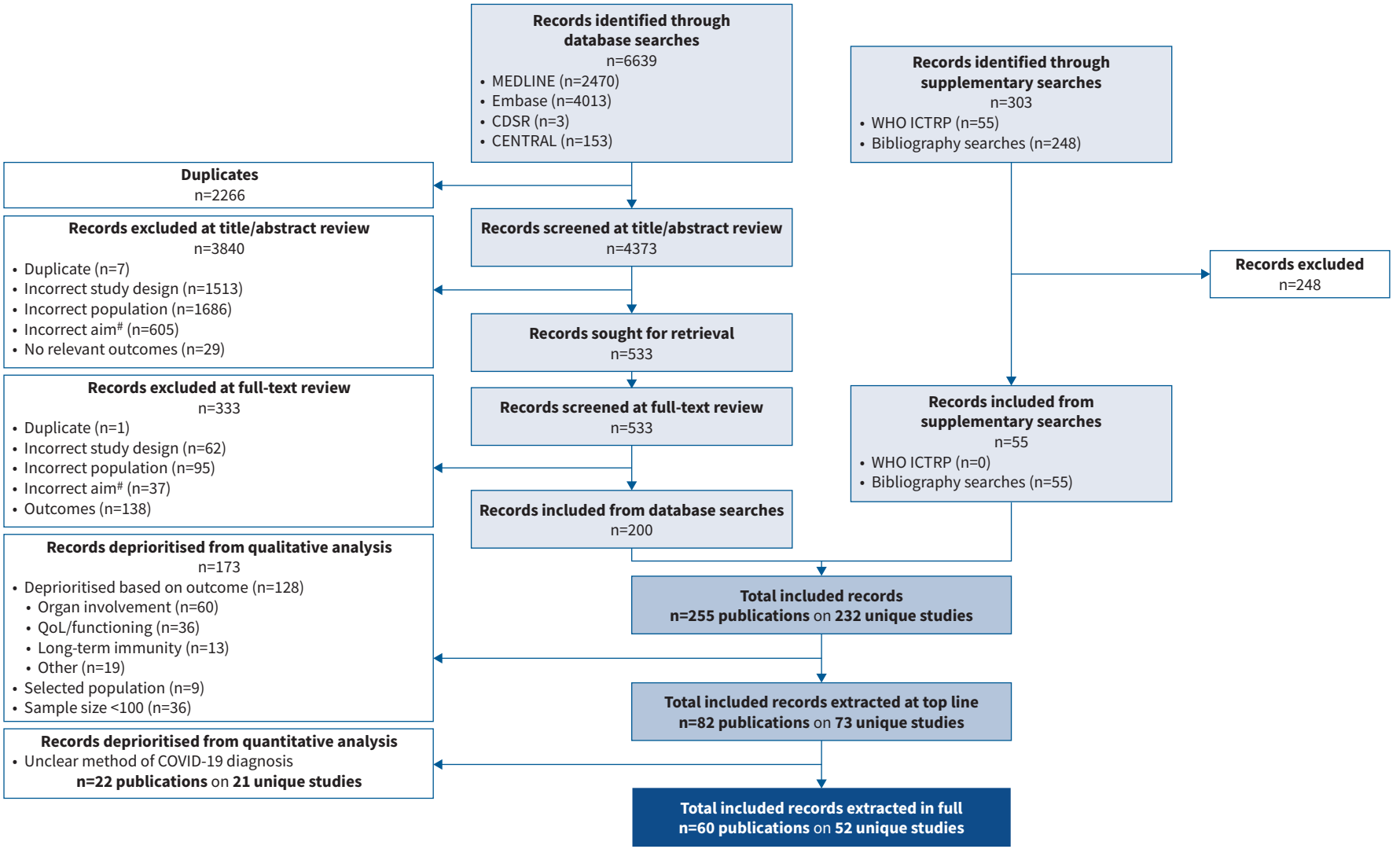

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. #: studies were required to have the aim of characterising "long COVID". CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform; QoL: quality of life; COVID-19: coronavirus disease 2019.

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TABLE 1 Summary of study characteristics for extracted studies

Study	Study design	Country; setting	Sampling method	Population	Sample size (n)	Method of confirming COVID-19
Aranda, 2021 [40]	Prospective cohort	Spain; single centre	Convenience sampling	Patients >18 years old with COVID-19 and severe COVID-19 pneumonia who had suffered ARDS during hospital admission and survived to hospital discharge	113	RT-PCR
Asadi-Pooya, 2022 [41]	Prospective cohort	Iran; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	2696	RT-PCR
Aul, 2021 [42]	Prospective cohort	UK; single centre	Judgemental sampling[#]	Discharged adults (⩾18 years) with COVID-19	387	RT-PCR or clinico-radiological diagnosis
Ayoubkhani, 2021 [43]	Retrospective cohort	UK; multicentre	Judgemental sampling[#]	Hospitalised patients with a primary diagnosis of COVID-19, identified by ICD-10 codes U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus unidentified)	47 780	Positive laboratory test or clinical diagnosis
Bai, 2021 [44]	Prospective cohort	Italy; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	377	RT-PCR
Caruso, 2021 [45]	Prospective cohort	Italy; single centre	Convenience sampling	Patients with moderate to severe COVID-19 with a diagnosis of interstitial pneumonia who had undergone baseline chest CT with positive results that was performed at admission	118	RT-PCR
Clavario, 2021 [46]	Prospective cohort	Italy; single centre	Convenience sampling	Patients with COVID-19 with a complete CPET evaluation	200	RT-PCR
DISCOVER [34]	Prospective cohort	UK; single centre	Convenience sampling	Adult hospitalised patients (⩾18 years): 1) typical symptoms of COVID-19 (*e.g.* influenza-like illness with fever and muscle pain or respiratory illness with cough and shortness of breath) and positive PCR result for SARS-CoV-2, using the established PHE assay in use at the time, or 2) suspected SARS-CoV-2 infection, namely presenting with a) typical symptoms (*e.g.* influenza-like illness with fever and muscle pain or respiratory illness with cough and shortness of breath); and b) compatible chest radiography findings (consolidation or ground-glass shadowing); and c) alternative causes considered unlikely or excluded (*e.g.* heart failure, influenza)	131	Positive PCR result for SARS-CoV-2 or clinico-radiological diagnosis of COVID-19
Fernández-de-las-Peñas 2021 [47]	Prospective cohort	Spain; multicentre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	1142	RT-PCR and clinical and radiological findings
Fernández-de-las-Peñas, 2022 [48]	Prospective cohort	Spain; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	1969	RT-PCR and radiological findings

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TABLE 1 Continued

Study	Study design	Country; setting	Sampling method	Population	Sample size (n)	Method of confirming COVID-19
Fernández-de-las-Peñas, 2021 [49]	Retrospective case–control/ matched cohort	Spain; multicentre	Judgemental sampling#	Hospitalised adults (⩾18 years) with COVID-19	183	RT-PCR
Fernández-de-las-Peñas, 2021 [28]	Retrospective cohort	Spain; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	1950	RT-PCR and radiological findings
Fernández-de-las-Peñas, 2021 [50]	Prospective case–control/ matched cohort	Spain; single centre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	738	RT-PCR and consistent clinical and radiological findings
FrenchCOVID [51]	Prospective cohort	France; multicentre	Judgemental sampling#	Discharged adults (⩾18 years) with COVID-19 followed up at 6 months	1137	RT-PCR
Froidure, 2021 [52]	Retrospective cohort	Belgium; single centre	Convenience sampling	Hospitalised patients with critical or severe COVID-19 who survived and underwent a 3-month follow-up in the study hospital	134	Positive PCR on NPS and lung infiltrates on lung HRCT or chest radiography at admission
Frontera, 2021 [53]	Prospective cohort	USA; multicentre	Convenience sampling	Age ⩾18 years; hospital admission; survival to discharge; consent to participate in a follow-up interview	382	RT-PCR
Carfì, 2020 [54]	Prospective cohort	Italy; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	143	RT-PCR
Garrigues, 2020 [55]	Prospective cohort	France; single centre	Convenience sampling	Patients with positive COVID-19 diagnoses who responded to follow-up questionnaire	120	RT-PCR and/or typical abnormalities on chest CT
Gautam, 2022 [56]	Retrospective cohort	UK; multicentre	Convenience sampling	Hospital admission for >3 days, with F_{IO_2} >40% for >6 h; new stroke; pulmonary embolism; DVT; delirium; elevated high-sensitivity troponin levels; residual AKI; tachycardia (pulse rate >100 beats·min^{-1}) at discharge	200	Laboratory-confirmed SARS-CoV-2 infection
Gherlone, 2021 [57]	Prospective cohort	Italy; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	122	RT-PCR
Gonzalez-Hermosillo, 2021 [58]	Prospective cohort	Mexico; single centre	Convenience sampling	Adult patients hospitalised with moderate to severe confirmed COVID-19 pneumonia at hospital admission	130	Positive real-time RT-PCR test
Halpin, 2021 [59]	Retrospective cohort	UK; multicentre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	100	RT-PCR
Han, 2021 [60]	Prospective cohort	China; multicentre	Judgemental sampling#	Patients ⩾18 years old diagnosed with respiratory rate >30 breaths·min^{-1}, S_{pO_2} <90% on room air or severe respiratory distress	114	RT-PCR
Huang, 2021 [61]	Ambidirectional cohort	China; single centre	Convenience sampling	Patients who were discharged from the hospital	1276	Laboratory confirmed

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TABLE 1 Continued

Study	Study design	Country; setting	Sampling method	Population	Sample size (n)	Method of confirming COVID-19
Jacobs, 2020 [62]	Prospective cohort	USA; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19 who had been hospitalised for a duration of at least 3 days	183	RT-PCR
LinCoS [63]	Prospective cohort	Sweden; multicentre	Judgemental sampling#	Hospitalised adults (⩾18 years) with COVID-19	433	Laboratory confirmed
Lindahl, 2021 [64]	Retrospective cohort	Finland; single centre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	101	Laboratory confirmed
Lombardo, 2021 [65]	Prospective cohort	Italy; multicentre	Judgemental sampling#	Discharged adults (⩾18 years) with COVID-19	303	RT-PCR
Mahajan, 2021 [66]	Prospective cohort	India; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	134	RT-PCR
Meije, 2021 [67]	Prospective cohort	Spain; single centre	Convenience sampling	Discharged aged >15 years with COVID-19	302	Confirmed cases: met clinical criteria (acute respiratory syndrome), radiological criteria and had a positive PCR; probable cases: met clinical criteria (acute respiratory syndrome), radiological criteria, but with negative or inconclusive PCR
Mendez, 2021 [68]	Prospective cohort	Spain; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	171	Laboratory confirmed
Moradian, 2020 [69]	Cross-sectional	Iran; single centre	Convenience sampling	Hospitalised patients ⩾18 years of age with moderate to severe COVID-19 recovered and then discharged 4 weeks earlier	200	RT-PCR
Morin, 2021 [70]	Prospective cohort	France; single centre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	478	RT-PCR; CT lung scan associated with clinical features; or both
Munblit, 2021 [71]	Retrospective cohort	Russia; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	2649	RT-PCR or clinically confirmed infection
Bellan, 2021 [72]	Prospective cohort	Italy; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	238	RT-PCR (97.5%), bronchial swab, serological testing or suggestive CT results
NutriCoviDom [73]	Prospective cohort	France; single centre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	288	Positive SARS-CoV-2 RT-PCR test on NPS and/or on a typical chest CT scan
Ong, 2021 [74]	Prospective cohort	Singapore; multicentre	Convenience sampling	Hospitalised with COVID-19	288	SARS-CoV-2-specific PCR
Pellaud, 2020 [75]	Retrospective cohort	Switzerland; multicentre	Convenience sampling	Hospitalised with COVID-19	196	RT-PCR
PHOSP-COVID [76]	Prospective cohort	UK; multicentre	Judgemental sampling#	Discharged adults (⩾18 years) with COVID-19	1077	Confirmed or clinician-diagnosed COVID-19

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TABLE 1 Continued

Study	Study design	Country; setting	Sampling method	Population	Sample size (n)	Method of confirming COVID-19
PROLUN [77]	Prospective cohort	Norway; multicentre	Judgemental sampling[#]	Patients aged >18 years; admitted for >8 h with discharge diagnosis of ICD-10 U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus unidentified) or J12.x (viral pneumonia) with COVID-19	103	Diagnosis of U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus unidentified) or J12.x (viral pneumonia, in combination with positive SARS-CoV-2 identification in NPS)
Qu, 2021 [78]	Prospective cohort	China; multicentre	Convenience sampling	Patients hospitalised with fever, respiratory rate >24 breaths·min^{-1} or cough; clinical type of COVID-19 at hospital admission mild to severe	540	Positive results from real-time PCR test for nucleic acid in respiratory or blood samples
Rass, 2021 [79]	Prospective cohort	Austria; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	135	RT-PCR and typical clinical presentation
REACT [80]	Retrospective cohort	UK; single centre	Convenience sampling	Patients aged 18–90 years with a confirmed COVID-19 diagnosis	101	PCR testing performed by combined nose and throat swabs
Romero-Duarte, 2021 [81]	Retrospective cohort	Spain; multicentre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	797	Positive PCR test for SARS-CoV-2
Sathyamurthy, 2021 [82]	Prospective cohort	India; single centre	Convenience sampling	Age ⩾65 years; hospitalised with acute COVID-19; discharged in a stable condition	288	RT-PCR
Shang, 2021 [83]	Prospective cohort	China; multicentre	Convenience sampling	Hospitalised and discharged	796	RT-PCR
Shoucri, 2021 [84]	Retrospective cohort	USA; single centre	Convenience sampling	Age ⩾18 years; hospitalised	929	RT-PCR
Suárez-Robles, 2020 [85]	Retrospective cohort	Spain; single centre	Convenience sampling	Hospitalised adults (⩾18 years) with COVID-19	134	RT-PCR
Taylor, 2021 [86]	Prospective cohort	UK; multicentre	Convenience sampling	Presumed or confirmed COVID-19 pneumonia	675	NR
Weng, 2021 [87]	Retrospective cohort	China; multicentre	Convenience sampling	Hospitalised patients admitted for respiratory symptoms	117	RT-PCR
Xiong, 2021 [88]	Prospective cohort	China; single centre	Convenience sampling	Inpatients aged 20–80 years from Renmin Hospital of Wuhan University (Wuhan, China); diagnosed with COVID-19 and discharged according to WHO interim guidance	538	According to WHO interim guidance
Zhang, 2021 [89]	Retrospective cohort	China; multicentre	Convenience sampling	Discharged adults (⩾18 years) with COVID-19	2433	Laboratory confirmed

[#]: in studies described as employing judgemental sampling, participants were included in studies based on clinicians' decision, rather than including all eligible patients at a study site. COVID-19: coronavirus disease 2019; ARDS: acute respiratory distress syndrome; RT: reverse transcription; ICD-10: International Classification of Diseases, 10th Revision; CT: computed topography; CPET: cardiopulmonary exercise testing; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PHE: Public Health England; NPS: nasopharyngeal swab; HRCT: high-resolution computed topography; F_{IO_2}: inspiratory oxygen fraction; DVT: deep venous thrombosis; AKI: acute kidney injury; S_{pO_2}: peripheral oxygen saturation; NR: not reported; WHO: World Health Organization.

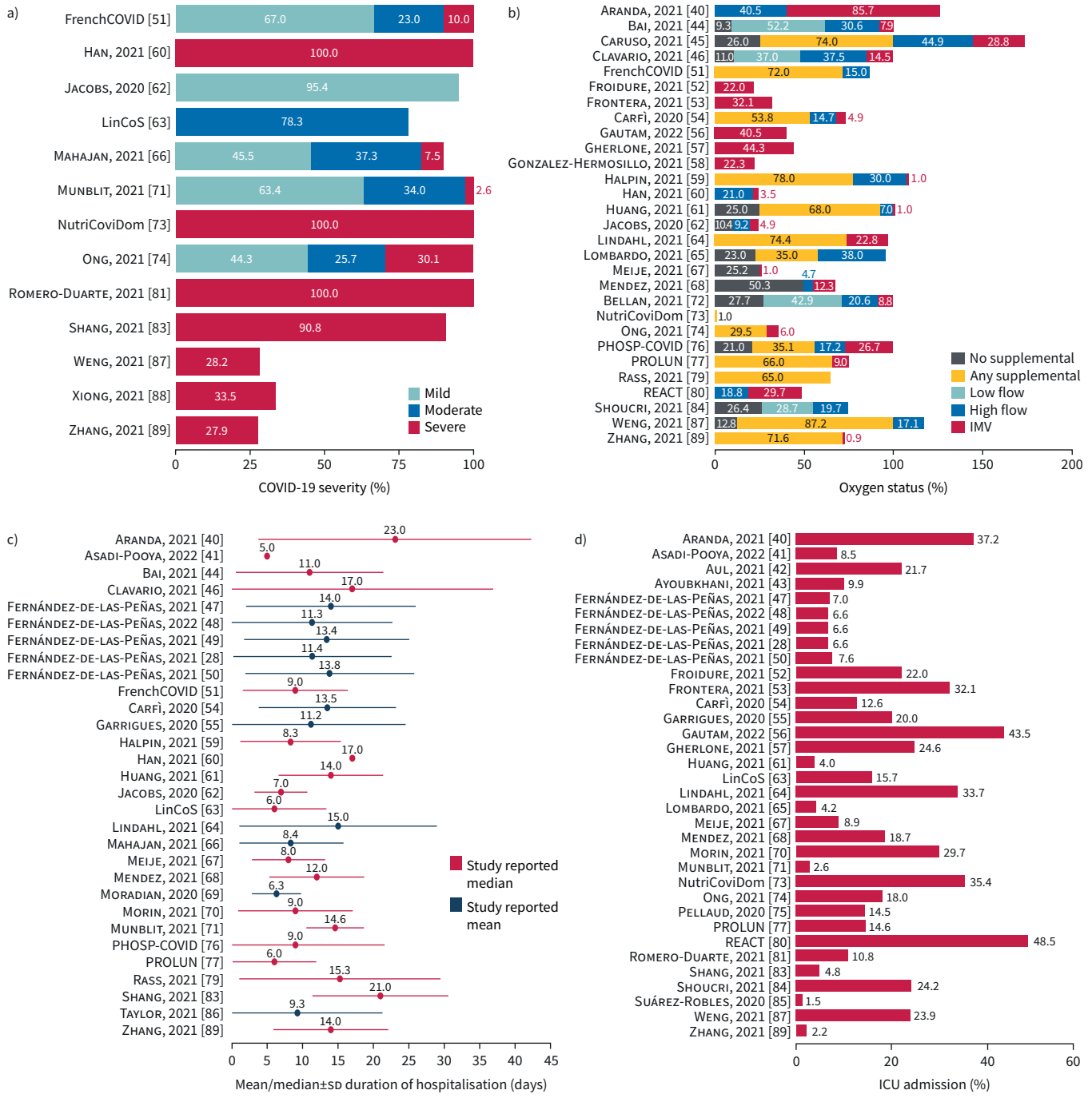

FIGURE 3 Key study characteristics assessed in feasibility assessment: a) coronavirus disease 2019 (COVID-19) disease severity (reported by 13 out of 52 studies), b) oxygen status (reported by 29 out of 52 studies), c) duration of hospitalisation (reported by 30 out of 52 studies) and d) intensive care unit (ICU) admission (reported by 34 out of 52 studies). Disease severity was recorded either at admission or during the period of hospitalisation; oxygen status was recorded over the period of hospitalisation. Duration of hospitalisation was reported by studies as either mean or median; in the heterogeneity assessment these values were assumed to be equivalent as per standard practice and the standard deviation was calculated from the interquartile range for studies reporting the median. IMV: invasive mechanical ventilation.

PASC outcomes

76 PASC symptoms were extracted from the analysed studies. Subsequently, 13 symptoms, including two composite symptoms (combined anosmia/ageusia and combined arthralgia/myalgia), were prioritised for the meta-analysis, selected based on the number of studies that reported on each symptom and based on

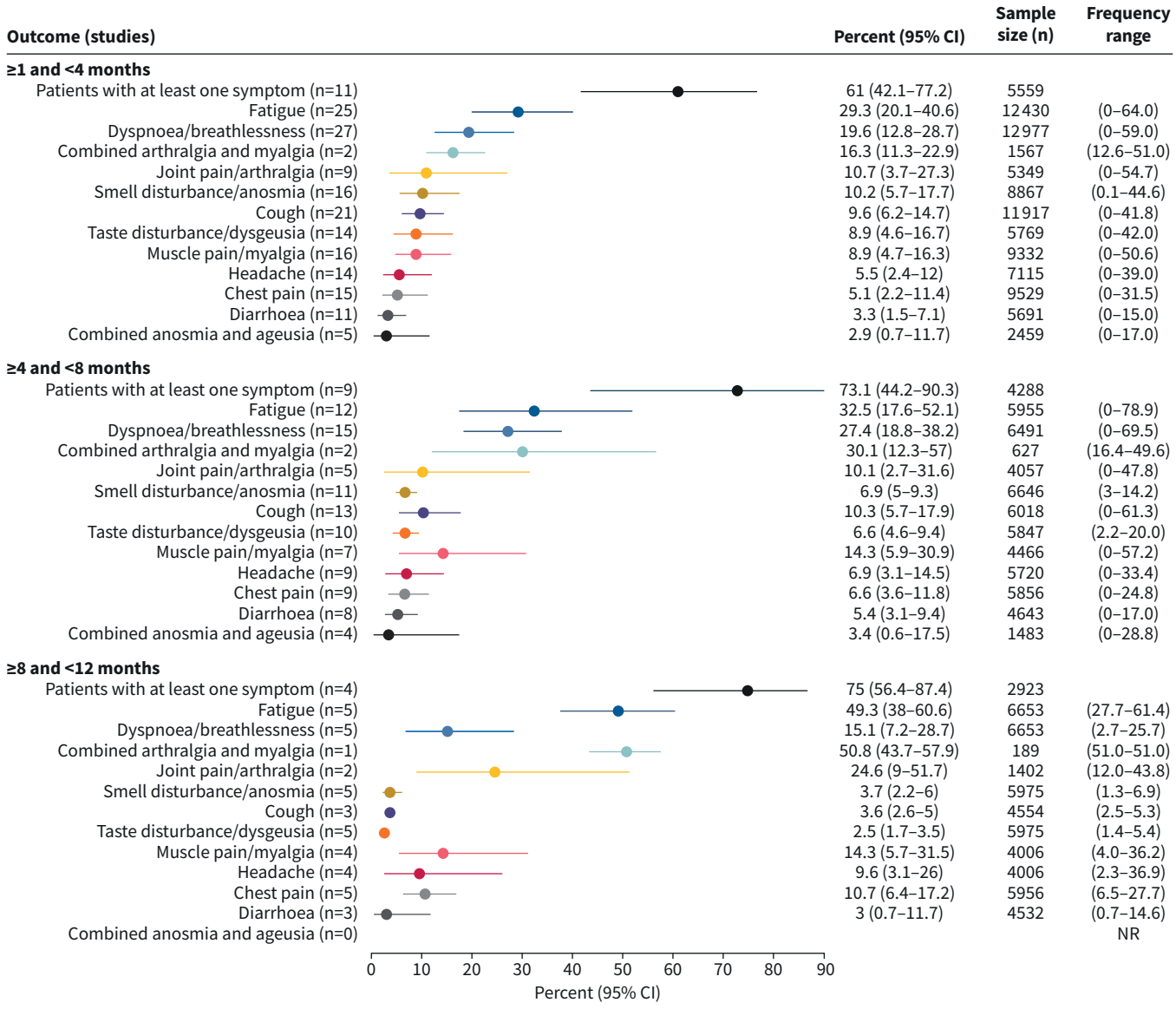

FIGURE 4 Meta-analysis summary estimates for each of the 13 symptoms of interest at each of the three time periods of interest. Combined anosmia and ageusia and combined arthralgia and myalgia were both extracted as a single outcome for when studies reported both anosmia and ageusia or arthralgia and myalgia as a single outcome. NR: not reported.

their clinical relevance (figure 1b). The percentages of patients experiencing each of the 13 symptoms were meta-analysed at each of the three periods of interest and pooled estimates for each meta-analysis were generated (figure 4).

The majority of patients reported at least one symptom at all time-points: 61.0% (95% CI 42.1–77.2%) at ⩾1 to <4 months, 73.1% (95% CI 44.2–90.3%) at ⩾4 to <8 months and 75.0% (95% CI 56.4–87.4%) at ⩾8 to <12 months. Symptom burden generally persisted at ⩾4 to <8 and ⩾8 to <12 months, and the frequency of some reported symptoms indicated a potential increase over time, although this was not formally tested as most studies only reported data at one time-point (supplementary table S1). The two most frequent individual symptoms were fatigue (⩾1 to <4 months: 29.3% (95% CI 20.1–40.6%); ⩾4 to <8 months: 32.5% (95% CI 17.6–52.1%); ⩾8 to <12 months: 49.3% (95% CI 38.0–60.6%)) and dyspnoea/breathlessness (⩾1 to <4 months: 19.6% (95% CI 12.8–28.7%); ⩾4 to <8 months: 27.4% (95% CI 18.8–38.2%); ⩾8 to <12 months: 15.1% (95% CI 7.2–28.7%)) (figures 5 and 6).

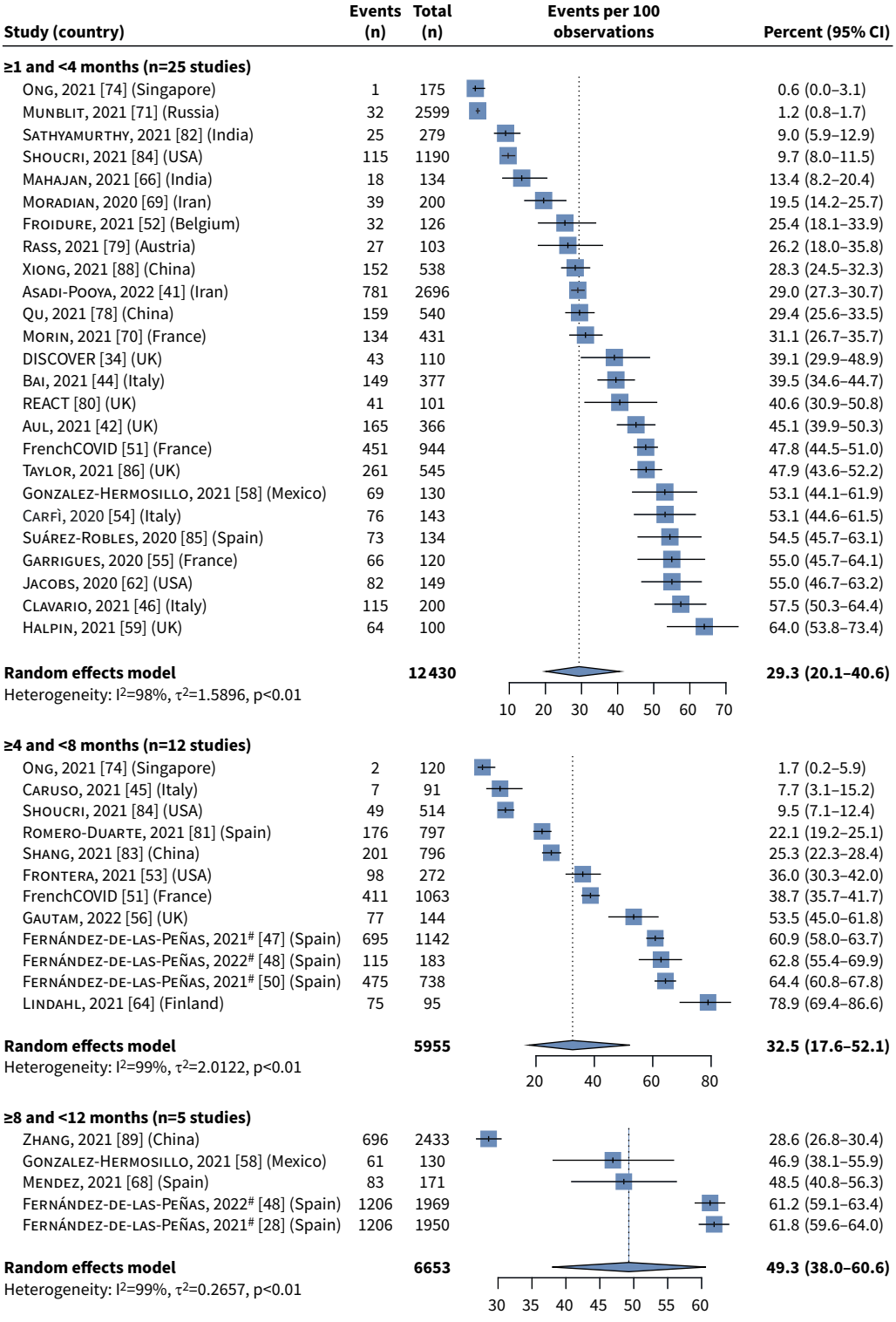

FIGURE 5 Meta-analysis summary estimates for fatigue at each of the three time periods of interest. #: the Fernández-de-las-Peñas *et al.* [28, 47, 48, 50] studies were conducted by the same group of authors but included distinct patient groups. I^2>50% and p<0.05 indicates substantial heterogeneity.

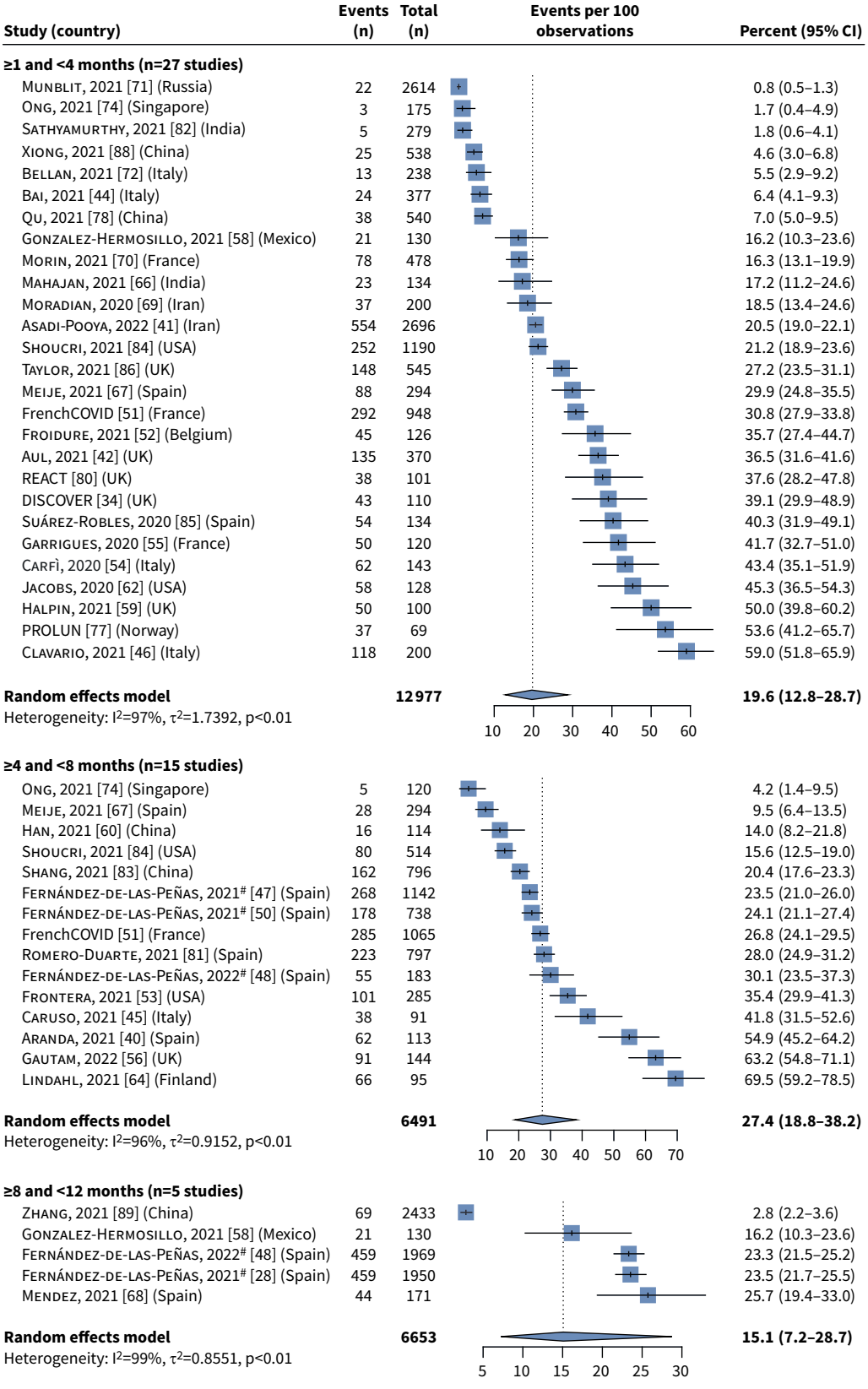

FIGURE 6 Meta-analysis summary estimates for dyspnoea/breathlessness at each of the three time periods of interest. #: the Fernández-de-las-Peñas *et al.* [28, 47, 48, 50] studies were conducted by the same group of authors but included distinct patient groups. I^2>50% and p<0.05 indicates substantial heterogeneity.

Heterogeneity and risk of bias

Substantial heterogeneity was found across studies, indicated by I^2>50% for each symptom at each time-point. Despite this heterogeneity, no study was identified as an outlier; therefore, no studies warranted exclusion from the meta-analysis.

Studies were of moderate quality and all had at least one element in their design, conduct or analysis that contributed to an increased risk of bias. 32 studies did not have an adequate description of subjects and setting, 37 studies did not have an appropriate participant response rate or did not provide enough information to determine their response rate and 48 studies did not provide enough information to determine whether the sample size was appropriate for the target population. However, all included studies had an appropriate aim of characterising PASC and valid SARS-CoV-2 infection identification methods since these were prespecified inclusion criteria (supplementary figure S1).

Although asymmetry in some funnel plots suggested potential publication bias, all Egger's tests were p>0.05, indicating no significant publication bias for any symptom throughout all time-points (sample funnel plot in supplementary figure S2a), with the exception of diarrhoea at ⩾4 to <8 months (p=0.0242) (supplementary figure S2b).

Discussion

In this SLR and meta-analysis, 52 studies of moderate quality reported symptoms of PASC. Most patients reported at least one symptom at all time-points up to 12 months of follow-up. Of 76 different PASC symptoms identified, the most common symptoms were fatigue, dyspnoea/breathlessness and combined arthralgia/myalgia. Other symptoms reported across different time-points included cough, chest pain, palpitations, diarrhoea, smell disturbance, taste disturbance and headache. These symptoms spanned many organ systems without apparent patterns. Where data were available, symptom burden was present at both ⩾4 to <8 and ⩾8 to <12 months, with 75% of patients reporting at least one symptom at the longest time-point.

The findings of this analysis build upon and are supported by other published literature. Across the wide volume of published SLRs on PASC, the reported symptom profile is varied, both in terms of the number and prevalence of different clinical symptoms identified. Nonetheless, similar symptoms across the literature are consistently cited as being the most common, including fatigue, dyspnoea, headache and chest pain. Some symptoms such as memory or concentration disorder, or "brain fog", have since become recognised as a common symptom of PASC [1, 18–22]; however, during the early pandemic, the suspected symptoms of PASC were poorly understood and may not have been rigorously captured in these studies.

This work adds value to previously published findings as it considers a wide range of follow-up durations (from 1 to 12 months) and reports results separately at different time-points using appropriate grouping of time periods based on the spread of available data and clinician input. Most other studies had shorter follow-up times of up to 3 or 6 months at the longest and/or did not report results separately at different time-points [18–21, 23]. Our findings are similar to those of a study by Alkodaymi *et al.* [24], even though they assessed PASC symptoms in a broader study population (hospitalised and non-hospitalised patients) and at slightly different time-points (⩾3 to <6, ⩾6 to <9, ⩾9 to <12 and ⩾12 months). The prevalence of most common symptoms was similar during the second follow-up period (fatigue: 33% (95% CI 18–52%) in our study *versus* 36% (95% CI 27–46%) in Alkodaymi *et al.* [24]; dyspnoea: 27% (95% CI 19–38%) *versus* 25% (95% CI 20–30%), respectively) and third follow-up period (fatigue: 49% (95% CI 38–61%) *versus* 37% (95% CI 16–62%), respectively; dyspnoea: 15% (95% CI 7–29%) *versus* 21% (95% CI 14–28%), respectively); and the 95% confidence intervals overlap with our results [24]. A meta-analysis by Han *et al.* [25] focused solely on studies with at least a 1-year follow-up in both hospitalised and non-hospitalised patients. Similarly to our meta-analysis, frequently reported symptoms in Han *et al.* [25] were fatigue (28% (95% CI 18–39%)), dyspnoea (18% (95% CI 13–24%)) and arthralgia/myalgia (26% (95% CI 8–44%)); the 95% confidence intervals again overlap with our results [25]. Two recent studies, both published after our searches were conducted, report further evidence on the outcomes of previously hospitalised patients. A prospective, observational study found that the most common residual symptoms at 6-month follow-up were dyspnoea (35% of patients), cardiovascular symptoms (including fatigue; 10% of patients) and neurocognitive symptoms (13% of patients) [26]. In addition, an ambidirectional, longitudinal cohort study measured health outcomes of previously hospitalised individuals at three time-points of interest (6 months, 12 months and 2 years after symptom onset) [27]. Fatigue was the most prevalent symptom at all three time-points (6 months: 52%; 12 months: 20%; 2 years: 30%), while dyspnoea was present in 26% of patients at 6 months and 14% of patients after 2 years of follow-up [27]. While there is some variation in symptom prevalence between studies, our

findings generally align with those of recently conducted studies, reaffirming the long-term relevance and importance of our analysis within the broader context of research on PASC.

A recently published SLR and meta-analysis reported that the global prevalence of PASC was higher in hospitalised than non-hospitalised patients (54% *versus* 34%), suggesting that a higher burden may be felt among the former [21]. A meta-analysis by Fernández-de-las-Peñas *et al.* [28] reported that the most common PASC symptoms among non-hospitalised patients were smell disturbance (∼20%), taste disturbance (∼18%) and dyspnoea (∼16%). Fatigue was not as commonly reported among non-hospitalised patients as observed among hospitalised patients. These and other studies demonstrate ways that select symptoms may differ in prevalence and pattern among hospitalised and non-hospitalised patients [21, 29, 30]. We further categorised studies according to the severity of COVID-19, but not enough data per severity status were available to stratify our results by severity. Future work should examine differences in PASC for patients with differing severity of SARS-CoV-2 infection, as well as for patients whose acute condition was managed in the community rather than in the hospital.

The findings of this and other work reflect that PASC is a complex, multisystem condition with overlapping clinical phenotypes.

Strengths and limitations

The SLR was designed and carried out in accordance with robust, systematic methodology and benefited from valuable clinician input from experts in infectious diseases. A large volume of moderate quality, peer-reviewed literature was identified for hospitalised patients with confirmed SARS-CoV-2 infection. Studies were identified from a diverse spread of geographies and limiting the meta-analysis to studies with 100 patients or higher increased the precision of the estimated prevalence of symptoms.

Similar to other meta-analyses of PASC symptoms [24, 31], several limitations were identified in this work and may limit the generalisability of the findings. All included studies collected data from the early phase of the pandemic and therefore are less representative of the current state of PASC. For example, the findings relate only to the ancestral strain of the SARS-CoV-2 virus rather than other variants and cannot account for the effects of vaccination. While no eligibility criteria were in place to specifically exclude studies with vaccinated patients, vaccines were not yet widely available at the time when the included studies were published, resulting in a lack of data on vaccinated populations. A recent SLR investigated the impact of vaccination on the risk of developing PASC and found a relatively small number of studies, with mixed results: some showed improvements following vaccination, while others showed no change or worsening [32]. Furthermore, the population was limited to hospitalised patients, whereas acute COVID-19 has largely become an outpatient disease [33]. In addition, in order to meet the urgent need for information on SARS-CoV-2, many early studies collected and published data very rapidly, which likely resulted in lower quality and contributed to high between-study heterogeneity, resulting in wide confidence intervals and high I^2-values. Along with between-study heterogeneity, Alkodaymi *et al.* [24] and many others have noted poor reporting of illness severity as a limitation of the PASC evidence base. Indeed, our work found that many studies used inconsistent definitions for levels of severity and limited availability of data per severity status precluded the stratification of results by severity. The lack of stratification further contributed to the level of heterogeneity of patient characteristics within the analyses, complicating the interpretation and generalisation of the pooled results. However, in our SLR the inclusion of only patients who were hospitalised helps to standardise this factor; patients would have been more likely to have illness severe enough to warrant hospitalisation. Patients who recovered well from acute illness may be less likely to remain enrolled in long follow-up studies, resulting in selection bias that may result in overestimation of PASC symptom frequency within general populations. The choice of symptoms measured in different studies and lack of consistent definitions or pooling of different outcomes may also impact the estimates. Measurement bias may also exist in the findings since few studies reported on PASC symptoms from ⩾8 to <12 months, limiting the strength of findings for this time interval. Additionally, although three time periods were evaluated, most studies only reported on one time-point and therefore the prevalence of symptoms could not be tracked across time periods for the same group of patients.

Questions for future research

Challenges in establishing a definition of PASC

There is currently no consensus on a definition of PASC [5]. Several challenges in defining PASC have also affected this study. First, the lack of well-defined, objective clinical criteria, such as laboratory tests, radiographic studies or other procedures, for patients who have PASC is a barrier to clinical diagnosis. Therefore, studies rely on subjective reports of symptoms, and the volume of reported symptoms, lack of

symptom clustering and heterogeneity in patient population characteristics (including pre-existing conditions and treatment received for acute infection) contribute to the variable presentations of PASC. However, primary research and meta-analyses of PASC symptoms including studies with COVID-19-negative comparator groups have mostly found significant associations between SARS-CoV-2 infection and long-term symptoms [21, 24, 25, 34, 35].

The pathogenic mechanisms underlying PASC have been an area of active research [36] and there is a growing body of literature supporting evidence of viral persistence [37–39]. While it could not be assessed in the current analysis, a useful future approach for defining PASC could involve connecting pathogenic mechanisms to clinical phenotypes, defined by multiple symptoms and test results from a combination of imaging and other diagnostic modalities.

Conclusions

This work has contributed to understanding the natural history and prevalence of PASC for previously hospitalised patients with SARS-CoV-2 infection up to 12 months after hospital discharge. A significant proportion of infected individuals have persistent symptoms for a long period after acute infection. Even in an era of SARS-CoV-2 vaccination and viral evolution, PASC continues to be reported in a substantial proportion of individuals, but lack of symptom patterns and biomarkers have been barriers to defining this clinical entity. Nonetheless, PASC poses a significant clinical, psychosocial and economic burden on society, underscoring the need for deeper clinical phenotyping and more pathogenesis studies, both of which will inform the definition of PASC while developing prevention and treatment strategies. As this study included data only from previously hospitalised patients, future analyses should consider both hospitalised and non-hospitalised patients to ensure that the results are more broadly generalisable to all infected individuals.

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