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REVIEW

Sequelae of COVID-19 among previously hospitalized patients up to 1 year after discharge: a systematic review and meta-analysis

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Abstract

Objective Although complications and clinical symptoms of COVID-19 have been elucidated, the prevalence of long-term sequelae of COVID-19 is less clear in previously hospitalized COVID-19 patients. This review and meta-analysis present the occurrence of different symptoms up to 1 year of follow-up for previously hospitalized patients.

Methods We performed a systematic review from PubMed and Web of Science using keywords such as "COVID-19", "SARS-CoV-2", "sequelae", "long-term effect" and included studies with at least 3-month of follow-up. Meta-analyses using random-effects models were performed to estimate the pooled prevalence for different sequelae. Subgroup analyses were conducted by different follow-up time, regions, age and ICU admission.

Results 72 articles were included in the meta-analyses after screening 11,620 articles, identifying a total of 167 sequelae related to COVID-19 from 88,769 patients. Commonly reported sequelae included fatigue (27.5%, 95% CI 22.4–33.3%, range 1.5–84.9%), somnipathy (20.1%, 95% CI 14.7–26.9%, range 1.2–64.8%), anxiety (18.0%, 95% CI 13.8–23.1%, range 0.6–47.8%), dyspnea (15.5%, 95% CI 11.3–20.9%, range 0.8–58.4%), PTSD (14.6%, 95% CI 11.3–18.7%, range 1.2–32.0%), hypomnesia (13.4%, 95% CI 8.4–20.7%, range 0.6–53.8%), arthralgia (12.9%, 95% CI 8.4–19.2%, range 0.0–47.8%), depression (12.7%, 95% CI 9.3–17.2%, range 0.6–37.5%), alopecia (11.2%, 95% CI 6.9–17.6%, range 0.0–47.0%) over 3–13.2 months of follow-up. The prevalence of most symptoms reduced after > 9 months of follow-up, but fatigue and somnipathy persisted in 26.2% and 15.1%, respectively, of the patients over a year. COVID-19 patients from Asia reported a lower prevalence than those from other regions.

Conclusions This review identified a wide spectrum of COVID-19 sequelae in previously hospitalized COVID-19 patients, with some symptoms persisting up to 1 year. Management and rehabilitation strategies targeting these symptoms may improve quality of life of recovered patients.

Keywords COVID-19 · Sequelae · Consequences · Post COVID-19 · Long-term · Meta-analysis

Introduction

Since its emergence in December 2019, SARS-CoV-2 has rapidly spread around the world, leading to > 480 million confirmed cases and > 6 million deaths as of March 2022 [1]. As more people have recovered from COVID-19, the long-term sequelae of the disease and its impact to the healthcare system have become an important consideration.

Evidence has shown that hospitalized COVID-19 patients would develop various complications, including pneumonia (75%), acute liver injury (19%), heart injury (7% to 17%), acute respiratory distress syndrome (15%), acute kidney injury (9%), acute heart failure, disturbance of consciousness, etc. [2] A noticeable portion of hospitalized patients would also show symptoms such as fever (70–90%),

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shortness of breath (53–80%), dry cough (60–86%), myalgia (15–44%), fatigue (38%), nausea/vomiting or diarrhea (15–39%), weakness (25%), headache, loss of taste, loss of smell, etc. [3] Although these complications and symptoms have been elucidated in hospitalized patients, their persistence after recovery has not been clearly described to assess how quality of life is affected among the recovered patients. Up to now, 12 meta-analyses studied the long-term sequelae with follow-up time > 3 months [4–15]. Only two of them stratified the prevalence of headache, myalgia, arthralgia, and chest pain among hospitalized patients by < 6 and > 6 months follow-up [9, 10]. However, none of them reported prevalences of a wide range of symptoms among previously hospitalized patients at different months of follow-up which showed the time trend [11]. Hospitalized patients are more likely to suffer from more severe post-COVID symptoms; hence there is a need to clarify their severity and persistence.

Here we carried out a systematic review and meta-analysis of sequelae of hospital discharged COVID-19 patients to identify all aftermaths of COVID-19, which can help to prevent and manage the long-term sequelae of the discharged COVID-19 patients. In our study we focused on previously hospitalized patients who had more severe symptoms and more sequelae, and also focused on articles with at least a 3-month follow-up time, to study sequelae which likely have a longer impact on their quality of life. Our study will also provide pooled estimates at 12 months follow-up. Such information would inform health management strategies of COVID-19 patients by identifying sequelae that may persistently affect the quality of life.

Methods

Search strategy and eligibility criteria

This systematic review and meta-analysis followed the PRISMA guidelines [16]. The protocol was registered in PROSPERO (register no: CRD42022314319). Studies about long-term sequelae of COVID-19 were identified through PubMed and Web of Science for publications up to 1 March 2022 Search queries included terms such as "COVID-19", "SARS-CoV-2", "2019-nCoV", "sequelae", "long-term effect", "long-term consequence", "long-term manifestations", "persistent effect", "persistent symptom", "persistent manifestations", "post COVID-19 effect", "post COVID-19 symptom", "post COVID-19 manifestations" and "post COVID-19 syndrome" (Appendix 1). Reference lists of systematic reviews were also reviewed. We included studies published in English.

The eligibility criteria were as follows:(1) study designs included cohort studies, case–control studies, and cross-sectional studies with a clear follow-up duration.; (2) patients should be hospital discharged adult patients aged 18 years or above representative of the general population without any age restriction, with a pathologically confirmed COVID-19 infection; (3) patients should be confirmed before 2022 to exclude patients infected with the omicron variant which may have a different symptom profile (4). Outcomes were defined as all clinical symptoms after at least 90 days after discharge, admission, diagnosis or symptom onset, consistent with case definition of post COVID-19 condition by the World Health Organization [17]. Sequelae of COVID-19 included respiratory, cardiovascular, psychosocial, neurological, dermatological, digestive, endocrinological symptoms and other symptoms. Studies reporting serological, immunological results or CT scores only were excluded. (5) Sample size > 100.

Data extraction and quality assessment

Data Extraction and Quality Assessment were conducted by two independent reviewers (TY & XL). Any disagreement was solved by a senior author (EHYL). Extracted data included the first author, year of publication, sample size, disease severity, average follow-up period, the average age of participants, and clinical symptoms defined before.

Study quality was evaluated by using the Newcastle–Ottawa Scale (NOS) [18]. Studies with 7–9 stars were perceived as high quality and studies with < 4 stars were perceived as poor quality. We assessed quality in selection strategies (representativeness of the exposed cohort, ascertainment of exposure, etc.), comparability, and outcome (outcome assessment, follow-up rate, etc.).

Statistical analysis

For those sequelae reported in two or more studies, the pooled prevalence and 95% CI were estimated in a meta-analysis using a random-effects model (the variance component was estimated using the DerSimonian–Laird estimator) and inverse variance methods following logit transformation [19]. For those sequelae reported only in a single study, the prevalence was estimated by directly dividing the number of cases who shown symptoms by the total sample size, and the 95% CI was estimated by using the Clopper-Pearson interval. Boxplots, median and interquartile ranges (IQR) were present for sequelae reported by ten or more studies.

The chi-square-based Cochran's Q test and Higgins (I^2) statistics were used to assess the heterogeneity of studies included in the meta-analysis. The significance level of Cochran's Q test was 0.05. Studies were regarded as having low, moderate and high heterogeneity with $I^2 = <30\%$, 30–60% and > 60%, respectively. Subgroup analysis was conducted for those meta-analyses which included 15 or

more studies, by different follow-up duration, regions, ICU admission and age. Meta-regression was used to test whether the difference of estimates between subgroups is significant. The pooled follow-up duration was weighted by sample size of each study. All statistical analyses were conducted in R version 4.0.3 (R Development Core Team).

Results

Study characteristics

A total of 11,620 studies were identified from PubMed and Web of Science, and one study was identified from other systematic reviews (Fig. 1). After removing 1301 duplicates, 10,320 articles were screened against title and abstract, and 10,062 articles not meeting the eligibility criteria were excluded. Finally, a total of 72 articles were included in the meta-analysis by screening the full texts of 256 articles: 19 articles did not have clinical symptoms as outcomes; 35 articles had a less than 3-month follow-up time; 40 articles included less than 100 participants; 70 articles did not only include hospitalized patients; 4 articles did not report follow-up time; 3 articles did not report prevalence in sequelae; 13 duplicate publications were further identified.

All included articles were published between 2020 and 2022. Of the 72 studies included in our analysis, 15 studies were from China, 11 each from Italy and Spain, 5 from England, 4 from France, 3 each from America and Mexico, 2 each from India, Germany, Switzerland and Belgium, 1 each from Iran, Australia, Egypt, Brazil, Peru, Turkey, Pakistan, Singapore, Austria, Kingdom of Saudi Arabia, Denmark and Netherlands (Table 1). All studies were observational studies: 62 non-controlled cohort studies, 5 controlled cohort studies, 4 cross-sectional studies and 1 case–control study. Data from the control groups (non COVID-19 cases) were not included in our analysis. One article conducted two independent telephone and outpatient follow-ups [35]. The two surveys reported different sequelae, and hence were regarded as two independent studies and included in the meta-analysis, while data on cough was included from the telephone follow-up only. Four articles which included one same cohort were included in the meta-analysis as four independent studies as they reported different symptoms [21–24]. The average follow-up time ranged from 90 days to 13.2 months and the size of follow-up cohorts ranged from 101 to 47,780. Only patients hospitalized for COVID-19 were included (Fig. 2).

The quality of studies was assessed by NOS and no articles were rated as poor quality (Appendix 2). Only

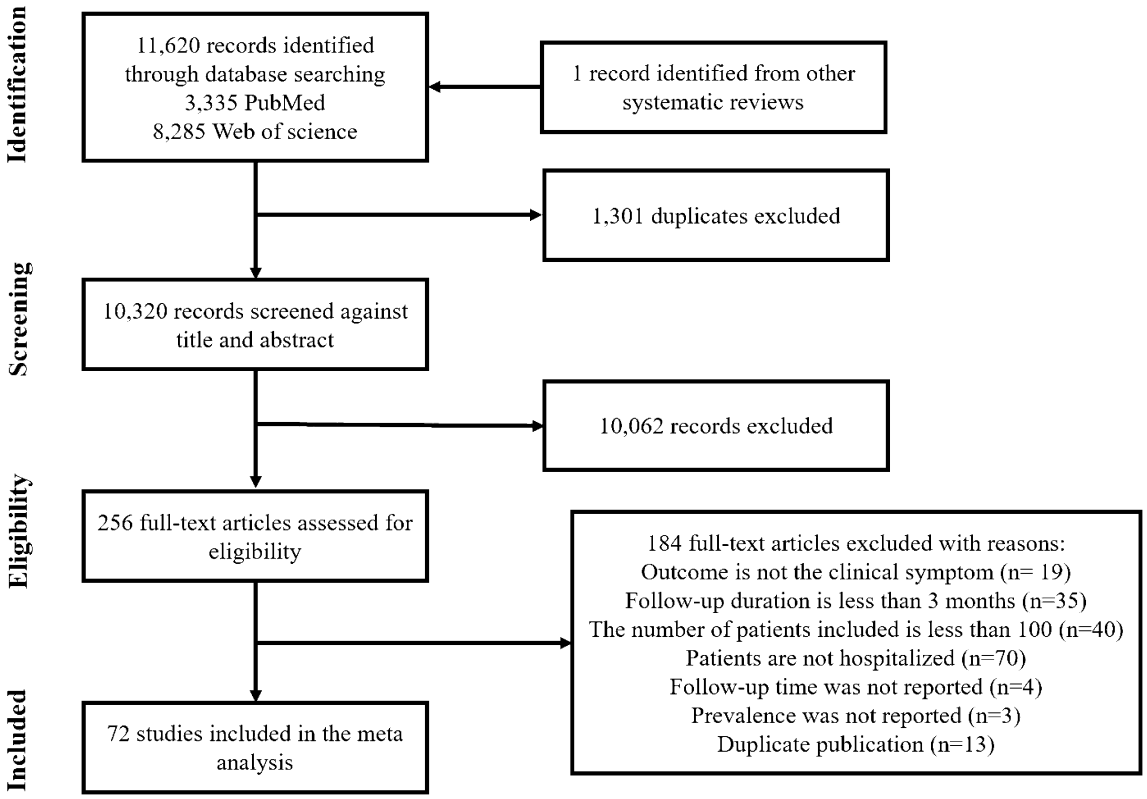

Fig. 1 Flow-chart for the literature selection process

Table 1 General characteristics of studies included in the meta-analysis

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Xiong et al. [20] (2020)	Wuhan, China	538	General, severe, critical	Median (IQR): 97.0 (95.0–102.0) days	Median (IQR): 52.0 (41.0–62.0) Male 46%	Physical decline/fatigue, sweating, myalgia, arthralgia, chills, limb oedema, dizziness, post activity polypnea, nonmotor polypnea, chest distress, chest pain, cough, sputum, sore throat, resting heart rate increase, discontinuous flushing, newly diagnosed hypertension, somnipathy, depression, anxiety, dysphoria, feelings of inferiority, alopecia	7
Fernández-de-las-Peñas et al. [21–24], (2021, 2022)	Madrid, Spain	1969	Hospitalized ICU 7%	11.2 ± 0.5 months	61 ± 16 Male 54%	Cough, chest pain, dyspnea, and fatigue	6
				8.4 ± 1.5 months		Loss memory, skin rashes, brain fog, attention disorders, palpitations, gastrointestinal disorders, ocular/vision disorders, anosmia, ageusia, sore throat, diarrhea, voice problems, musculoskeletal pain	
				Mean (range): 13.2 (11–15) months		Anxiety, depression, poor sleep quality	
Bellan et al. [25], (2021)	Novara, Italy	200	Hospitalized ICU 12%	12 months	Median (IQR): 62 (51–71) Male 61%	Fever, cough, dyspnea, ageusia, anosmia, diarrhea, arthralgia/myalgia, chest pain, sore throat, alopecia, fatigue	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Romero-Duarte et al. [26], (2021)	Spain	797	Hospitalized ICU 11%	6 months	63 ± 14.4 Male 54%	Fever, fatigue, muscle weakness, musculoskeletal pain, general malaise, oedema, pressure ulcers, dyspnea, rib pain, thoracic pain, persistent cough, persistent pharyngeal symptoms, icu-related polyneuropathy, headache, paresthesia, movement disturbances, disorientation or confusion, persistent anosmia or dysgeusia, depressive symptoms, anxiety symptoms, sleep disturbances, thrombotic manifestations, pruritus, alopecia, exanthema, eczema, renal insufficiency de novo, glycaemia uncontrol, vertigo symptoms, otoacoustic symptoms, diarrhea, constipation, vomiting, abdominal pain, anorexia, hypotension or syncope, arrythmia or palpitations, urinary tract infection, pneumonia, mycosis	6
Simani et al. [27], (2021)	Iran	120	Hospitalized	6 months after infection	54.62 ± 16.94 Male 67%	Fatigue, post-traumatic stress disorder (PTSD)	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Mei et al. [28], (2021)	Wuhan, China	3677	Mild, Severe, Critical	Median (IQR): 144 (135–157) days	Median (IQR): 59 (47–68) Male 46%	Shortness of breath, cough/sputum, pharyngitis/foreign body feeling, dyspnea, pulmonary fibrosis, lung damage, bronchitis, COPD, hemoptysis, chest pain/tightness, palpitation, cardiac disease, tachycardia, angina pectoris, heart attack, insomnia, joint pain/back pain/lumbago, fatigue, headache/dizziness/poor memory, change of taste and smell, myalgia, impaired vision, leg numbness/finger stiffness, neuralgia, paralysis, tinnitus, confusion, coma, cerebral infarction, hair loss, bitter/dryness in mouth, high blood sugar, diabetes, gastrointestinal complaints/poor appetite, diarrhea, constipation, emesis, hidrosis, erythra, allergy, hepatic insufficiency, edema, antiadoncus, hypertension, kidney insufficiency, reduction of physical strength, dryness/excessive secretion in eye	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Qu et al. [29] (2021)	China	540	Mild, moderate, severe	3 months	Median (IQR): 47.5 (37.0–57.0) Male 50%	Fatigue, cough, sputum, dyspnea, diarrhea, shortness of breath, joint pain, dysbasia, palpitations	4
Shang et al. [30], (2021)	Wuhan, China	796	Severe, critical ICU 38%	6 months	Median (IQR): 62.0 (51.0–69.0) Male 51%	Cough, throat itching, shortness of breath, chest pains, dizziness/ headache, muscle joint pain, back-ache, fatigue, sleep disorder, hypomnesia, hair loss, sweat, new hypertension	4
Suárez-Robles et al. [31], (2021)	Spain	134	Hospitalized ICU 2%	90 days	58.53 ± 18 Male 46%	Fatigue, dyspnea, loss of weight, loss of appetite, cough, anosmia, headaches, arthritis, palpitations, dysgeusia, general malaise, dysphonia, sensitivity disorders, sputum, walking disturbances	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Huang et al. [32], (2021)	Wuhan, China	1733	Hospitalized ICU 4%	Median (IQR): 153.0 (146.0–160.0) days	Median (IQR): 57.0 (47.0–65.0) Male 52%	Fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, diarrhea or vomiting, chest pain, sore throat or difficult to swallow, skin rash, myalgia, headache, low grade fever, anxiety or depression, problems with walking around, problems with washing or dishing, problems with usual activity, pain or discomfort	5
Tarsitani et al. [33], (2021)	Rome, Italy	115	Hospitalized	3 months	Median (IQR): 57 (48–66) Male 54%	PTSD	5
Froidure et al. [34], (2021)	Belgium	126	Severe, critical ICU 22%	Median (IQR): 95 (86–107) days	Median (IQR): 60 (53–68) Male 59%	Fatigue, dyspnea, chronic dry cough, chest oppression	5
Morin et al. [35], (2021)	France	478 (telephone assessment)	Hospitalized ICU 30%	Median (IQR): 113 (94–128) days	60.9 ± 16.1 Male 58%	Dyspnea, cough, chest discomfort/pain, fatigue, anorexia, weight loss, anosmia, headaches, paresthesia, memory difficulties, mental slowness, concentration problems	5
		177 (in-person outpatient)	Hospitalized ICU 55%	Median (IQR): 125 (107–144) days	56.9 ± 13.2 Male 62%	Persistent cough, cognitive complaint, cognitive impairment, anxiety, depression, insomnia, PTSD	
Ayoubkhani et al. [36], (2021)	England	47,780	Hospitalized ICU 10%	140 ± 50 days	64.5 ± 19.2 Male 55%	Diabetes (new onset)	7

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Sykes et al. [37], (2021)	England	134	Hospitalized ICU 20%	Median (IQR): 113 (46–167)	Median (IQR): 58 (25–89) Male 66%	Breathlessness, myalgia, anxiety, extreme fatigue, low mood, memory impairment, sleep disturbance, cough, attention deficit, pleuritic chest pain, sore throat, fever, anosmia, cognitive impairment, taste deficiency, rash	5
Arnold et al. [38], (2020)	England	110	Mild, moderate, severe	Median (IQR): 90 (80–97)	Median (IQR): 60 (46–73) Male 62%	Fever, cough, breathlessness, anosmia, fatigue, myalgia, headache, chest pain, arthralgia, diarrhea, abdominal pain, nausea, insomnia	6
Garrigues et al. [39], (2020)	France	120	Hospitalized ICU 20%	110.9 ± 11.1	63.2 ± 15.7 Male 63%	Cough, chest pain, fatigue, dyspnea, ageusia, anosmia, hair loss, attention disorder, memory loss, sleep disorder	5
Caruso et al. [40], (2021)	Rome, Italy	118	Moderate, severe	6 months	65 ± 12 Male 47%	Dyspnea, cough, fever, fatigue, olfactory dysfunction, gustatory dysfunction, hair loss, decline of visual acuity	5
Castro et al. [41], (2021)	Boston, America	5571	Hospitalized ICU 13%	120 days	Median (IQR): 63 (50–76) Male 53%	Fatigue, anxiety, sleep disruption, headache, impaired cognition, anosmia, memory, language disturbance, hallucinations	7

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Darcis et al. [42], (2021)	Belgium	101	Moderate, severe ICU 26%	3 months	60.5 ± 13.9 Male 63%	Exertional dyspnea, fatigue, dry cough, chest pain, headaches, loss of appetite, myalgia, dyspnea at rest, anosmia, ageusia, rhinorrhea, paresthesia/dysesthesias, memory impairment, diarrhea, productive cough, pharyngeal pain, confusion, nauseas, vomiting, fever	4
González-Hermosillo et al. [43], (2021)	Mexico	130	Moderate, severe	6 months	51 ± 14 Male 65%	Fatigue, resting dyspnea, dyspnea on effort, concentration impairment, short-term memory loss, inability to focus vision, light sensitivity, anosmia, ageusia, tingling, disturbance of sleep, unrefreshing sleep, postural dizziness, lightheadedness when prolonged standing, chest pain, tachycardia, change pattern of sweating, intolerance to temperature, stomach bloated after meals, abdominal pain, diarrhea, constipation, nausea, urinary frequency, difficulty emptying bladder, difficulty with sexual function, headache, muscle pain, joint pain, anxiety, depression	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Gramaglia et al. [44], (2021)	Novara, Italy	237	Severe ICU 12%	4 months	Median (IQR): 61 (50–71) Male 60%	Anxiety, depressive symptoms, changes in appetite and sleep patterns	5
Bozzetti et al. [45], (2021)	Verona, Italy	107	Hospitalized	6 months	Median (range): 63 (32–90) Male 65%	Hyposmia, hypogeusia, vertigo, fatigue, headache, myalgia, impaired memory	5
Maestre-Muñiz et al. [46], (2021)	Spain	445	Severe, critical	12 months	71.5 ± 14.3 Male 45%	Breathlessness, tiredness, loss of taste, loss of smell, hair loss, memory lapses, sleep difficulties, muscular weakness, headache, myalgia, low-grade fever, mood changes, gastrointestinal symptoms, chest pain, skin rash, palpitations, concentration difficulties, sore throat	5
Vincent et al. [47], (2021)	Switzerland	108	Hospitalized ICU 17%	90 days	58.4 ± 15.8 Male 59.0%	Anxiety, depression, PTSD	5
Sun et al. [48], (2021)	Wuhan, China	932	Non-severe, severe	3 months	Median (IQR): 58 (48–67) Male 40%	Cough, fatigue, dysgeusia, dysosmia, anorexia, dyspnea	5
Vlake et al. [49] (2021)	Netherlands	116	Hospitalized ICU 14%	3 months	Median (95% range): 61 (35–85) Male 64%	PTSD, anxiety, depression	7

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Huang et al. [50] (2021)	Wuhan, China	1276	Hospitalized ICU 4%	Median (IQR): 185.0 (175.0–198.0) days Median (IQR): 349.0 (337.0–361.0) days	Median (IQR): 59.0 (49.0–67.0) Male 53%	Fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, diarrhea or vomiting, chest pain, sore throat or difficult to swallow, skin rash, myalgia, headache, anxiety or depression, problems with walking around, problems with washing or dishing, problems with usual activity, pain or discomfort	7
Li et al. [51], (2021)	Shenzhen, China	147	Hospitalized	90 days	Not reported Male 49%	Dyspnea, exercise limitation, cough, fatigue, chest tightness, hyposmia	5
Sibila et al. [52], (2021)	Spain	172	Moderate, severe ICU 43%	3 months	56.1 ± 19.8 Male 57%	Dyspnea, cough, joint pain, diarrhea, sputum production, headache, chest pain	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Liu et al. [53], (2021)	Wuhan, China	594	Moderate, severe, critical 11%	12 months	Median (IQR): 63 (53–68) Male 46%	Cough, fatigue, myalgia, dyspnea, chest tightness, chest pain, heart palpitations, sputum production, diarrhea, nausea, loss of appetite, abdominal pain, headache, dizziness, night sweats, insomnia, numbness in limbs, joint pain, memory loss, decreases taste, vision loss, hearing loss, smell loss, hair loss, edema, backache, skin pruritus, mouth and pharynx discomfort, thrombosis	5
Lombardo et al. [54], (2021)	Milan, Italy	189	Hospitalized ICU 4%	12 months	Median (IQR): 57 (47–68) Male 52%	Fatigue and weakness, muscle and joint pain, sleep disorders, respiratory disorders, neurological and cognitive impairments, sensory alterations, movement impairments, gastrointestinal symptoms	5
Maestrini et al. [55], (2021)	Rome, Italy	118	Hospitalized ICU 29%	347 ± 10 days	Median (IQR): 70.5 (56.2–80.0) Male 57%	Fatigue, dyspnea, impaired memory, palpitations, arthromyalgia, cutaneous manifestations, chest pain, ageusia, gastrointestinal symptoms, ocular manifestations	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Sigfrid et al. [56], (2021)	England	327	Hospitalized ICU 40%	Median (IQR): 222 (189–269)	Median (IQR): 59.7 (51.7–67.7) Male 59%	Fatigue, shortness of breath, problems sleeping, headache, limb weakness, joint pain or swelling, persistent muscle pain, dizziness/light headedness, problems with balance, swollen ankle, palpitations, constipation, problems seeing, diarrhea, stomach pain, chest pains, persistent cough, erectile dysfunction, pain on breathing, loss of smell, persistent fevers, loss of taste, nausea/vomiting, loss of appetite, problems swallowing, skin rash, weight loss, problems passing urine, hemiplegia/paraesthesiae, toe lesions	4
Ahmed et al. [57], (2021)	Egypt	182	Non-severe, severe, critical	6 months	46.5 ± 17.4 Male 46%	Somatization, obsessive–compulsive, interpersonal sensibility, depression, anxiety, anger-hostility, phobic-anxiety, paranoid ideation, psychosis	4
Anjana et al. [58], (2021)	India	154	Mild, moderate, severe	3 months	31.5 ± 18.4 Male 37%	Fatigue, headache, myalgia, exertional dyspnea, joint pain, orthopnea, dry cough	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Bai et al. [59], (2022)	Italy	377	Hospitalized	Median (IQR): 102 (86—126) days	Median (IQR): 57 (49–68) Male 64%	Anosmia, dysgeusia, fever, joint pain or myalgia, rest dyspnea, exertional dyspnea, fatigue, brain fog, PTSD, depression, anxiety	4
Chen et al. [60], (2021)	China	715	Mild, moderate, severe, critical ICU 6%	Median (IQR): 225.0 (222.0–228.0) days	Median (IQR): 69 (67–73) Male 51%	Fatigue, cough, sputum, exertional or resting dyspnea, chest tightness, palpitation, orthopnea, lower limb edema	4
Damiano et al. [61], (2021)	Brazil	425	Hospitalized ICU 50%	207 ± 20.4 days	55.7 ± 14.2 Male 52%	Anxiety, depression, PTSD, specific phobia with COVID, obsessive compulsive disorder, delusions, hallucinations	4
Eloy et al. [62], (2021)	French	324	Hospitalized ICU 19%	185 days 95% CI [182–191]	Median (IQR): 61 (52–69) Male 63%	Fatigue, myalgia, headache, cough, nasal obstruction, sore throat, feverishness, joint pain, dyspnea, anosmia, ageusia, depression, anxiety	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Evans et al. [63], (2021)	UK	1077	Mild, moderate, severe, critical	Median (IQR): 5.9 (4.9–6.5) days	57.9 ± 13.0 Male 64%	Anxiety, depression, PTSD, cognitive impairment, aching in your muscles, physical slowing down, slowing down in your thinking, joint pain or swelling, limb weakness, difficulty with concentration, short term memory loss, headache, tingling feeling/pins and needles, confusion/fuzzy head, dizziness or lightheaded, chest tightness, problems with balance, altered personality/behavior, chest pain, palpitations, leg/ankle swelling, skin rash, diarrhea, pain on breathing, weight loss, tremor/shakiness, constipation, erectile dysfunction, loss of sense of smell, can't fully move or control movement, abdominal pain, loss of control of passing urine, loss of appetite, loss of taste, can't move and/or feel one side of your body or face	4
Gamberini et al. [64] (2021)	Italy	178	Mild, moderate, severe ICU 100%	12 months	Median (IQR): 64 (55–70) Male 73%	Cough, arthromialgia, palpitations, dyspnea	4
Garcia-Abellan et al. [65], (2021)	Spain	146	Hospitalized	6 months	Median (IQR): 64 (54–76) Male 60%	Fatigue, myalgia, dyspnea, cough, nasal congestion	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Ghosn et al. [66], (2021)	French	1137	Hospitalized ICU 29%	Median (IQR): 194 (188—205) days	Median (IQR): 61 (51–71) Male 63%	Fatigue, dyspnea, joint pain, myalgia, headache, rhinorrhea, cough, sore throat, ageusia, anosmia	4
Hodgson et al. [67], (2021)	Australia	160	ICU 100%	6 months	Median (IQR): 62 (55–71) Male 61%	Shortness of breath, loss of strength, fatigue, persistent cough, loss of taste, loss of smell, headache, persistent chest pain, palpitations, myalgia/arthralgia, loss of sensation, hair loss, weight loss, anxiety, depression, ptsd, cognitive dysfunction	4
Horwitz et al. [68], (2021)	USA	126	Hospitalized ICU45%	6 months	Median (IQR): 62 (52–68) Male 60%	Memory changes, brain fog, difficulty sleeping, dizziness, headache, ringing in ears, altered/loss of smell, altered/loss of taste, fatigue, weakness, muscle/body ache, joint pain, tremors, rash, palpitations, nausea, diarrhea	5
Huang et al. [69], (2021)	China	574	Hospitalized	194.0 ± 15.3 days	57.7 ± 11.4 Male 39%	Sweating, myalgia or joint pain, chills, shortness of breath, chest distress, chest pain, cough, sputum. decreased qppetite, abdominal distention, diarrhea, forgetfulness, hypopsia, hearing losing, sleep difficulty, PTSD	4
Huarcaya-Victoria et al. [70], (2021)	Peru	318	Mild, moderate, severe, critical	102.1 days (95% CI, 98.3–106.0)	Median (IQR): 53.1 (51.8–54.4) Male 61%	Depression, anxiety, somatic symptom, PTSD	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Karaarslan et al. [71], (2021)	Turkey	285	Hospitalized	6 months	52.3 ± 12.1 Male 60%	Fatigue, myalgia, joint pain, back pain, neck pain, fever, cough, lack of appetite, dyspnea, diarrhea, sore throat, headache, dizziness, absence of taste, absence of smell, sweat, hair loss	5
Boglione et al. [72], (2021)	Italy	449	Hospitalized ICU 14%	Median (IQR): 178.5 (165.5 – 211.5) days	Median (IQR): 65.0 (56.0–75.5) Male 78%	Fatigue, myalgias/ arthralgias, fever, headache, dyspnea, cough, chest pain, brain fog, dizziness, memory impairment, anosmia, ageusia, peripheral neuropathy, tachyarrhytmias, pericarditis/myocarditis, sleeping disorders, PTSD, anxiety, depression, psychosis, behavior disorder, weight loss, hair loss, diabetes, hypertension, psoriasis, venous thromboembolism, thyroid dysfunction	5
Chand et al. [73], (2021)	USA	103	Hospitalized ICU 100%	Median (IQR): 216.5 (200–234.5) days	Median (IQR): 54.0 (46.0–61.0) Male 52%	Cough, shortness of breath, anosmia, PTSD, depression	5
Kumar et al. [74], (2021)	Pakistan	817	Hospitalized	90 days	41 ± 9 Male 63%	Insomnia, altered sense of smell, headache, altered sense of taste, altered vision, dizziness, stroke	6
Mei et al. [75], (2022)	Tianjin, China	144	Hospitalized	3 months	Not reported Male 50%	PTSD	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Nesan et al. [76], (2021)	India	1354	Mild, moderate, severe ICU 2%	3 months	Not reported Male 73%	Tiredness/fatigue, stress and anxiety, change in mood, myalgia, loss of appetite, sleep disturbances, muscular weakness, constipation, loss of taste, nausea and vomiting, loss of smell, headache, abdominal discomfort, breathing difficulty, confusion, numbness, sore throat, chest pain, palpitations, burning and pricking pain sensation on body, reduced urine output	5
Ong et al. [77], (2021)	Singapore	183	Mild, moderate, severe ICU 18%	180 days	Median (IQR): 44 (33–56) Male 75%	Cough, dyspnea, sputum production, chest pain, myalgia, fatigue, joint pain, memory loss, limb numbness, limb weakness, diarrhea, headache, fever, sweats, abdominal pain, anosmia/ageusia, blocked nose, rhinorrhea, sore throat	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Rass et al. [78], (2021)	Austria	103	Moderate, severe ICU 30%	3 months	Median (IQR): 56 (48–68) Male 70%	Hyposmia, anosmia, hypogeusia, new cephalea, vertigo/dizziness/lightheadedness, neck stiffness, myalgia, decreased consciousness, dysarthria, aphasia, positive frontal release signs, blurring vision, oculomotor nerve palsy, facial palsy, dysphagia, bradykinesia, dystonia, chorea, myoclonus/jerks, asterixis, dysmetria, tremors, abnormal muscle tone, muscle atrophy, decreased/disturbed sensibility, paresis, babinski sign, gait abnormality, PTSD, depression, anxiety, persistent fatigue, sleep disturbances, forgetfulness, trouble concentrating, difficulty thinking	4
Righi et al. [79], (2022)	Italy	235	Mild, moderate, severe	9 months	Median (IQR): 61.9 (54–71) Male 69%	Cough, Breathlessness, Fatigue, Anosmia, Dysgeusia, Myalgia, Diarrhoea	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Rivera-Izquierdo et al. [80], (2022)	Spain	453	Hospitalized ICU 11%	12 months	61.2 ± 14.3 Male 57%	Fatigue, Muscle Weakness, Muscle or Joint Pain, Dyspnoea, Chest Pain, Pharyngeal Symptoms, Headache, Sensitivity Disorders, Movement Disorders, Confusion, Memory Loss, Depressive Symptoms, Anxiety Symptoms, Sleep Disturbances, Thrombotic Events, Diarrhoea, Constipation, Abdominal Pain	6
Sibila et al. [81], (2022)	Spain	215	Hospitalized ICU 44%	6 months	61.4 ± 11.8 Male 61%	Dyspnea, fatigue, cough, joint pain, diarrhea, sputum production, headache, chest pain	5
Staudt et al. [82], (2022)	Germany	101	Hospitalized ICU 20%	10 months	Median (IQR): 60.0 (50.8–66.0) Male 58%	Shortness of breath, voice alteration, impaired taste, excessive sweating, fatigue, sleeping disorder, cognitive impairment, disturbed balance, hair loss	4
Tessitore et al. [83], (2021)	Switzerland	165	Hospitalized ICU 16%	12 months	Median (IQR): 58 (50–69) Male 62%	Fever, dyspnea, cough, myalgia, tiredness/fatigue, headache, expectorations, altered smell or taste sensation, runny nose, depression	5
Tleyjeh et al. [84], (2022)	Kingdom of Saudi Arabia	222	Hospitalized	Median (IQR): 122 (109—158) days	Not reported	Dyspnea, fatigue	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Torres-Ruiz et al. [85], (2021)	Mexico	103	Hospitalized	107.8 days	Median (IQR): 50 (41–58) Male 46%	Confusion, fatigue, cough, dyspnea, headache, wheezing, fever, joint pain, increased joint size, inability to dress, inability to walk, inability to open jars, chest pain, orthopnea, peripheral oedema, myalgia, dermatosis, paresthesia, decreased visual acuity, decreased concentration, memory decline, alopecia, back pain, anosmia, dysgeusia	5
Vejen et al. [86], (2022)	Denmark	128	Hospitalized	Median (IQR): 140 (119–157) days	Median (IQR): 64.5 (51.0–75.0) Male 58%	Fatigue, dyspnea, cough, memory loss, chest or muscle pain, phlegm, attention loss, loss of smell/taste	4
Wang et al. [87], (2021)	China	199	Asymptomatic, mild, moderate, severe, critical ICU 3%	6 months	42.7 Male 47%	PTSD	4

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Wong-Chew et al. [88], (2022)	Mexico	4670	Hospitalized ICU 5%	90 days	Median (IQR): 48 (37–58) Male 50%	Alopecia, fatigue, insomnia, headache, desire to cry, sadness, back pain, anguish, anhedonia, anger, joint pain, paraesthesia, pharyngodynia, lack of concentration, lower back pain, rhinorrhea, hypo- or polyphagia, muscle pain, loss of memory, sweating, lethargy, cough, chest pain, difficulty breathing, dizziness, anxiety, globus, tearing, bradyphrenia, slow walking, general discomfort, anosmia, nausea, diarrhea, rash, weight loss, increase respiration, dysgeusia, chills, tremors, abdominal pain, disorientation, spots on the skin, fever, cyanosis	4
Zhang et al. [89], (2021)	China	2433	Non-severe, severe ICU 2%	Median (IQR): 364.0 (357.0–371.0) days	Median (IQR): 60.0 (49.0–68.0) Male 50%	Fatigue, sweating, chest tightness, anxiety, myalgia, palpitation, cough, shortness of breath, dizziness, expectoration, dyspnea, headache, edema of lower limbs, taste change, impaired sense of smell, sore throat, anorexia, diarrhea, hemoptysis, nausea, chill, vomiting, fever	5

Table 1 (continued)

Study, (year)	City/country	Sample size	Disease severity	Mean follow-up period[a]	Mean age (years)/male (%)	Clinical symptoms	NOS score
Zhou et al. [90], (2021)	China	120	Non-severe, severe	Median (IQR): 314.5 (296–338) days	51.6 ± 10.8 Male 41%	Shortness of breath, fatigue, sleep difficulties, joint pain, loss of smell, constipation, diarrhea, anxiety, depression	4
Zuschlag et al. [91], (2022)	Germany	162	Asymptomatic, mild, moderate, severe, critical ICU 7%	12 months	65.1 Male 54%	Fatigue, cognitive dysfunction, shortness of breath, pain in muscles and joints, headache, cough, altered smell/taste, posttraumatic stress symptoms, sleep problems, anxiety, depression, disturbance of sensitivity in one leg, loss of appetite and weight, nausea, pain in hands and feet, pruritus, thoracic burning, vertigo, weakness of forefoot	4

[a]Follow up after hospital discharge (mean ± SD) if not specified

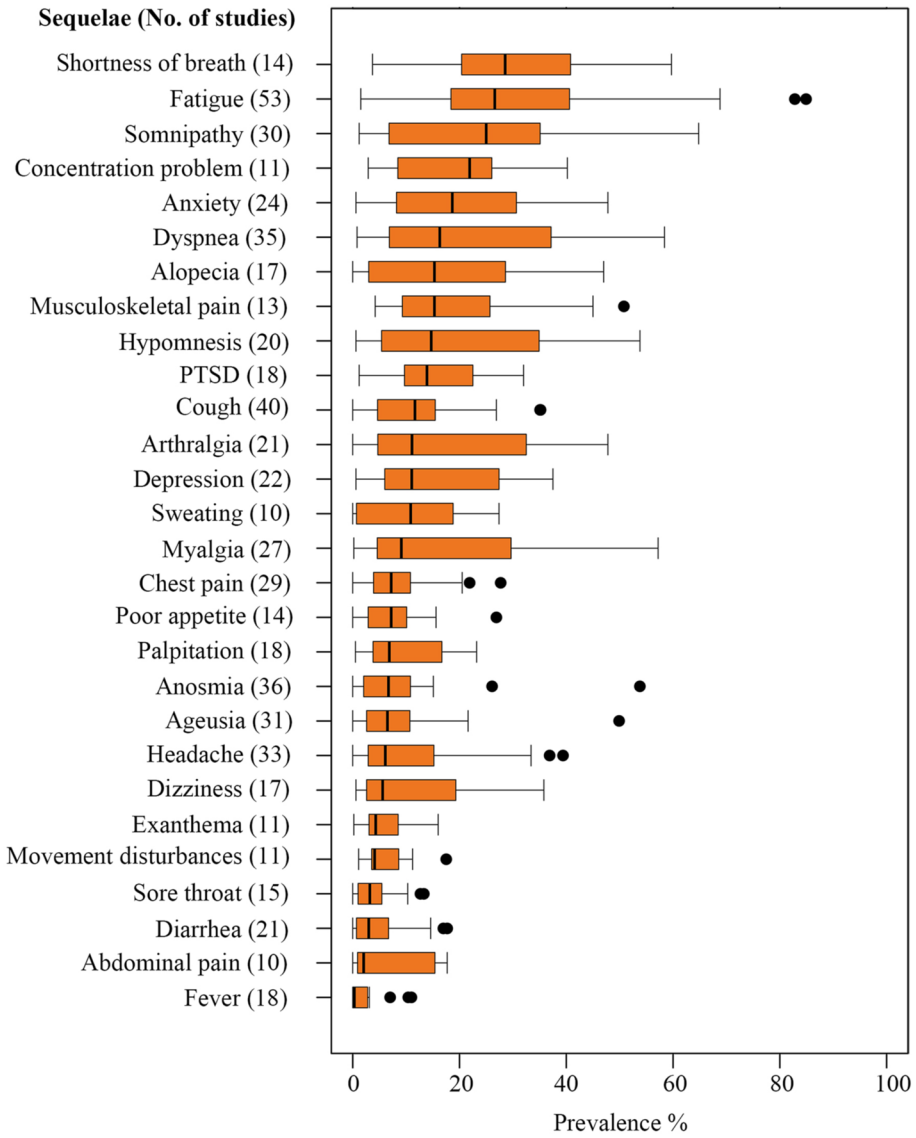

Fig. 2 The boxplots for the prevalence of post-COVID sequelae among previously hospitalized patients with ten or more studies

five studies (6.9%) were rated high quality. The majority of studies were non-controlled cohort studies and did not meet the standard of comparability.

Meta-analysis of prevalence of sequelae related to COVID-19

A total of 167 sequelae related to COVID-19 were identified in the systematic review, including respiratory/lung function, cardiovascular, psychosocial, neurological, dermatological, digestive system, endocrinological system and other sequelae. 92 sequelae were reported by two or more studies and their pooled prevalence was presented (Table 2). These sequelae were reported during 90 days to 13.2 months of follow-up.

Respiratory/lung function sequelae

The most common sequelae in the respiratory system were shortness of breath (14 studies) with a prevalence of 25.6% (95% CI 15.1–39.8%, range 3.7–59.7%) and post-activity polypnea (3 study) with the prevalence of 29.8% (95% CI 20.5–41.3%, range 21.4–42.3%), followed by dyspnea (35 studies), pain on breathing (2 studies), chest distress (8 studies), cough (40 studies), with prevalence of 15.5% (95% CI 11.3–20.9%, range 0.8–58.4%), 13.9% (95% CI 11.9–16.2%, range 13.1–14.3), 10.8% (95% CI 6.8–16.8%, range 3.2–29.6%) and 9.8% (95% CI 7.8–12.4%, range 0.0–35.2%), respectively.

Table 2 167 sequelae in patients who recovered from COVID-19

Symptom	Number of studies	Prevalence (%)[a]	95 CI (%)	Range (%)	I^2 (%)	P_H
Respiratory/lung function sequelae						
Post–activity polypnea	3	29.8	[20.5–41.3]	(21.4–42.3)	91.7	< 0.001
Shortness of breath	14	25.6	[15.1–39.8]	(3.7–59.7)	98.9	< 0.001
Dyspnea	35	15.5	[11.3–20.9]	(0.8–58.4)	98.4	< 0.001
Pain on breathing	2	13.9	[11.9–16.2]	(13.1–14.3)	0.0	0.628
Chest distress	8	10.8	[6.8.–16.8]	(3.2–29.6)	97.2	< 0.001
Cough	40	9.8	[7.8–12.4]	(0.0–35.2)	95.60	< 0.001
Sputum production	3	9.3	[3.2–24.1]	(3.3–22.7)	91.4	< 0.001
Nonmotor polypnea	3	7.9	[3.8–15.7]	(4.6–16.2)	90.0	< 0.001
Chest pain	29	6.9	[5.3–9.0]	(0.0–27.7)	94.9	< 0.001
Globus	1	5.9	[4.5–7.6]	–	–	–
Rib pain	1	4.5	[3.3–6.2]	–	–	–
Sputum	9	4.2	[2.8–6.2]	(1.0–10.0)	87.8	< 0.001
Sore throat	15	3.4	[2.2–5.3]	(0.0–13.3)	94.6	< 0.001
Swallowing problem	2	2.9	[0.2–33.5]	(0.0–8.6)	76.7	0.038
Persistent pharyngeal symptoms	4	2.7	[0.9–8.3]	(1.1–8.4)	97.3	< 0.001
Wheezing	2	2.7	[1.9–3.9]	(1.9–2.8)	0.0	0.613
Throat itching	1	1.4	[0.8–2.5]	–	–	–
Pneumonia	1	0.8	[0.3–1.7]	–	–	–
Thoracic burning	1	0.6	[0.0–3.4]	–	–	–
Orthopnea	3	0.6	[0.3–1.3]	(0.0–0.6)	0.0	0.984
Pulmonary fibrosis	1	0.6	[0.4–0.9]	–	–	–
Lung damage	1	0.3	[0.2–0.6]	–	–	–
Hemoptysis	2	0.1	[0.0–0.4]	(0.1–0.2)	60.4	0.112
Bronchitis	1	0.1	[0.0–0.3]	–	–	–
COPD	1	0.1	[0.0–0.3]	–	–	–
Cardiovascular sequelae						
Resting heart rate increase	1	11.2	[8.8–14.1]	–	–	–
Tachycardia	3	7.5	[0.8–44.5]	(0.4–35.4)	99.2	< 0.001
Palpitations	18	6.6	[4.4–9.8]	(0.5–23.2)	97.5	< 0.001
Hypotension or syncope	2	5.5	[1.5–18.6]	(2.9–10.7)	92.4	< 0.001
Discontinuous flushing	1	4.8	[3.3–7.0]	–	–	–
Newly diagnosed hypertension	4	1.1	[0.1–11.4]	(0.2–14.0)	98.2	< 0.001
Cardiac disease	1	0.4	[0.2–0.6]	–	–	–
Angina pectoris	1	0.1	[0.0–0.3]	–	–	–
Heart attack	1	0.03	[0.0–0.2]	–	–	–
Psychosocial sequelae						
Somatization	2	37.5	[30.2–45.3]	(34.0–41.8)	66.8	0.083
Phobic–anxiety	1	24.2	[18.2–31.1]	–	–	–
Somnipathy	30	20.1	[14.7–26.9]	(1.2–64.8)	98.9	< 0.001
Anxiety	24	18.0	[13.8–23.1]	(0.6–47.8)	97.8	< 0.001
Sadness	1	16.0	[13.7–18.5]	–	–	–
PTSD	18	14.6	[11.3–18.7]	(1.2–32.0)	91.8	< 0.001
Anger–hostility	2	13.4	[10.5–17.0]	(12.3–15.9)	44.3	0.180
Depression	22	12.7	[9.3–17.2]	(0.6–37.5)	96.0	< 0.001
Paranoid ideation	1	10.4	[6.4–15.8]	–	–	–
Psychosis	2	6.4	[0.7–39.7]	(2.1–17.6)	97.2	< 0.001
Behavior disorder	2	5.9	[0.4–52.4]	(1.4–20.8)	97.9	< 0.001
Obsessive–compulsive	2	5.7	[0.4–49.7]	(1.4–19.8)	97.5	< 0.001

Table 2 (continued)

Symptom	Number of studies	Prevalence (%)[a]	95 CI (%)	Range (%)	I^2 (%)	P_H
Specific phobia—with covid	1	2.8	[1.5–4.9]	–	–	–
Dysphoria	1	1.7	[0.9–3.2]	–	–	–
Interpersonal sensibility	1	0.6	[0.0–3.0]	–	–	–
Feelings of inferiority	1	0.6	[0.2–1.7]	–	–	–
Neurological sequelae						
Bradykinesia	1	49.9	[46.0–53.7]	–	–	–
Cognitive complaint	1	49.7	[42.0–57.4]	–	–	–
Inability to focus vision	1	33.1	[25.1–41.9]	–	–	–
Problems with balance	3	28.3	[20.8–37.3]	(16.8–35.6)	85.9	< 0.001
Fatigue	53	27.5	[22.4–33.3]	(1.5–84.9)	98.9	< 0.001
Abnormal reflex status	1	26.2	[18.0–35.8]	–	–	–
Sensory alterations	1	25.9	[19.8–32.8]	–	–	–
Brain fog	4	25.0	[10.3–49.1]	(9.6–43.9)	99.0	< 0.001
Arthritis	1	24.6	[18.1–32.6]	–	–	–
Unrefreshing sleep	2	21.9	[2.6–74.9]	(7.8–48.5)	99.2	< 0.001
Cognitive impairment	8	21.2	[11.0–36.9]	(5.8–38.6)	98.5	< 0.001
Neck pain	1	21.1	[16.5–26.3]	–	–	–
Voice alteration	1	20.8	[13.4–30.0]	–	–	–
Light sensitivity	1	20.0	[13.5–27.9]	–	–	–
General malaise	6	19.9	[8.8–39.1]	(0.0–46.3)	98.2	< 0.001
Peripheral neuropathy	1	17.9	[14.4–21.9]	–	–	–
Lightheadedness when prolonged standing	1	16.9	[10.9–24.5]	–	–	–
Concentration problem	11	15.6	[9.1–25.4]	(2.9–40.2)	97.8	< 0.001
Discomfort	3	15.5	[7.6–29.2]	(3.7–29.2)	98.8	< 0.001
Low mood	3	14.5	[3.8–42.4]	(5.8–39.6)	98.4	< 0.001
Mental slowness	3	14.1	[2.7–48.8]	(5.0–42.4)	99.3	< 0.001
Hypomnesia	20	13.4	[8.4–20.7]	(0.6–53.8)	98.5	< 0.001
Arthralgia	21	12.9	[8.4–19.2]	(0.0–47.8)	98.4	< 0.001
Anguish	1	12.7	[10.6–15.0]	–	–	–
Anhedonia	1	12.6	[10.5–14.9]	–	–	–
Tingling	3	12.5	[2.5.1–44.6]	(0.4–46.9)	98.6	< 0.001
Delusions	1	12.5	[9.5–16.0]	–	–	–
Myalgia	27	10.9	[6.8–16.9]	(0.2–57.2)	98.7	< 0.001
Tremors	4	8.3	[3.5–18.7]	(2.5–13.9)	95.1	< 0.001
Muscle atrophy	1	7.8	[3.4–14.7]	–	–	–
Headache	33	7.5	[5.3–10.6]	(0.0–39.4)	97.8	< 0.001
Backache	5	6.9	[2.4–18.1]	(2.0–32.3)	97.8	< 0.001
Dizziness	17	6.9	[3.9–12.1]	(0.6–35.8)	98.4	< 0.001
Paresthesia	7	6.9	[4.6–10.2]	(3.4–12.1)	85.7	< 0.001
Reduction of physical strength	2	6.5	[0.5–50.8]	(1.7–21.7)	99.1	< 0.001
Abnormal muscle tone	1	5.8	[2.2–12.3]	–	–	–
Gait abnormality	1	5.8	[2.2–12.3]	–	–	–
Ageusia	31	5.8	[3.7–8.8]	(0.0–49.9)	97.3	< 0.001
Tearing	1	5.8	[4.4–7.5]	–	–	–
Anosmia	36	5.7	[3.8–8.3]	(0.0–53.8)	97.6	< 0.001
Movement disturbances	11	5.7	[4.0–8.0]	(1.1–17.5)	91.1	< 0.001
Sensitivity disorders	4	4.4	[1.3–14.0]	(0.6–16.5)	91.3	< 0.001
Muscle weakness	4	4.3	[2.6–6.8]	(3.1–9.1)	83.7	< 0.001
ICU-related polyneuropathy	1	3.1	[2.1–4.6]	–	–	–

Table 2 (continued)

Symptom	Number of studies	Prevalence (%)[a]	95 CI (%)	Range (%)	I^2 (%)	P_H
Impaired vision	9	2.9	[1.3–6.3]	(0.0–18.0)	96.0	< 0.001
Facial palsy	2	2.5	[0.2–21.9]	(0.0–5.9)	69.0	0.073
Dysphonia	3	2.1	[0.3–14.1]	(0.6–8.2)	96.5	< 0.001
Hallucinations	2	1.9	[0.1–29.6]	(0.4–8.5)	99.2	< 0.001
Dysmetria	1	1.9	[0.2–6.8]	–	–	–
Babinski sign	1	1.9	[0.2–6.8]	–	–	–
Disorientation or confusion	7	1.8	[0.4–8.5]	(0.0–30.2)	98.6	< 0.001
Problems with usual activity	2	1.5	[1.1–2.0]	(1.4–1.6)	0.0	0.766
Problems with washing or dishing	2	1.1	[0.5–2.4]	(0.7–1.6)	80.3	0.024
Myoclonus	2	1.0	[0.5–2.1]	(0.0–1.1)	0.0	0.584
Tinnitus	2	0.9	[0.0–66.5]	(0.1–11.9)	98.1	< 0.001
Paralysis	2	0.7	[0.0–44.2]	(0.1–6.8)	97.3	< 0.001
Hearing loss	2	0.7	[0.1–4.9]	(0.2–1.6)	73.5	0.052
Leg numbness/finger stiffness	4	0.4	[0.2–1.1]	(0.1–0.8)	70.1	0.018
Coma	2	0.3	[0.0–18.1]	(0.0–2.3)	94.6	< 0.001
Cerebral infarction	2	0.1	[0.0–1.4]	(0.0–0.4)	80.3	0.024
Neuralgia	1	0.1	[0.0–0.2]	–	–	–
Aphasia	1	0.0	[0.0–3.5]	–	–	–
Asterixis	1	0.0	[0.0–3.5]	–	–	–
Chorea	1	0.0	[0.0–3.5]	–	–	–
Decreased consciousness	1	0.0	[0.0–3.5]	–	–	–
Dystonia	1	0.0	[0.0–3.5]	–	–	–
Neck stiffness	1	0.0	[0.0–3.5]	–	–	–
Oculomotor nerve palsy	1	0.0	[0.0–3.5]		–	–
Dermatological sequelae						
Changing pattern of sweating	1	28.5	[20.9–37.0]	–	–	–
Sweating	10	6.4	[3.5–11.7]	(0.0–28.5)	98.1	< 0.001
Exanthema	11	4.6	[2.7–7.7]	(0.2–16.0)	97.0	< 0.001
Psoriasis	1	4.1	[2.5–6.5]	–	–	–
Pressure ulcers	1	1.8	[1.0–2.9]	–	–	–
Eczema	1	1.5	[0.8–2.6]	–	–	–
Pruritus	3	1.2	[0.4–3.6]	(0.6–2.5)	70.0	0.036
Cyanosis	1	0.4	[0.1–1.1]	–	–	–
Allergy	1	0.1	[0.0–0.2]	–	–	–
Sequelae related to digestive system						
Stomach bloated after meals	2	15.3	[2.1–59.8]	(5.8–34.6)	98.6	< 0.001
Hypolyphagia	1	9.5	[7.7–11.6]	–	–	–
Poor appetite	14	5.7	[3.5–9.0]	(0.0–26.9)	96.6	< 0.001
Constipation	8	4.6	[1.9–10.7]	(0.1–27.7)	97.8	< 0.001
Abdominal pain	10	3.5	[1.6–7.3]	(0.0–17.7)	96.5	< 0.001
Diarrhea	21	2.9	[1.8–4.9]	(0.0–17.7)	96.1	< 0.001
Nausea	8	1.6	[0.5–5.0]	(0.0–16.9)	93.9	< 0.001
Anorexia	2	0.9	[0.6–1.3]	(0.8–1.0)	0.0	0.632
Vomiting	4	0.3	[0.0–2.2]	(0.0–2.0)	91.3	< 0.001
Hepatic insufficiency	1	0.2	[0.1–0.4]	–	–	–
Sequelae related endocrinological system						
Alopecia	17	11.2	[6.9–17.6]	(0.0–47.0)	98.5	< 0.001
Diabetes (new onset)	3	1.1	[0.2–7.1]	(0.1–9.0)	99.1	< 0.001
Glycaemia uncontrol	1	0.9	[0.4–1.8]	–	–	–

Table 2 (continued)

Symptom	Number of studies	Prevalence (%)[a]	95 CI (%)	Range (%)	I^2 (%)	P_H
Bitter/dryness in mouth	1	0.3	[0.2–0.6]	–	–	–
High blood sugar	1	0.2	[0.1–0.4]	–	–	–
Dryness/excessive secretion in eye	1	0.1	[0.0–0.2]	–	–	–
Other sequelae						
Intolerance to temperature	1	30.8	[23.0–39.5]	–	–	–
Urinary frequency	1	23.1	[16.1–31.3]	–	–	–
Musculoskeletal pain	13	17.3	[11.1–25.8]	(4.2–50.8)	98.3	< 0.001
Erectile dysfunction	3	17.2	[12.2–23.6]	(13.8–23.4)	76.0	0.015
Difficulty emptying bladder	1	10.8	[6.0–17.4]	–	–	–
Loss of weight	7	10.6	[5.4–19.6]	(2.9–37.3)	96.8	< 0.001
Problems passing urine	2	8.9	[6.0–13.1]	(7.0–10.6)	68.5	0.075
Thyroid dysfunction	1	8.1	[5.7–11.0]	–	–	–
Rhinorrhea	5	8.0	[5.6–11.1]	(0.0–10.9)	71.3	0.008
Loss of control of opening bowels	1	5.5	[3.9—7.5]	–	–	–
Blocked nose	3	5.1	[1.1–19.8]	(0.8–16.0)	88.7	< 0.001
Toe lesions	1	4.0	[2.1–6.7]	–	–	–
Urinary tract infection	1	3.9	[2.8–5.5]	–	–	–
Lumpy lesions on toes	1	2.9	[1.7–4.5]	–	–	–
Chills	4	2.7	[0.6–11.6]	(0.1–20.0)	98.4	< 0.001
Oedema	9	2.3	[0.7–7.4]	(0.2–28.3)	98.8	< 0.001
Thrombotic manifestations	4	1.8	[0.9–3.6]	(0.2–3.1)	73.2	0.011
Mycosis	1	1.4	[0.8–2.5]	–	–	–
Otoacoustic symptoms	1	1.3	[0.7–2.3]	–	–	–
Fever	18	1.1	[0.6–2.2]	(0.0–11.0)	89.4	< 0.001
Increased joint size	1	1.0	[0.0–5.3]	–	–	–
Renal insufficiency de novo	2	0.4	[0.1–2.0]	(0.2–0.9)	89.1	0.002
Reduced urine output	1	0.3	[0.1–0.8]	–	–	–
Antiadoncus	1	0.03	[0.0–0.2]	–	–	–

[a]Using estimates at the longest follow-up time for those studies have multiple follow-up time

Cardiovascular sequelae

The most common sequela was resting heart rate increase (1 study) with prevalence of 11.2% (95% CI 8.8–14.1%). 18 studies reported palpitations with pooled estimate of 6.6% (95% CI 4.4–9.8%, range 0.5–23.2%).

Psychosocial sequelae

Somatization (2 studies) was the most common psychosocial sequela with a prevalence of 37.5% (95% CI 30.2–45.3%, range 34.0–41.8%). More than ten studies measured somnipathy, anxiety, PTSD and depression with a pooled prevalence of 20.1% (14.6–26.9%, range 1.2–64.8%), 18.0% (95% CI 13.8–23.1%, range 0.6–47.8%), 14.6% (95% CI 11.3–18.7%, range 1.2–32.0%) and 12.7% (95% CI 9.3–17.2%, range 0.6–37.5%), respectively.

Neurological sequelae

More than ten studies reported that recovered patients had fatigue, concentration problem, hypomnesia arthralgia, myalgia, headache, dizziness, ageusia, anosmia and movement disturbances, among which fatigue had the highest prevalence of 27.5% (95% CI 22.4–33.3%, range 1.5–84.9%). Meanwhile, one study each reported that the prevalence of bradykinesia and cognitive complaint were up to 49.9% and 49.7%.

Dermatological sequelae

10 and 11 articles reported sweating (6.4% 95% CI 3.5–11.7%, range 0.0–28.5%) and exanthema (4.6% 95% CI 2.7–7.7%, range 0.2–16.0%), respectively. However, a study reported that the prevalence of changing pattern of sweating was 28.5% (95% CI 20.9–37.0%).

Sequelae related to the digestive system

Poor appetite, abdominal pain and diarrhea were reported by more than ten studies, respectively, with a pooled prevalence of 5.7% (95% CI 3.5–9.0%, range 0.0–26.9%), 3.5% (95% CI 1.6–7.3%, range 0.0–17.7%) and 2.9% (95% CI 1.8–4.9%, range 0.0–17.7%), respectively. In addition, two studies reported that 15.3% (95% CI 2.1–59.8%, range 5.8–34.6%) of patients had stomach bloated after meals.

Sequelae-related endocrinological system

The prevalence of dermatological sequelae was generally low. The most common sequela related to the endocrinological system was alopecia, with a pooled prevalence of 11.2% (95% CI 6.9–17.6%, range 0.0–47.0%) from 17 articles.

Other sequelae

Among the remaining sequelae, intolerance to temperature, urinary frequency, musculoskeletal pain and erectile dysfunction were common, with prevalences of 30.8% (95%CI 23.0–39.5%), 23.1% (95% CI 16.1–31.3%), 17.3% (95% CI 11.1–25.8%, range 4.2–50.8%) and 17.2% (95% CI 12.2–23.6%, range 13.8–23.4%), respectively.

Heterogeneity analysis and sensitivity analysis

Most of the sequelae prevalence had high heterogeneity across studies ($I^2 > 60\%$, $P_H < 0.05$). Six meta-analyses showed low heterogeneity (pain on breathing: $I^2 = 0.00\%$, $P_H = 0.628$, wheezing: $I^2 = 0.00\%$, $P_H = 0.613$, orthopnea: $I^2 = 0.00\%$, $P_H = 0.984$, problems with usual activity: $I^2 = 0.00\%$, $P_H = 0.766$, myoclonus: $I^2 = 0.00\%$, $P_H = 0.584$, anorexia: $I^2 = 0.00\%$, $P_H = 0.632$), one showed moderate heterogeneity (anger-hostility: $I^2 = 44.3\%$, $P_H = 0.180$).

Subgroup analysis

Temporal trend of symptoms

We present prevalence of symptoms at different follow-up time (3–4, 5–8 and > 9 months). Overall, the prevalence of all symptoms showed higher prevalences at 5–8 months' follow-up (Appendix 3 and Fig. 3). The prevalence of most symptoms decreased at > 9 months, except fatigue, dyspnea, depression, arthralgia, anosmia, ageusia and dizziness. The prevalence of PTSD and chest pain decreased from 3–4 to > 9 months with significant difference, and alopecia decreased significantly from 3–4 to 5–8 months. Heterogeneity in most symptoms was still high after stratification by follow-up duration ($I^2 > 60.0\%$, $P_H < 0.05$). Only fever at > 9 months' follow-up had a low heterogeneity ($I^2 = 22.0\%$, $P_H = 0.279$).

Symptoms by geographic regions

We further analyzed the prevalence of symptoms by geographic regions. Overall, the pooled prevalence of symptoms in Asia was lower than that in Europe and other regions (Appendix 4 and Fig. 4). Additionally, the heterogeneity in symptoms was still high ($I^2 > 60.0\%$, $P_H < 0.05$), except fever in regions out of Asia and Europe ($I^2 = 0.0\%$, $P_H = 0.628$). Europe reported higher prevalences than Asia in fatigue, dyspnea, anxiety, anosmia, ageusia and headache with significant difference.

Symptoms by age

We estimated the prevalence of symptoms by age (< 60 years old and ≥ 60 years old). Overall, the pooled prevalence of symptoms in < 60 years old was higher than that in ≥ 60 years old (Appendix 5 and Fig. 5), except dyspnea, PTSD, anosmia, myalgia, cough, ageusia and headache. The heterogeneity in symptoms was still high ($I^2 > 60.0\%$, $P_H < 0.05$). Patients < 60 years old reported higher prevalences than those ≥ 60 years old in palpitation and sore throat with significant difference.

Symptoms by ICU admission

We showed the prevalence of symptoms by ICU admission (< 20% and ≥ 20%). Overall, the pooled prevalence of symptoms in < 20% ICU admission was lower than that in 20% ICU admission (Appendix 6 and Appendix 7), except depression and alopecia. The heterogeneity in symptoms was still high ($I^2 > 60.0\%$, $P_H < 0.05$). Studies with < 20% ICU admission reported lower prevalences than studied ≥ 20% ICU admission in dizziness and fever.

Discussion

This systematic review and meta-analysis identified 167 sequelae related to COVID-19 from 88,769 patients at least 90 days follow-up after hospital discharge. These included respiratory/lung function, cardiovascular, psychosocial, neurological, dermatological, digestive system and endocrinological system sequelae. We identified symptoms such as fatigue, somnipathy, dyspnea, anxiety, depression, PTSD and arthralgia which persisted for 1 year in the discharged COVID-19 patients. The prevalence of some neurological symptoms (fatigue, arthralgia, anosmia, ageusia and dizziness) did not show decreasing trends up to 1 year of

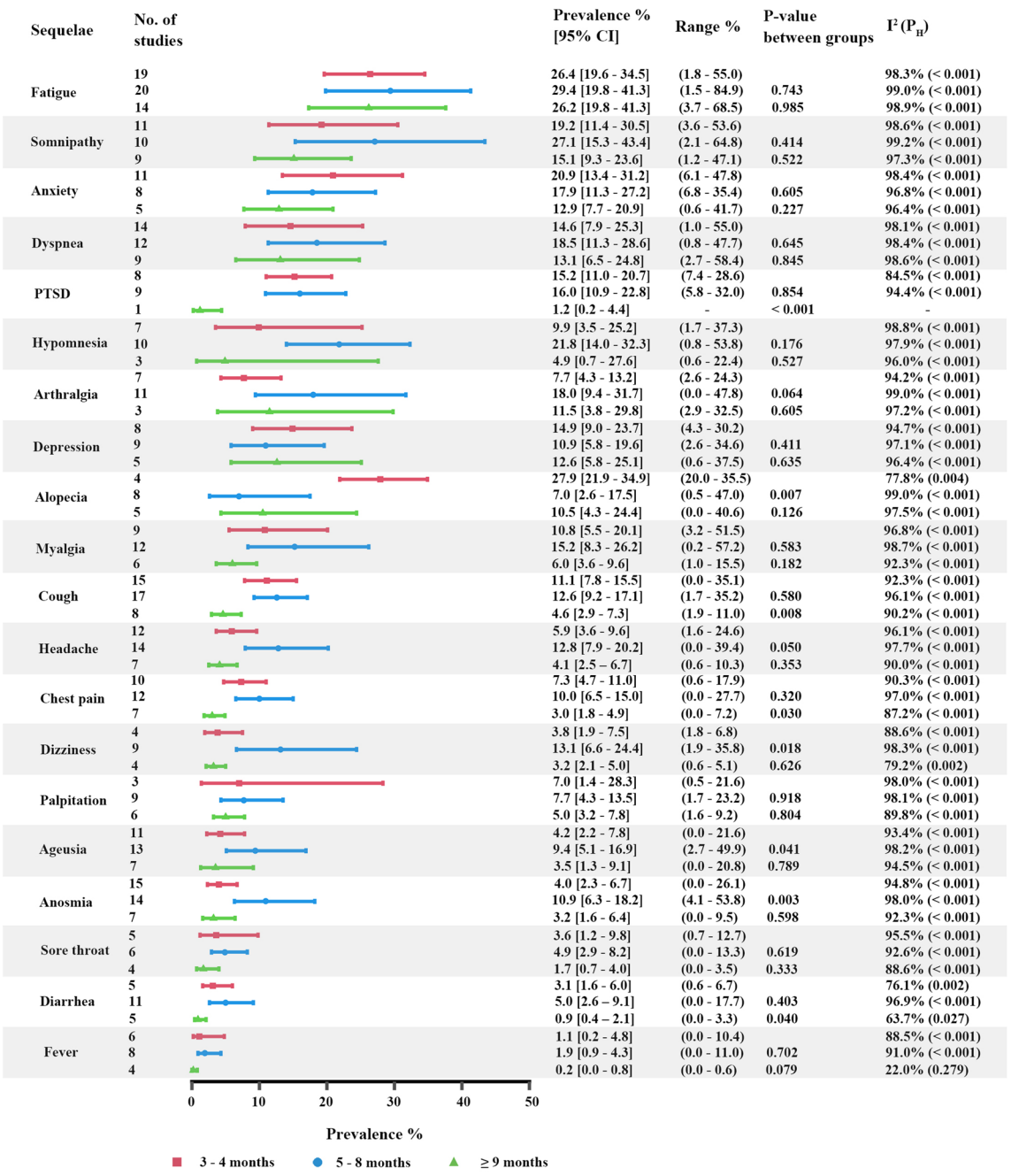

Fig. 3 Pooled prevalence of sequelae at 3–4, 5–8 and ≥ 9 months (9–13 months) follow-up among previously hospitalized patients

follow-up, while most of the other symptoms resolved over time.

Respiratory/lung function sequelae

Shortness of breath (25.6%) and post-activity polypnea (29.8%) were the 2 most common sequelae in the respiratory system. Furthermore, some patients who recovered from COVID-19 would develop symptoms, including dyspnea (15.5%), pain on breathing (13.9%), chest distress (10.8%), cough (9.8%), etc. These symptoms can be explained by the influence of COVID-19 on the lungs. The current evidence indicates that the organ most affected by COVID-19 is the lung, which may cause a variety of pathophysiological events, including capillary damage and bleeding, hyaline membrane formation, pulmonary consolidation, diffuse alveolar epithelium destruction, and alveolar septal fibrous proliferation [92, 93]. COVID-19 can extensively damage the alveolar epithelial cell and the endothelial cell with secondary fibroproliferation, which may cause lung fibrosis or

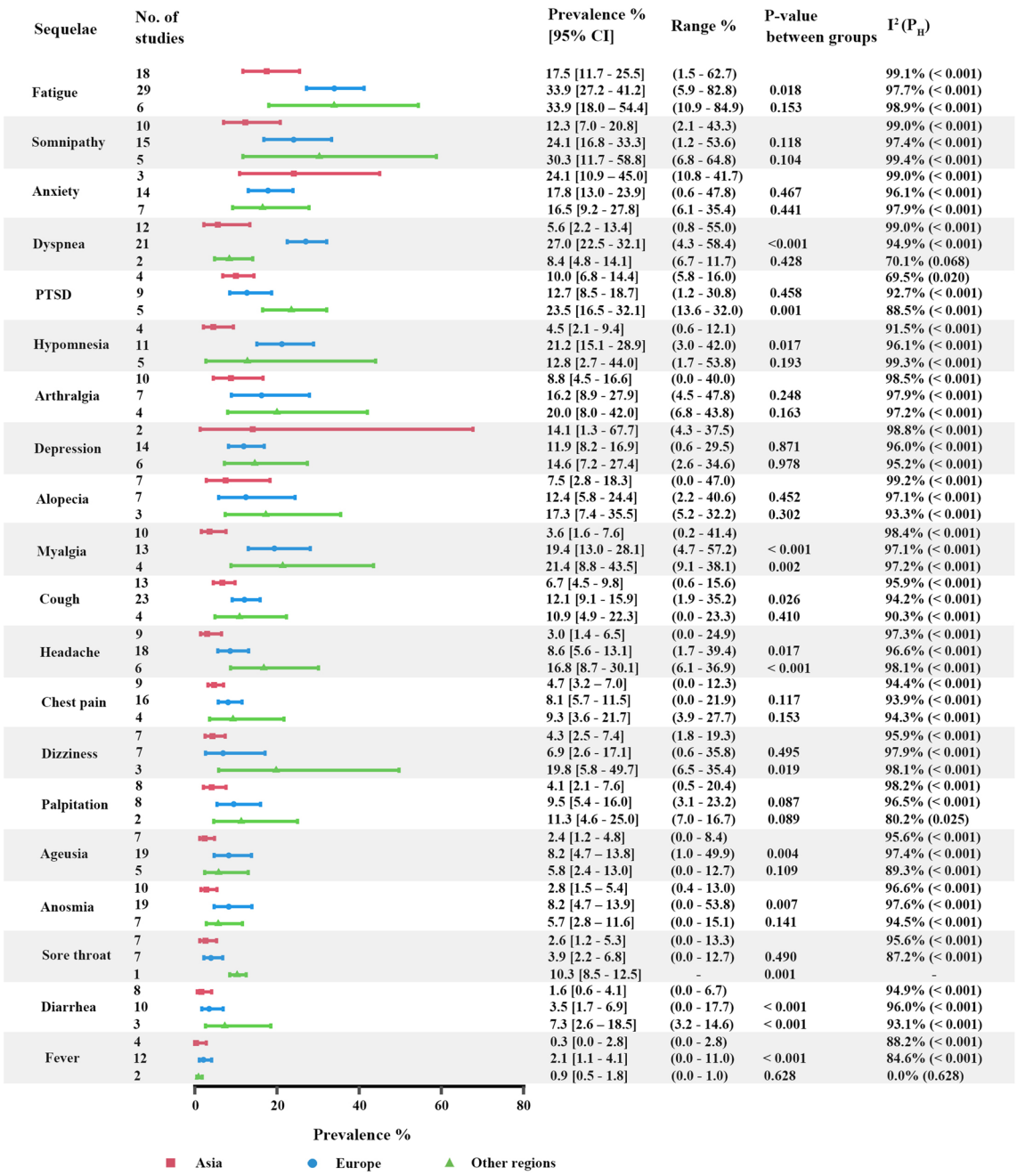

Fig. 4 Pooled prevalence of sequelae among previously hospitalized patients in Asia, Europe and other regions

pulmonary hypertension by chronic vascular and alveolar remodeling [94, 95].

Clinically, the pathological changes can significantly affect activities of daily living, by reduction of walking distance in the 6-min walking test [32]. A systematic review and meta-analysis have found that 39%, 15% and 7% of COVID-19 patients had altered diffusion capacity, restrictive pattern, and obstructive pattern, respectively, in lungs [96]. Radiological and pathological report showed pulmonary fibrosis, parenchymal bands, irregular interfaces, reticular opacities and traction bronchiectasis with or without honeycomb lung [97–100]. Additionally, varying degrees of alveolar structure destruction and pulmonary interstitial fibrosis were observed in the autopsy of patients with COVID-19 [101].

The underlying pathophysiology of post-COVID sequelae is multifaceted and subject to debate. It can be classified into lung-dependent direct tissue injury, and lung-independent pathological inflammation such as viral persistence, immune dysregulation, and autoimmunity [102, 103]. Radiologically, post-COVID decline in pulmonary function is closely

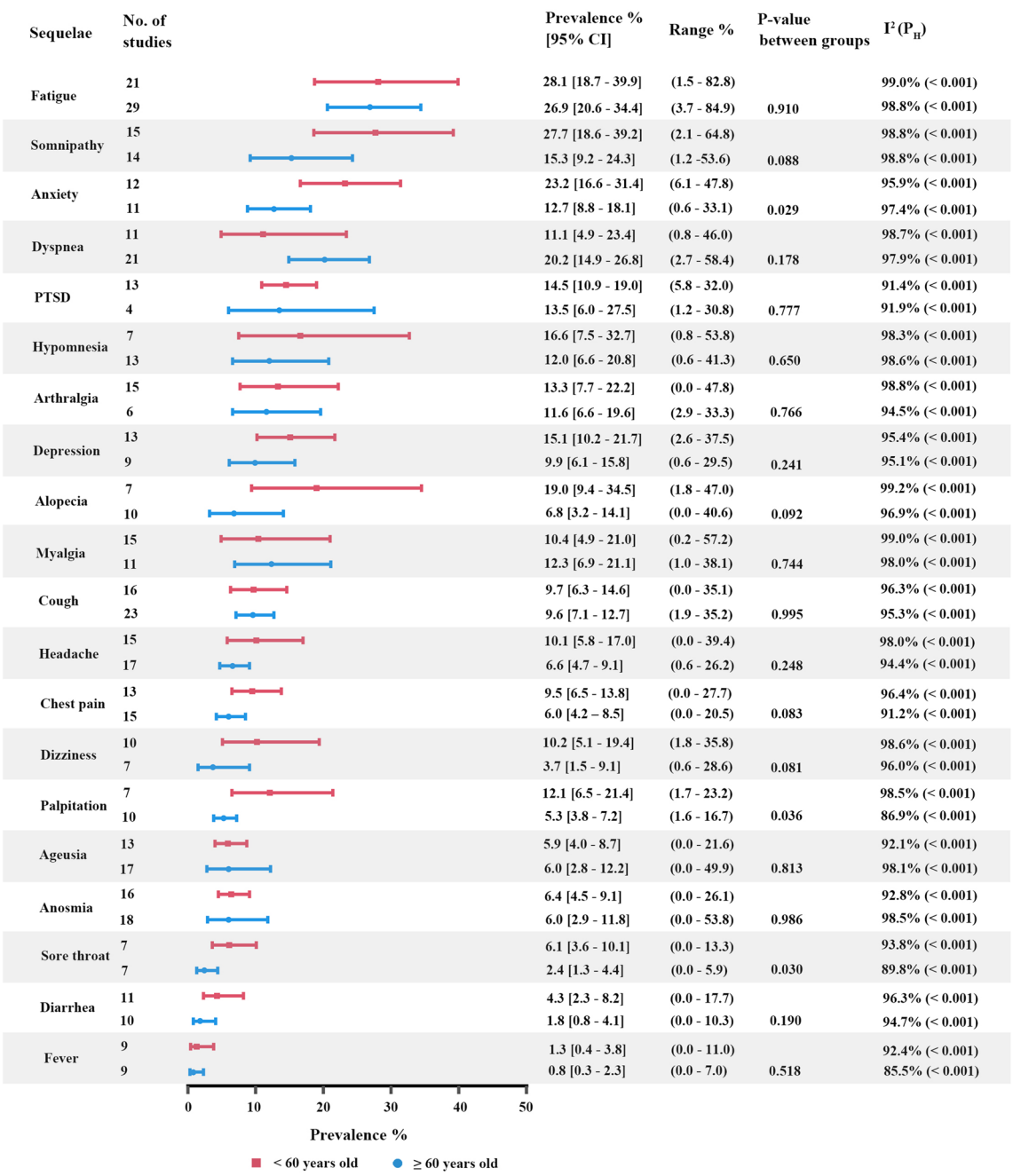

Fig. 5 Pooled prevalence of sequelae among previously hospitalized patients in < 60 years old and ≥ 60 years old

associated with pulmonary fibrosis and ground glass opacification [35, 104–106]. An investigation of autopsy samples demonstrated viral persistence, resulting in multiple organ injury and various clinical presentations [107]. The role of inflammatory biomarkers in its pathogenesis is discordant since some studies have observed a persistently elevated biomarkers [103, 108, 109], while some researchers also show there is no direct correlations between them [110].

The evidence showed that the lungs have the potential to heal after severe injury, which is consistent with the downtrend of the prevalence in cough, chest pain and sore throat [111]. However, we also observed that dyspnea persisted in 13.1% of the discharged COVID-19 patients for over a year, which suggested that lung injury may affect patients for a longer duration. Evidence from SARS and MERS reported that some patients still have lung damage even 15 years later [112]. Therefore, a specialized rehabilitation program is important. One study has shown that a 6-week rehabilitation program can significantly improves pulmonary functions, quality of life and anxiety

in COVID-19 survivors [113]. Early rehabilitation is beneficial to functional recovery and functional independence of patients [114, 115]. Therefore, several professional bodies advocated the need of early detection and rehabilitations. The British Thoracic Society recommended regular follow-up of high-risk patients 4 months after infection; and the Swiss COVID group and Swiss Society for Pulmonology recommended detailed pulmonary assessments and rehabilitations, if resources are available [116, 117].

Cardiovascular sequelae

Resting heart rate increase were the most common sequelae in the cardiovascular system with the prevalence of 11.2%, which may be related to heart damage caused by COVID-19. A study of recovered COVID-19 patients reported that almost 78% of patients had heart involvement and 60% of them had persistent inflammation of the heart muscle unrelated to a pre-existing condition [118]. Cardiovascular sequelae may recover as we found that the prevalence of palpitation decreased slightly over time. It is important to note that even with a significant recovery of heart function, there may still be a risk of coronary artery disease, atrial fibrillation, or ventricular arrhythmias due to myocardial injury [119].

Patients with cardiovascular sequelae require close monitoring because the post-discharge mortality rate is high, with near half of the patients dying 3 months after discharge [120]. These patients should be referred for clinical reviews and reassessment 1–2 months after discharge [121, 122]. Postural Orthostatic Tachycardia Syndrome (POTS) has been reported in COVID-19 survivors [123]. They may be presented as easy fatigue, postural tachycardia, dizziness and exercise intolerance [124]. The proposed mechanism has been an alteration of autonomic nervous system regulated by angiotensin converting enzyme 2 (ACE2) protein found on neurons [125].

Psychosocial sequelae

The sequelae related to mental health were of common occurrence in COVID-19, such as somatization (37.5%), phobic-anxiety (24.2%), somnipathy (20.1%), anxiety (18.0%), PTSD (14.6%) and depression (12.7%). Meanwhile, the experience with SARS and MERS also showed that the prevalence of depression, anxiety and post-traumatic stress disorder remained high even after 39 months, which indicates that the mental health of patients is of great concern after they recovered from COVID-19 [126]. We observed that the prevalence of somnipathy, anxiety and depression was still high after a year (15.1%, 12.9% and 12.6%, respectively). Reason of psychosocial sequelae is proposed to be inflammatory marker-mediated neuroinflammatory damages since cytokines IL-4 and IL-6 are persistently elevated in patients reported with neurological or psychological symptoms [127]. Other inflammatory markers reported include amyloid-beta, neurofilament light, neurogranin, total tau and p-T181-Tau [128]. Nearly half of survivors without prior psychiatric conditions live with depression after 3 months of recovery from severe COVID-19 associated respiratory failure [129].

Neurological sequelae

A great number of neurological sequelae have been found in this systematic review and meta-analysis. Among these sequelae, bradykinesia (49.9%), cognitive complaint (49.7%), inability to focus vision (33.1%), problems with balance (28.3%), fatigue (27.5%), abnormal reflex status (26.2%), sensory alterations (25.9%), brain fog (25.0%), arthritis (24.6%), unrefreshing sleep (21.9%), cognitive impairment (21.2%), neck pain (21.1%), voice alteration (20.8%) and light sensitivity (20.0%) had a relatively high prevalence. They may be related to viral infection, physiological impairment (e.g., hypoxia), cerebrovascular disease, immunoreaction, side effects of medication, etc. [126] Reason of neurological dysfunction can be explained macroscopically and microscopically. Macroscopically, hypoxic nerve damage leads to mitochondrial swellings in various brain sites, such as cerebral white matters, brainstem, parahippal gyrus, thalamus and sites with high metabolic requirements [130–133]. Neurons do not readily regenerate; thus, these clinical presentations may be long-lasting, leading to Long COVID-19 syndrome [134]. Microscopically, persistently elevated cytokines were observed in patients with neurological presentations. Multifocal neurological damages in patients with Long COVID-19 Syndrome may be a result from indirect T-cell and microglia damage in the brain, similar to stroke and neuroinflammatory diseases [135]. Additionally, lung sequelae are also believed to be a major cause of fatigue [136].

However, the downtrend was not observed in neurological sequelae, and the prevalence was still high in fatigue (26.2%) and arthralgia (11.5%) after a year.

Dermatological sequelae

Ten and 11 articles reported that COVID-19 recovered patients would have sweating and exanthema with a low prevalence of 6.4% and 4.6%, respectively. González-Hermosillo et al. reported that 28.5% of patients would change pattern of sweating at 6-month follow-up after discharge [43]. These dermatological sequelae may be caused by the drug used to treat COVID-19, maybe because of the long-term effect of COVID-19, or maybe because of some random effects (wrong measurement, the patient happened to have

this sequela, etc.). Further studies are needed to determine whether COVID-19 can cause dermatological sequelae.

Sequelae related to the digestive system

14 studies reported poor appetite, with a pooled prevalence of 5.7%. This may be related to the anosmia and the ageusia caused by COVID-19, and elevated levels of inflammatory cytokines are also a common cause of anorexia [137]. Stomach bloated after meals and hyplyphagia occurred frequently (15.3% and 9.5%). Additionally, a small number of patients also had abdominal pain, diarrhea, vomiting, and other sequelae, which are also developed during the acute phase of COVID-19. This may be because the SARS-CoV-2 replicates in the gastrointestinal tract and then infects and destroys absorbent intestinal cells. Or the gastrointestinal system is directly damaged by the COVID-19 induced inflammation [138]. Meanwhile, we observed that the prevalence of diarrhea decreased with the increase of follow-up time.

Although the observed prevalence of hepatic insufficiency was low (0.2%), liver injury has been observed in various studies of COVID-19 survivors [139, 140]. Majority of the survivors showed gradual normalization of liver function enzymes within 2 months after discharge [141]. However, patients with chronic liver conditions (such as liver cirrhosis) are associated with a fourfold increase of mortality risk after COVID-19 infections, compared with those without [142]. Thus, COVID-19 survivors with chronic liver conditions should be prioritized for rehabilitations follow-up.

Sequelae-related endocrinological system

Alopecia was the most common sequela related to the endocrinological system with a pooled prevalence of 11.2%. However, it is apparently lower than another systematic review which reported a pooled prevalence of 25% [143]. It may be because the follow-up time of this systematic review is shorter than mine, the symptom of alopecia may have been alleviated. The alopecia developed after COVID-19 can be referred to as telogen effluvium, defined as a diffuse hair loss after significant systemic stressors or infection, which is due to premature follicular transitions from the active growth phase (anagen) to the resting phase (telogen) [144]. Generally, it will last about 3 months. Therefore, we observed that the prevalence of alopecia decreased by 20.9% from 3 – 4 months to 5 –8 months.

Another Long-COVID related endocrinopathy is diabetes mellitus (DM). Proposed pathogenic mechanism is SARS-CoV-2 binding to ACE2 receptors of pancreatic beta-islet cells, triggering autoimmune response and type I DM [145, 146]. Thus, hyperglycemia without DM and new-onset DM are associated with poor prognosis COVID-19 after excluding risk factors such as obesity and corticosteroid administration [147].

Other sequelae

Weight loss (10.6%) and malnutrition are common in patients who recover from COVID-19. Another study that evaluated the COIVD-19 patients after clinical remission, also found that more than 50% of them were at risk of malnutrition and approximately 30% of them lost more than 5% of weight compared with baseline [148]. This may be because acute systemic inflammation can severely affect several metabolic and hypothalamic pathways, leading to decreased anorexia and food intake as well as increased resting energy expenditure and muscle catabolism [149]. Additionally, erectile dysfunction (18.6%) was found as a sequela of COVID-19, which may be because of psychological distress, endothelial dysfunction, subclinical hypogonadism, or impaired pulmonary hemodynamics [149]. Moreover, the urinary symptoms (urinary frequency, difficulty emptying bladder, problems passing urine) may be because of viral cystitis caused by SARS-COV-2, and further research is needed [150]. The musculoskeletal pain is also a common post-COVID symptom. The muscular nociception is neurologically and immunologically mediated in Long COVID-19 Syndrome. Its pathogenesis is related to muscle injury secondary to hyperinflammatory state [71, 151, 152], leading to to ACE-2 mediated injury with elevated inflammatory & nociceptive immune markers, e.g. IL2, IL7, IL10, IL-6, TNFα. These are amendable by pharmacological and non-pharmacological interventions by pain-modulation pathways to facilitate future rehabilitations. High prevalence of intolerance to temperature (30.8%) reported by González-Hermosillo et al. cannot be explained yet, and needs more further researches.

Our subgroup analysis showed that the prevalence of most COVID-19 sequelae decreased after > 9 months of follow-up, except that fatigue, somnipathy, dyspnea, depression, arthralgia, anosmia and ageusia remained stable for a longer time. However, the prevalence of most sequelae increased at 5 – 8 months. A similar pattern in a meta-analysis by Alkodaymi et al., prevalences of symptoms at 6 – 9 months were higher than others and did not decrease noticeably afterwards for some symptoms such as fatigue, dyspnea and sleep disorder [11]. Other explanation could be studies reporting sequelae at 5–8 months had a higher proportion of ICU admission, and were mostly from regions out of Asia, while studies of 3–4 months and ≥ 9 months were all from Asia. Furthermore, Asia showed lower prevalence than regions out of Asia, except for anxiety and depression. As a majority of Asian studies (15/22) were from China, the lower prevalence may be explained by admission of milder patients in China, whereas most mild patients were treated at home in

other regions. A study from Wuhan, China reported that the condition of 93% of patients in the general ward was not serious, compared to 77% in East London, UK [153, 154]. It may also be explained by younger age and lower pre-existing medical comorbidities among Chinese patients [155]. Additionally, some symptoms in patients aged < 60 years had significantly higher prevalence than that in patients aged ≥ 60 years, such as anxiety, palpitation and sore throat (Appendix 5 and Fig. 5), while other studies found that COVID-19 patients of different age groups may exhibit different sets of clinical symptoms [156]. Finally, the pooled prevalence of symptoms tends to be higher among studies with more severe patients (i.e. higher % of ICU admission). Other factors such as treatment, rehabilitation, race and blood type may also affect symptom persistence [157, 158].

The heterogeneity of most meta-analyses was high and from our subgroup analyses it could not be explained by follow-up time, regions, age or ICU admission. Possible source of heterogeneity may include differences in the determination of symptoms (questionnaire or self-report or diagnosis by doctors), the proportion of sex, drug use, etc. We did not perform meta-regression analysis to further identify the source of heterogeneity due to the limited number of studies for each symptom.

One strength of this study is that this systematic review and meta-analysis studied all potential long-term sequelae (> 3 months) in hospital discharged COVID-19 patients. The review presented a wide spectrum of health burdens among hospital recovered COVID-19 patients and informed management strategies of COVID-19 discharged patients. Currently, different long COVID-19 clinical assessment tools have been proposed, such as Newcastle post-COVID syndrome Follow Up Screening Questionnaire and COVID-19 Yorkshire Rehabilitation Scale [159, 160]. This study provided clues for standardization of rehabilitation baseline assessment based on symptom prevalence and severity. The focus on hospitalized patients would be of clinical significance and provided most relevant information for hospital-based rehabilitation strategies and services. The meta-analysis by Maglietta et al. described symptoms > 3 months for hospitalized COVID-19 patients, but did not further analyze the prevalence over time [14]. The meta-analysis by Alkodaymi et al. presented symptom prevalence over time, but did not stratify by hospitalized and non-hospitalized COVID-19 patients [11].

There are also some limitations. First, there was large heterogeneity in the prevalence estimates and hence the pooled prevalence should be interpreted with caution. There could be differences in the assessment or reporting of symptoms which contributed to the heterogeneity between studies. Second, some sequelae had a small sample size so that the pooled estimate may not be generalized. Third, clinical symptoms may have various diagnostic standards and symptoms such as cough and chest pain were mainly self-reported [20, 25, 29–31, 36, 38, 40–43, 46, 47, 51–58, 60, 62, 74, 80, 81, 86, 88, 89, 91], as healthcare resources were already stretched coping with the evolving pandemic. Finally, the excess burden of each sequela compared to the general population was not quantified which were available from a limited number of controlled cohort studies only.

This systematic review and meta-analysis indicated that post-COVID symptoms are common in hospital discharged patients. A noticeable proportion of discharged COVID-19 patients still reported fatigue and somnipathy after 1 year of follow-up. Therefore, it is imperative to develop and implement effective preventive and rehabilitative measures for hospitalized COVID-19 patients and COVID-19 survivors after discharge, such as inhibiting viral replication, blocking the inflammatory response and early preventive treatment. Furthermore, post-discharge monitoring is essential to monitor the progress of these sequelae and take treatment measures timely. A recent study suggested community rehabilitative approach in COVID-19 survivors stratified by different clinical severity [161]. In view of the enormous populations, patients with mild severity should be monitored with digital interventions, while moderate and severe patients should have regular follow-up and rehabilitation sessions. Additionally, the mental health of COVID-19 recovered patients is deeply influenced because of social isolation, the psychological impact of new and potentially fatal diseases, fear of infecting others and stigma [126]. Therefore, continuous psychological evaluation after hospital discharge is necessary. Individuals who have depression, anxiety, or PTSD may need psychological intervention from an occupational therapist, social worker, or rehabilitation psychologist [162]. Moreover, because recovered COVID-19 patients often experience weight loss and malnutrition, diagnosis, prevention and treatment of malnutrition should be considered in the previously hospitalized COVID-19 patient management strategy to improve short- and long-term outcomes, as suggested by the European Society of Enteral and Parenteral Nutrition (ESPEN) [163]. Meanwhile, there are still limited therapeutic options for COVID-19 infections and long COVID-19, preventive measures such as vaccinations, masks, personal hygiene and social distancing should be stressed [164, 165].

Conclusion

Post-COVID symptoms affected some of the hospital discharged patients persistently for around 1 year, such as fatigue (26.2%), somnipathy (15.1%), anxiety (12.9%), dyspnea (13.1%), arthralgia (11.5%), depression (12.6%), alopecia (10.5%), etc. A multidisciplinary approach is required to develop preventive measures, rehabilitation techniques

and clinical management strategies to reduce the impact of COVID-19 sequelae on patients' lives.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval is not required for this systematic review and meta-analysis as only secondary analysis of data already available in scientific databases will be conducted.

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