




Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review

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Abstract

Background Long COVID-19 may affect patients after hospital discharge.

Aims This study aims to describe the burden of the long-term persistence of clinical symptoms in COVID-19 patients.

Methods We conducted a systematic review by using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. The PubMed and Google Scholar databases were searched for studies that included information on the prevalence of somatic clinical symptoms lasting at least 4 weeks after the onset of a PCR- or serology-confirmed diagnosis of COVID-19. The prevalence of persisting clinical symptoms was assessed and risk factors were described when investigated. Psychological symptoms and cognitive disorders were not evaluated in this study.

Results Thirty-seven articles met the inclusion criteria. Eighteen studies involved in-patients only with a duration of follow-up of either less than 12 weeks, 12 weeks to 6 months, or more. In these studies, fatigue (16–64%), dyspnea (15–61%), cough (2–59%), arthralgia (8–55%), and thoracic pain (5–62%) were the most frequent persisting symptoms. In nineteen studies conducted in a majority of out-patients, the persistence of these symptoms was lower and 3% to 74% of patients reported prolonged smell and taste disorders. The main risk factors for persisting symptoms were being female, older, having comorbidities and severity at the acute phase of the disease.

Conclusion COVID-19 patients should have access to dedicated multidisciplinary healthcare allowing a holistic approach. Effective outpatient care for patients with long-COVID-19 requires coordination across multiple sub-specialties, which can be proposed in specialized post-COVID units.

Keywords Sequelae symptoms · Long-term persistence · COVID-19 · Long COVID

Introduction

At the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the pathogen responsible for coronavirus disease 2019 (COVID-19) in Wuhan, China. This virus caused an epidemic in China which then spread rapidly to other countries and continents worldwide and impacts all life aspects, including health, economy, and community life [1]. As of 23 January 2022,

352,323,862 confirmed cases of COVID-19 and 5,615,210 deaths have been reported worldwide [2]. A variety of clinical manifestations has been observed in COVID-19 patients, ranging from asymptomatic presentation to critical forms with multiple organ failure and death [3, 4]. The incubation periods of SARS-CoV-2 are in the range of 2–14 days after exposure to the transmissible sources, including direct contact, droplets, airborne, fomites, fecal–oral, and animal-to-human transmission. The early phase of the infection may be asymptomatic or characterized by upper and lower respiratory tract infection symptoms, including general symptoms, and frequently associated with taste and smell disorders or with gastro-intestinal symptoms. Some patients may present a sudden clinical worsening 7 to 10 days post onset of the symptoms, characterized by pneumonia symptoms that may be associated with thromboembolic complications. Finally, acute respiratory distress syndrome has been identified as a later phase in the acute evolution of SARS-CoV-2 [5].

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In addition, COVID-19 has long-term consequences and complications even after hospital discharge [6], as previously observed with SARS-CoV-1 [7]. Because SARS-CoV-2 is an emerging pathogen, there is a lack of detailed information about the long-term persistence of symptoms in COVID-19 patients. Currently, there is no agreed definition of “long COVID.” It has been proposed to distinguish post-acute COVID (from 4 to 12 weeks after the onset of symptoms) and long COVID (more than 12 weeks post onset) [8, 9]. According to the definition proposed by the British National Institute for Health and Care Excellence (NICE), post-COVID-19 syndrome is defined by the persistence of symptoms for at least 12 weeks after onset [10]. In France, the French National Authority for Health has identified the long-term persistence of COVID-19 by the persistence of one or more initial symptoms for at least 4 weeks after onset, when none of these symptoms can be explained by another cause [11]. According to WHO, post COVID-19 case defined in individuals with a history of probable or confirmed SARS-CoV-2 infection and symptoms onset persist at least two months without other reason for explaining [12]. In this review, we aim to give an overview of the prevalence of the long-term persistence of somatic clinical symptoms in discharged COVID-19 patients. We also describe the potential risk factors that have been identified so far.

Methods

Protocol and search strategy

We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (<http://www.prisma-statement.org>). All relevant studies were identified by searching the following databases: PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Google Scholar (<http://scholar.google.fr>). The current search was performed on 23 January 2022 by combining the key words:

- # 1: “COVID-19” OR “SARS-CoV-2”
- # 2: “sequelae” OR “persistence” OR “persistant” OR “long-COVID” OR “long-haul COVID” OR “post-acute COVID syndrome” OR “persistent COVID-19” OR “long-hauler COVID” OR “post-acute sequelae” of “SARS-CoV-2 infection” OR “chronic COVID syndrome”
- # 3: #1 AND #2

The keywords were identified by combining the synonym words and using MeSH terms in order to have an expanded comprehension of the literature.

Inclusion criteria

In this review, we included only articles written in English, with three criteria: (1) patients with a reverse-transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 infection (studies with only-serology-based diagnosis of COVID-19 were excluded from this review), (2) the reported prevalence of the persistence of clinical symptoms in COVID-19 patients after at least 4 weeks of follow-up post-onset, and (3) reporting on somatic clinical symptoms. Psychological and psychiatric disorders and memory, sleep, and attention disorders were not assessed in this study because we felt that such subjective symptoms may be either linked to SARS-CoV-2 infection itself or to the subjective perception of COVID-19 severity, due to the dramatic and pessimistic tone of public health communication in many countries and to the sometimes sensationalist media coverage of the epidemic that has prevailed until recently. For the same reasons, studies addressing only quality of life were not included. Data on persisting disorders obtained through laboratory investigations, imagery, or functional tests requiring specialized devices were not assessed in this study. Studies where only patients with persistent symptoms were followed-up (without a denominator) were excluded.

Both case reports and review articles were eliminated from the search, but the bibliographies of selected articles were used to find additional studies relevant for this review. We excluded studies conducted on animal subjects.

We assessed the quality of studies by using Newcastle–Ottawa Scale (NOS) [13] for cohort studies and NOS adapted for cross-sectional studies. NOS contains 8 items with 3 subscales and a total maximum score is 9. Studies quality ranged by score: good (7–9), fair (4–6), and poor (0–3) (Supplementary table 1 and 2).

Data collection process

After searching and manually removing duplicates, three researchers independently screened the abstracts to identify relevant articles. When there was a discordant result between the three researchers, a consensus meeting was conducted to discuss and reach an agreement. The full texts were then screened for selection or rejection in this review using the inclusion criteria.

The following data (if available) were extracted from each article: country where the study was conducted, study design, period of inclusion, number of participants, type of medical structure where patients were admitted, comparison group when available, demographic information, duration of follow-up, clinical findings at follow-up, proportion of patients lost to follow-up, and risk factors.

As a consequence of the diversity in patient populations and nature of the studies that have been carried out, a formal meta-analysis was not possible. Therefore, the study results were summarized to give an overview of the long-term persistence of clinical symptoms in COVID-19 patient after an acute infection. When percentages were not presented in the articles, we performed the calculation from the available data.

The results of the review were divided into different paragraphs according to the duration of follow-up.

Results

General characteristics of studies

The search algorithm produced 9456 articles from the PubMed and Google Scholar databases (Fig. 1). After removing

duplicates, 5452 articles were screened by reading their title and abstract. In total, 362 articles were processed for the full-text screening. Finally, we selected 37 articles (Table 1) which met the inclusion criteria for the qualitative analysis of the systematic review.

The studies which met the inclusion criteria are presented in Tables 2, 3, and 4.

A total of 37 studies were included, 23 of which were conducted in Europe, including seven in Italy [14–20], four in France [21–24], three in Norway [25–27], two in Spain [28, 29], two in Germany [30, 31], one in Austria [32], one in Denmark [33], one in the Faroe Islands [34], one in Switzerland [35], and one in the UK [36]. Six studies were conducted in China [37–42], five in the United States (US) [43–47], two in Iran [48, 49], and one in Turkey [50]. The majority of the studies were conducted in a hospital setting and most were monocentric.

Fig. 1 PRISMA flowchart of selected studies

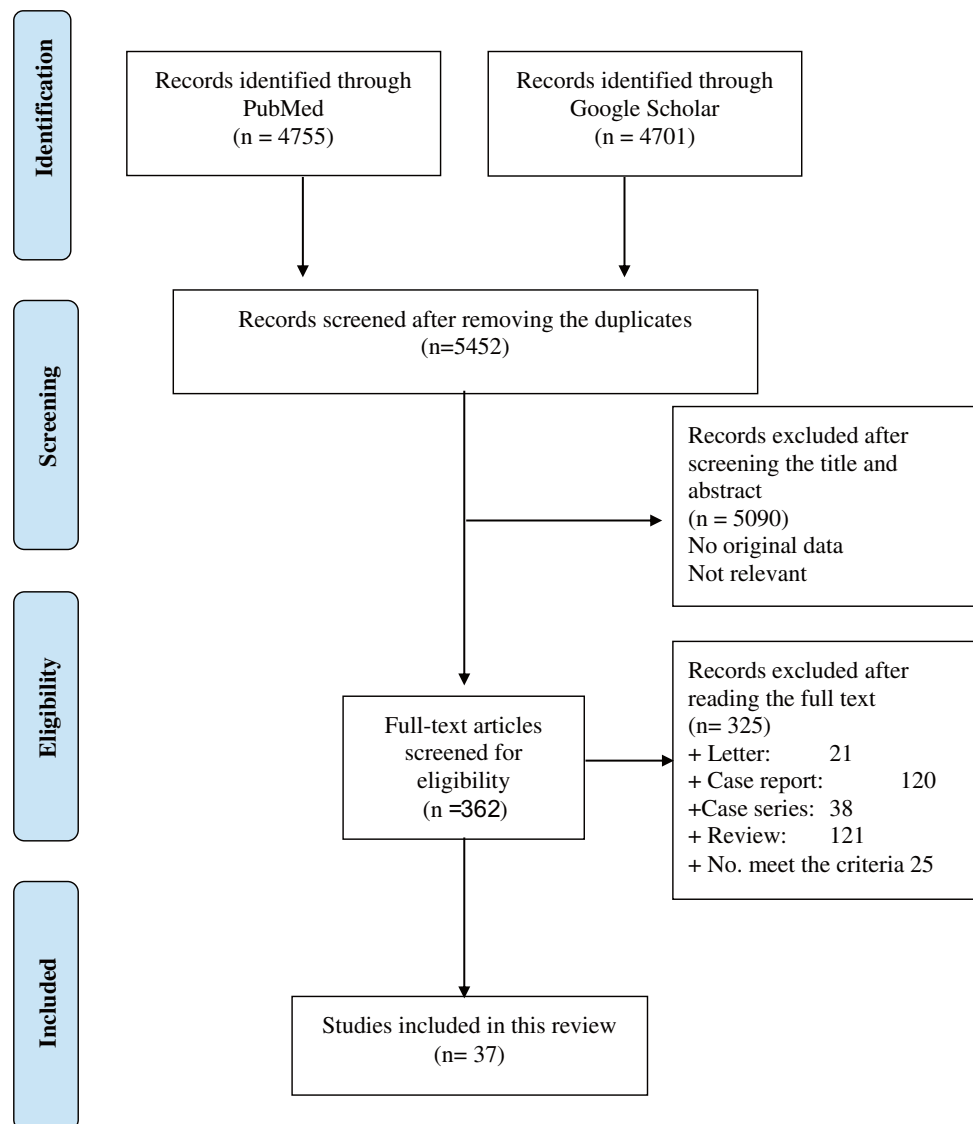


Table 1 Included articles

Citation number	1st Author, year	Title
[14]	Carfi, 2020	Persistent Symptoms in Patients After Acute COVID-19
[15]	Monti, 2021	Two-months quality of life of COVID-19 invasively ventilated survivors; an Italian single-center study
[16]	Baricich, 2021	Midterm functional sequelae and implications in rehabilitation after COVID-19: a cross-sectional study
[17]	Fortini, 2021	COVID-19: persistence of symptoms and lung alterations after 3–6 months from hospital discharge
[18]	Tosato, 2021	Prevalence and Predictors of Persistence of COVID-19 Symptoms in Older Adults: A Single-Center Study
[19]	Munblit, 2021	Preliminary Evidence on Long COVID in children
[20]	Boscolo-Rizzo, 2021	Long COVID In Adults at 12 Months After Mild-to-Moderate SARS-CoV-2 Infection
[21]	Carvalho-Schneider, 2021	Follow-up of adults with noncritical COVID-19 two months after symptom onset
[22]	Garrigues, 2020	Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19
[23]	Nguyen, 2021	Long-term persistence of olfactory and gustatory disorders in COVID-19 patients
[24]	Ghosn, 2021	Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort
[25]	Stavem, 2020	Persistent symptoms 1.5–6 months after COVID-19 in non-hospitalized subjects: a population-based cohort study
[26]	Soraas, 2021	Self-reported Memory Problems Eight Months after Non-Hospitalized COVID-19 in a Large Cohort
[27]	Blomberg, 2021	Long COVID affects home-isolated young patients
[28]	Rosales-Castillo	Persistent symptoms after acute COVID-19 infection: importance of follow-up
[29]	Fernández-de-Las-Peñas, 2021	Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability
[30]	Daher, 2020	Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae
[31]	Seeßle, 2021	Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study
[32]	Sonnweber, 2021	Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial
[33]	Bliddal, 2021	Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients
[34]	Petersen, 2020	Long COVID in the Faroe Islands—a longitudinal study among non-hospitalized patients
[35]	Nehme, 2020	COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings
[36]	Halpin, 2021	Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation
[37]	Zhao, 2020	Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery
[38]	Liang, 2020	Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge
[39]	Weng, 2021	Gastrointestinal sequelae 90 days after discharge for COVID-19
[40]	Xiong, 2021	Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study
[41]	Huang C, 2021	6-month consequences of COVID-19 in patients discharged from hospital: a cohort study
[42]	Huang D, 2020	Long-term outcomes and sequelae for 464 COVID-19 patients discharged from Leishan hospital in Wuhan, China
[43]	Jacobs, 2020	Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection
[44]	Jacobson, 2021	Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic
[45]	Chopra, 2020	Sixty-Day Outcomes Among Patients Hospitalized With COVID-19
[46]	Cellai, 2020	Characterization of prolonged COVID-19 symptoms in an outpatient telemedicine clinic
[47]	Graham, 2021	Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers”

Table 1 (continued)

Citation number	1st Author, year	Title
[48]	Simani, 2021	Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19
[49]	Asadi-Pooya, 2021	Risk Factors Associated with Long COVID Syndrome: A Retrospective Study
[50]	Kayaaslan, 2021	Post-COVID syndrome: A single-center questionnaire study on 1007 participants recovered from COVID-19

In addition, one study conducted in Norway used laboratory recruitment and one national study was conducted in Denmark and in the Faroe Islands.

A total of 33 studies were conducted prospectively in cohorts of patients mostly through consultations or telephone interview [14, 15, 17, 18, 20–36, 38–47, 49, 50], three studies were cross-sectional studies [16, 19, 48], and one was a retrospective cohort study [37]. Inclusion of patients at the acute phase took place in the first six months of 2020 for the majority of studies. The Danish and US studies ended in August 2020 [33, 44] and four studies ended in November 2020 [19, 29, 47, 49]; one Italian study ended in December 2020 [18].

A total of 9677 patients were included, with numbers by study ranging from 26 to 2685, with the mean age ranging from 11 to 73 years old and with the proportion of females ranging from 10 to 77%. Eighteen studies were conducted only among in-patients [14–16, 18, 22, 28–30, 36–43, 45, 48], eleven were conducted among in-patients and out-patients [19, 21, 23, 24, 27, 31, 32, 34, 44, 49, 50], and eight among out-patients only [17, 20, 25, 26, 33, 35, 46, 47]. Twenty-three studies included critically-ill patients, who required an oxygen therapy or admission to the ICU [14–16, 19, 20, 22, 24, 28, 31, 32, 36–45, 48–50].

Only three studies used non-COVID-19 patient comparison groups [26, 40, 47]. The proportion of patients lost to follow-up ranged from 4 to 73%, and in six studies this information was not provided [18, 19, 28, 44, 47, 49].

Twelve studies included follow-up that lasted from between 4 to less than 12 weeks (Table 1), nineteen studies lasted from 12 weeks to less than 6 months (Table 2), five studies lasted at least 6 months (Table 3), and one study with two times of follow-up (3–6 months and 6–12 months) [49]. Three studies exceeded after 1 year of follow-up [20, 31, 49].

In most studies, the overall persisting symptoms included general, neurological, respiratory, and cardiac symptoms. Some studies focused on specific symptoms such as taste and smell disorders, gastro-intestinal symptoms, or the impairment of physical activities, as evaluated by 2-min walking tests (short physical performance battery) [16].

Persistence of post-acute symptoms in studies with a follow-up of less than 12 weeks

A total of twelve studies were conducted with a follow-up of less than 12 weeks. Eight were conducted in Europe and four observed in the US.

Eight studies were conducted among in-patients only [14, 18, 19, 28, 30, 36, 43, 45] with the proportion of patients in the ICU and/or requiring mechanical ventilation ranging from 4.4 to 100%. In these eight studies, the most frequent symptoms persisting at 12 weeks were fatigue (31–64%) [14, 18, 28, 30, 36, 45], dyspnea (31–54%) [14, 15, 18, 28, 30, 36, 43], and arthralgia (22–55%) [14, 18, 43], although arthralgia was only assessed in two studies, and a dry or productive cough (5–46%) [14, 18, 28, 30, 36, 43].

Other relatively frequent persisting symptoms included thoracic pain/chest tightness (18–22%) [14, 30], ear, nose and throat-related symptoms (ENT) such as a sore throat (7–17%) [14, 30, 36], smell disorders (2–17%) [14, 15, 28, 30, 43], taste disorders (1–16%) [14, 15, 28, 30, 43], rhinitis (12–15%) [14, 30], dysphonia (20%) [36], swallowing problems (8%) [36], and general symptoms such as myalgia (1–22%) [14, 28, 30, 36, 43], or headache (9–15%) [14, 30, 43].

Persisting gastrointestinal symptoms were less frequently observed with diarrhea (3–9%) [14, 30, 43], anorexia (8%) [14, 36], nausea (6%) [30], stomach pain (3%) [30], ulcer (1%) [43], and dysphagia (8%) [36]. Persisting fever was rarely mentioned (1–3%) [30, 43].

Four studies were conducted in outpatients only or in populations of patients with a majority of outpatients [21, 35, 46, 47]. In these studies, persistent fatigue ranked first (12–84%) [35, 46, 47], while smell or taste disorders (4–74%) [46, 47], dyspnea (8–50%) [21, 35, 47], arthralgia (16–31%) [21, 46], cough (5–54%) [35], and thoracic pain/chest tightness (13–42%) [21, 47] were less prevalent than in studies conducted in in-patients. In addition, weight loss affected 17% patients in one study [21].

Risk factors were investigated in one study. In this study, the persistence of symptoms overall tended to be associated with older age, severity of symptoms at the acute phase, and abnormal auscultation at onset [21].

Table 2 Four to 12 weeks of follow-up

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Jacobs [43]	US, one hospital	Prospective cohort (telephone interview), 22/03/2020–16/04/2020	183 in-patients (requiring oxygen support during hospitalization: 164, requiring high-flow oxygen: 15, requiring intubation and mechanical ventilation: 8)	None	57 (range 48–68)	38	35 days (1 months)	48	Female sex and older age associated with persisting symptoms overall	Arthralgia (55), fatigue (44), dyspnea (32), cough (25), myalgia (21), sputum (15), headache (13), taste disorder (10), smell disorder (9), conjunctivitis (8), diarrhea (4), fever (1), ulcer (1)	–	Single center, small sample size, no control group, based on self-reported, not available data of pulmonary function and 6-min walking distance at baseline, for new symptoms onset, it didn't identify if these symptoms were persistent following COVID-19, worsened after recovery or occurred post-discharged, not evaluate the mild COVID

Table 2 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Cellai [46]	U.S., 4 hospitals	Prospective cohort (telephone interview), 24/03/2020–26/03/2020	26 out-patients	None	47.5 (range 23–78)	77	6 week (1,4)	Fatigue (65), cough (54), dyspnea with activity (50), headache (50), nasal congestion (46), chest tightness (42), smell disorder (31), joint pain (31), myalgia (27), weakness (27), fever (12), dizziness (12), chills (12), wheezing (12), sore throat (19), nausea (19), anorexia (12), dyspnea at rest (12), diarrhea (12), sweats (8), palpitation (23), taste disorder (4), rash (4)	10	Not evaluated	–	Small sample size, no control group, based on self-reported by telephone

Table 2 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Grahams [47]	US, one hospital	Prospective cohort (telephone interview), May to November 2020	50 out patients	50	43.2 ± 11.3	66	6 weeks (1.4 months)	Fatigue (84), headache (64), smell disorder (74), taste disorder (64), myalgia (60), dizziness (40), dyspnea (38), chest pain (28), gastrointestinal symptoms (diarrhea, nausea, vomiting, gastroptosis, 28), hearing problems (19), vision problems (18), seizure (1), dysphagia (2),	56	Not evaluated	-	Single center, small sample size, no control group, based on self-reported by telephone
Daher [30]	Germany, one hospital	Prospective cohort (follow-up consultation, February to May, 2020)	33 in-patients, not required mechanical ventilation	None	64 ± 3	33	6 weeks (1.5 months)	Fatigue (45), cough (33), dyspnea (33), thoracic pain (18), myalgia (15), headache (15), rhinitis (12), smell disorder (12), taste disorder (9), sore-throat (9), diarrhea (9), nausea (6), abdominal pain (3), fever (3)	42	Not evaluated	-	Single center, small sample size, no control group

Table 2 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Nehme [35]	Switzerland, one hospital	Prospective cohort (telephone interview), 18/03/2020–15/05/2020	510 out-patients	None	42.8 ± 13.7	60	43 (1.5 months)	Fatigue (12), taste and/or smell disorder (10), dyspnea (10), cough (5), headache (2), digestive symptoms (1)	24	Not evaluated	–	Single center, no control group, based on self-reported by telephone missing data and ascertainment bias at each assessment interval
Halpin [36]	United Kingdom, one hospital	Prospective cohort (telephone interview), March to May 2020	100 in-patients (ICU: 32)	None	65 (range 20–93)	46	48 days (1–2 months)	Fatigue (64), dyspnea (54), cough (46), pain (22), dysphonia (20), sore-throat (17), continence problem (10), dysphagia (8), anorexia (8)	48	Female sex associated with fatigue and dyspnea	–	Single center, small sample size, no control group based on self-reported by telephone
Rosales-Cas-tillo [28]	Spain, one hospital	Prospective cohort 13/03/2020–15/05/2020	118 in-patients (ICU: 9, invasive mechanical ventilation: 5, non-invasive mechanical ventilation: 4)	None	60.16 ± 15.08	44	51 days (2 months)	Fatigue (31), dyspnea (31), cough (5), smell disorder (2), taste disorder (1), myalgia (1)	Not provided	Not evaluated	COVID-19 diagnosis was assessed by serology in some cases	Single center, small sample size, no control group, included only the hospitalized patients

Table 2 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Carfi [14]	Italy, one hospital	Prospective cohort (follow-up consultation), 21/04/2020–29/05/2020	143 in-patients (non-invasive ventilation: 21, invasive ventilation: 7)	None	56.5 ± 14.6	37	60 days (2 months)	Fatigue (53), dyspnea (43), arthralgia (27), thoracic pain (22, cough (18), smell disorder (17), Sjögren's syndrome (16), rhinitis (15), conjunctivitis (10), taste disorder (10), headaches (9), sputum (8), anorexia (8), sore-throat (7), vertigo (6), myalgia (6), diarrhea (3)s	20	Not evaluated	–	Single center, small sample size, no control group, lack of information history before acute COVID-19 illness, lack of detail on symptom severity
Carvallho-Schneider [21]	France, one hospital	Prospective cohort (telephone interview), 17/03/2020–03/06/2020	130 non-critical adult patients (in patients: 53)	None	49 ± 15	56	2 months	Taste and smell disorders (23), myalgia, headaches and/or fatigue (22), weight loss (17), arthralgia (16), chest pain (13), diarrhea and/or vomiting (12), skin symptoms (12), palpitation (11), dyspnea (8)	43	Age from 40 to 60 years old, severity of symptoms onset and abnormal auscultation at onset associated with symptom persistence overall	–	Single center, small sample size, no control group, self-reported by telephone interview
Chopra [45]	US, 38 hospitals	Prospective cohort (telephone interview), 16/03/2020–01/07/2020	1250 (ICU: 165)	None	62 (range 50–72)	48.2	2 months	Smell and/or taste disorders (64)	24.2			No control group, self-reported by telephone interview

Table 2 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Monti [15]	Italy, one hospital	Prospective cohort (telephone interview), 25/02/2020–27/04/2020	39 ICU patients (mechanical ventilation: 38)	None	56 ± 10.5	10	61 days (2 months)	Exertional dyspnea (54), taste disorder (16), smell disorder (3)	7	Not evaluated	–	Single center, small sample size, no control group, based on self-reported by telephone
Tosato [18]	Italy, one hospital	Prospective cohort, one hospital, 21/04/2020–21/12/2020	137 patients discharged in-patients (only > 65 years)	None	73.1 ± 6.2	39	76.8 (2.5 months)	Fatigue (53), dyspnea (52), joint pain (22), cough (17)	Not provided	Supplementary oxygen and prescription of exoheparin during acute COVID-19 were associated with a higher likelihood of persistent symptoms	Study on people 65 years and older	Single center, small sample size, no control group

Persistence of symptoms in studies with a follow-up of between 12 weeks and 6 months

A total of twenty studies (Table 2) were conducted with a follow-up of between twelve weeks and six months (one study observed the persistence of symptoms at 3–6 month and 6–12 months [49]). Nine studies were conducted in Europe, six in China, one in Iran, and one in the US.

Nine studies [16, 22, 37–42, 48] were conducted among in-patients only, with the proportion of patients in the ICU and/or requiring mechanical ventilation ranging from 4 to 24%. In these studies, the most frequent symptoms persisting for 12 weeks to 6 months were fatigue (16–63%) [22, 37, 38, 40, 41, 48], dyspnea (15–61%) [22, 37, 38, 40–42], thoracic pain (5–62%) [22, 38, 40, 41], and a dry or productive cough (2–59%) [22, 37, 38, 40]. However, four studies addressing the persistence of thoracic pain/chest tightness [22, 38, 40, 41], its prevalence only ranged from 5 to 62%. The persistence of arthralgia was evaluated in only two studies, with a prevalence of 8% and 9% [40, 41].

Other relatively frequent persisting symptoms included related neurological-ENT (ear-nose-throat) symptoms with a smell disorder (6–13%) [22, 41, 42], taste disorder (4–11%) [22, 37, 41, 42], dysphonia (10%) [42], hearing problems (9%) [42], vision problems (8%) [42], swallowing problems (7%) [42], a sore throat (4%) [40, 41], and general symptoms such as hair loss (20–29%) [22, 40, 41], fever (< 1–20%) [38, 41], headache (2–18%) [37, 41], or sweating (24%) [40].

Persisting gastrointestinal symptoms ranged from 31 to 44% [38, 39], including diarrhea (5–26%) [38, 39, 41], anorexia (8–24%) [39, 41, 42], nausea (18%) [39], acid reflux (18%) [39], abdominal distension (14%) [39], vomiting (9%) [39], stomach pain (7%) [39], belching (10%) [39], discontinuous flushing (5%), and bloody stools (2%) [39].

Eleven studies were conducted in outpatients only or in a population of patients with a majority of outpatients [17, 19, 24, 25, 27, 32–34, 44, 49, 50]. In these studies, the persistence of dyspnea ranked first (8–37%) [17, 25, 27, 32–34, 44, 49, 50] while fatigue (11–42%) [17, 19, 33, 34, 44, 49, 50], thoracic pain (3–14%) [17, 19, 32, 34, 49, 50], and a persistent cough (4–17%) [17, 19, 25, 27, 32–34, 44, 49, 50] were less prevalent than in studies conducted in inpatients. Persistent arthralgia was reported in 7–18% of patients [17, 19, 25, 34, 49]. The persistence of related neurological-ENT symptoms was relatively frequent, including notably smell disorders (3–24%) [17, 19, 25, 27, 32–34, 49], taste disorders (2–17%) [17, 19, 25, 27, 33, 34, 49], and rhinitis (2–12%) [19, 25, 33, 34, 44].

Other persisting symptoms mentioned were general symptoms such as myalgia (7–24%) [17, 19, 25, 32, 34,

44, 49, 50], sweating (9–24%) [32, 49], alopecia/hair loss (12–17%) [44, 50], weight loss (3–9%) [19, 49, 50], and headache (6–12%) [17, 19, 25, 27, 33, 34, 44, 49, 50]. The persistence of gastrointestinal symptoms was rarely reported.

Risk factors were investigated in fourteen studies. The persistence of overall symptoms was associated with being female [24, 32, 33, 49], older [34], with a high body mass index [33], chronic respiratory disease [32], and a number of comorbidities and symptoms during the acute phase [25]. In one study, the persistence of at least two symptoms at follow-up was associated with dyspnea at the onset of symptoms [44]. Persistent fatigue was associated with troponin levels during the acute phase [38], and with being female [40, 41], while persistent dyspnea was associated with being female [27, 40–42] having increased levels of cholesterol, cancer [42], and the severity of initial symptoms [41]. The persistence of physical impairment was associated with admission to the intensive care unit and mechanical ventilation in one study [16]. In one study, persistent impaired cardiac function was associated with being female and having chronic respiratory disease [42]. Persistent hair loss was associated with being female in one study [40], while persistent muscle weakness was associated with being female and the severity of the initial symptoms [41]. Seven studies accessed the severity of illness at the acute phase and evidenced an association with symptoms persistence [17, 24, 27, 41, 42, 49, 50].

Persistence of symptoms in studies with more than 6 months follow-up

Only six studies were conducted with a follow-up time of more than six months (Table 3). Five of them were conducted in Europe and one in Iran.

One study was conducted among inpatients only [29], with a proportion of severe patients of 7%. In this study, the most frequent symptoms which persisted at eight months follow-up were fatigue (61%), dyspnea with activity (48%), dyspnea at rest (7%), thoracic pain (7%), palpitation (7), and cough (2%).

Five studies were conducted in outpatients only or in a population with a majority of outpatients [20, 23, 26, 31, 49]. In these studies, persistent fatigue ranked first (25–34%) [20, 26, 31, 49], while dyspnea (13–22%) [20, 26, 31, 49] was less frequent than in the only study conducted in inpatients. Other persisting symptoms which were mentioned were smell and or taste disorder (3–24%) [20, 23, 26, 31, 49] and a cough (2–13%) [20, 26, 31, 49]. Risk factors were investigated in four studies; females had more risk for symptoms persistence [20, 23, 31, 49].

Table 3 Twelve weeks to 6 months of follow-up

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Bliddal [33]	Denmark, national study	Prospective cohort (on line survey), 5 March to 12 August 2020	129 out-patients	None	45.6 ± 16.1	62	> 12 weeks (3 months)	Fatigue (16), dyspnea (11), smell disorder (8), headache (7), arthralgia/myalgia (6), taste disorder (5), cough (4), thoracic pain (3), sore-throat (3), rhinitis (2), diarrhea (2), anorexia (1), abdominal pain (1), nausea (1), conjunctivitis (< 1), chills/fever (< 1)	46	Being female and body mass index associated with persisting symptoms overall	-	Single center, small sample size, no control group
Liang [38]	China, one hospital	Prospective cohort (follow-up consultation), 31/01/2020–09/06/2020	76 in-patients (ICU: 7, invasive mechanical ventilation: 0)	None	41 ± 13.8	72	3 months	Thoracic pain on exertion (62), palpitation on exertion (62), dyspnea (61), fatigue (59), cough (59), sputum (43), diarrhea (26), fever (20)	44	Troponin-I levels during acute illness associated with fatigue at follow-up	-	Single center, small sample size, no control group, could not confirm abnormal lung function caused by the prior medical history or newly disease

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Weng [39]	China, 12 hospitals	Prospective cohort (telephone interview), 16/01/2020–07/03/2020	117 in-patients (required supplemental oxygen: 102, ICU: 28, requiring HFNC* or non-IMV or both: 20)	None	Age \geq 60 years (45.3)	44	3 months	Gastrointestinal symptoms overall (44), anorexia (24), nausea (18), acid reflux (18), diarrhoea (15), abdominal distension (14), belching (10), vomiting (9), abdominal pain (7), bloody stools (2)	Not documented	Not evaluated	–	Single center, small sample size, no control group, self-reported by telephone interview, missing of some blood biochemical test (markers for inflammation and serum titer of SARS-CoV-2), bias selection: 71% of discharged patients had sufficient data to include in this study
Zhao [37]	China, 4 hospitals	Retrospective cohort (follow-up consultation), 20/01/2020–24/02/2020	55 in-patients (requiring oxygen therapy: 14), mechanical ventilation: 0)	None	47.74 \pm 15.49	42	3 months	Gastrointestinal symptom (31), headache (18), fatigue (16), dyspnoea (15), taste disorder (4), cough (2)	29	Not evaluated	–	Small sample size, no control group, not evaluate the critical patients

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Xiong [40]	China, one hospital	Prospective cohort (telephone interview), before 01/03/2020	538 adult in-patients (severe: 180, critical: 27)	184 non-COVID-19 individuals with similar demographics	52 (range 41–62)	55	97 days (3 months)	Hair loss (29), fatigue (28), dyspnea (26), sweating (24), thoracic pain (12), tachycardia (11), cough (10), arthralgia (8), myalgia (5), chills (5), discontinuous flushing (5), limb oedema (3), dizziness (3), sore-throat (3), newly diagnosed hypertension (1)	40	Being female associated with fatigue, dyspnea and hair loss		Single center, small sample size, based on self-reported by telephone, interview, not critical patients
Sonneberger [32]	Austria, three hospitals	Prospective cohort (follow-up consultation), before 29/04/2020	133 patients (in-patients: 109 patients, ICU: 32 patients, no oxygen supply; non-invasive ventilation: 3, invasive ventilation: 29)	None	57 ± 14	43	100 days (3 months)	Dyspnea (36), pain (24), night sweet disorder (19), cough (17), vomiting or diarrhea (9)	30	Chronic respiratory disease and female sex were independent factors associated with persistent symptoms		Single center, small sample size, no control group, no available data of comorbidity before COVID-19 pandemic, chest thoracic scanner (according to ethics approval) had some limitation

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Garrigues [22]	France, one hospital	Prospective cohort (telephone interview), 15/03/2020–14/4/2020	120 in-patients (ICU: 24)	None	63.2 ± 15.7	37	110 days (3 months)	Fatigue (55), dyspnea (42), hair loss (20), cough (17), smell disorder (13), taste disorder (11), thoracic pain (11)	57	Not evaluated	–	Single center, small sample size, no control group, based on self-reported by telephone
Stavem [25]	Norway, three laboratories	Prospective cohort (postal survey), before 01/06/2020	451 out-patients	None	49.8 ± 15.2	56	117 days (1.5–6 months)	Dyspnea (16), smell disorder (12), taste disorder (10), cough (10), arthralgia (8), myalgia (7), headaches (6), sore-throat (5), rhinorrhea (4), visual impairment (4), abdominal pain (3), wheeze (3), nausea/vomiting (2), diarrhea (2), conjunctivitis (2), seizure (1), skin rash (1), ear pain (1), enlarged lymph node (1), chills (1), fever (< 1)	52	Number of comorbidities and symptoms at acute phase associated with persistent symptoms overall	Single center, no control group, self-reported by questionnaire, homogeneous ethnicity may be associated with health recall bias of symptoms during acute phase	

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age (mean \pm SD (years) of COVID-19 patients)	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Baricich [16]	Italy, one hospital	Cross-sectional (follow-up consultation).01/03/2020–31/05/2020	204 in-patients (ICU: 13 patients, mechanical ventilation: 10), ICU admission (13 patients), mechanical ventilation (10 patients)	None	58 \pm 12.8	40	3 to 6 months	Impaired mobility as assessed by 2 min walking test (32); impaired lower extremity functionality functional performance as assessed by Short Physical Performance Battery (14)	73	ICU and mechanical correlated with physical impairment	–	Single center, small sample size, no control group
Fortini [17]	Italy, one hospital	Prospective cohort (follow-up consultation), July to October 2020	59 out-patients	None	68.2 \pm 12.8	48	123 days	Fatigue (42), dyspnea (37), taste disorder (17), smell disorder (15), anorexia (15), confusion (14), cough (12), chest pain (10), arthralgia (9), myalgia (9), fever (9), headache (9), palpitation (7)	43.8	Not evaluated	–	Single center, small sample size

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Jacobson [44]	US, one hospital	Prospective cohort (follow-up consultation), before August 2020	118 patients (in-patients: 22, out-patients: 96, ICU: 11, intubation: 6)	None	43.4 \pm 14.4	47	3–4 months	Fatigue (30), dyspnea (27), smell/taste disorder (21), myalgia (18), thoracic pain (14), hair loss (12), cough (9), rhinorrhea (7), nausea/vomiting/diarrhea (7), headache (6), palpitation (6), sore throat (3), fever/chills (1)s	Not documented	Dyspnea at onset associated with persistent symptoms		Single center, small sample size, no control group, related to recruitment: hospitalized patients had longer time between COVID-19 diagnosis and follow-up, bias selection: participants in follow-up visit may have more persistent symptoms than the average patients
Petersen [34]	Faroe Island, national study	Prospective cohort (telephone interview), 03/03/2020–22/04/2020	180 patients (out-patients: 172, in-patients: 8)	None	39.9 \pm 19.4	54	125 days (1.5–7 months)	Fatigue (28), smell disorder (24), taste disorder (16), arthralgia (11), cough (11), rhinorrhea (9), dyspnea (8), myalgia (7), headache (7), chest tightness (6), chills (5), nausea (4), diarrhea (3), sore-throat (2), anorexia (2), rashes (2)	4	Age-group 50–66 associated significantly with persisting symptoms as compared to youngest group (0–17 years)		Single center, small sample size, no control group, self-reported by telephone interview, lacking the information on medical history before acute COVID-19 illness, lack of evaluation the severity of disease

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Kay-sassian [50]	Turkey, one hospital	Prospective cohort (self-questionnaire), 1/8/2020–31/10/2020	1007 patients (416 in-patients, ICU: 58)	None	45.0 \pm 16.4	54	20 weeks (4, 6 months)	Fatigue (24), dyspnea (21), hair loss (17), myalgia (13), chest pain (6), palpitation (6), headache (6), cough (5), wheezing (4), weight loss (3), smell disorder (3), taste disorder (2), rash (1), abdominal pain (0.4), constipation (0.3), diarrhea (0.1)	8	Severe acute illness, hospitalization, and presence of comorbidities were detected as independent factor for development of persistence symptoms	–	Single center, no control group, self-reported by questionnaire
Munblit [19]	Italy, one hospital	Cross-sectional (follow-up consultation and online-survey), March to November 2020	129 patients \leq 18 years (out-patients: 123, in-patients: 6, ICU: 3)	None	11 \pm 4.4	48	162 days (5 months)	Rhinorrhea (12), fatigue (11), lack of concentration (10), headaches (10), myalgia (10), weight loss (8), arthralgia (7), skin rashes (7), chest tightness (6), constipation (6), cough (5), smell disorder (5), palpitation (4), thoracic pain (3), taste disorder (3), diarrhea (2), abdominal pain (2), menstruation disorder (2)	Not documented	Not evaluated	–	Single center, small sample size, no control group

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Blomberg [27]	Norway, 2 hospitals	Prospective cohort (follow-up consultation), 28/02/2020–04/04/2020	247 out-patients	None	43 (range 27–55)	53	6 months	Fatigue (30), smell and/or taste disorder (27), dyspnea (15), headache (11), dizziness (10), cough (6), palpitation (6), fever(2)	11	mild COVID-19 out-patient were higher risk for dyspnea persistence		Small sample size, no control group
Ghosh [24]	France, 63 centers	Prospective cohort (follow-up consultation), 24/01/2020–10/4/2020	1137 patients (ICU: 288)	None	61 (range 51–71)	37	6 months	≥ 3 of symptoms (fatigue, dyspnea, joint pain, myalgia, headache, rhinorrhea, cough, sore throat, smell and taste disorders: 24), Smell and/or taste disorder (7)	60.2	Female, having ≥ 3 symptoms at admission and transfer to ICU during acute phase		No control group

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Huang C [41]	China, one hospital	Prospective cohort (follow-up consultation), 07/01/2020–29/05/2020	1733 discharged in-patients (requiring oxygen therapy: 1172, requiring HFNC, NIV or IMV: 122, ICU: 76) *	None	57 (range 47–65)	48	186 days (6 months)	Fatigue or muscle weakness (63), dyspnea (26), hair loss (22), smell disorder (11), palpitations (9), arthralgia (9), anorexia (8), taste disorder (7), dizziness (6), thoracic pain (5), diarrhea or vomiting (5), sore throat or difficult to swallow (4), skin rash (3), myalgia (2), headache (2), fever (< 1%)	30	Being female and severity of initial symptoms associated with fatigue or muscle weakness and dyspnea	Single center, no control group, not available data of pulmonary function and 6-min walking distance at baseline, for new symptoms onset, it didn't identify if these symptoms were persistent following COVID-19, worsened after recovery or occurred post-discharged, not evaluate the mild COVID-19 patients	

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Huang D [42]	China, one hospital	Prospective cohort (telephone interview), February–April 2020	464 discharged in-patients (ICU: 19)	None	57 (range 15–93)	49	6 to 8 months	Dyspnea (33), impaired cardiac function (22), pain (13), feeding difficulties (12), dysphonia (10), hearing impairment (9), visual impairment (8), swallowing difficulties (7), smell disorder (6), taste disorder (4)	53	Being female, increased levels of cholesterol and cancer associated with dyspnea Being female and chronic respiratory disease associated with impaired cardiac function Being female associated with pain ICU associated with smell and taste disorders	–	Single center, no control group, no control group, self-reported by telephone interview, data collected from medical record, may have missed some information, functional status before COVID-19 was based on the memory of patients
Simani [48]	Iran, one hospital	Cross-sectional (follow-up consultation), 22/2/2020–20/4/2020	120 in-patients (ICU: 9)	None	54.62 ± 16.94	33	6 months	Fatigue (18)	70	None identified	–	Single center, small sample size Patients' premorbid psychiatric status was not documented, not evaluate the patients' depression and quality of life score at the survey time

Table 3 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Asadi-Pooya [49]	Iran, 55 centers	Prospective cohort (telephone interview), 19/02/2020–20/11/2020	2915 discharged patients (ICU: 344)	None	52 ± 15	49		<p>3–6 months: Fatigue (32), exercise intolerance (26), myalgia (21), dyspnea (21), weakness (20), joint pain (18), headache (12), chest pain (11), palpitation (11), cough (10), sweating (9), weight loss (9), dizziness (8), sputum (6), smell disorder (5), score throat (5), weight gain (5), anorexia (4), taste disorder (3), diarrhea (3), abdominal pain (3)</p>	Not documented	Females, respiratory symptoms at admission and severity of the illness were associated with symptoms persistence	–	No control group, based on self-reported by telephone

Table 4 More than 6 months of follow-up

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Fernández-Las-Peñas [23]	Spain, four hospitals	Prospective cohort (telephone interview), 01/09/2020–30/11/2020	1142 inpatients (ICU: 80)	None	61 \pm 17	48	7 months	Fatigue (61), dyspnea with activity (48), dyspnea at rest (7), chest pain (7), tachycardia palpitation (7), cough (2)	4.8	Risk factor associated with fatigue and dyspnea: females gender, number of pre-existing comorbidities, number of symptoms at admission	No control group, self-reported by telephone interview	
Nguyen [23]	France, one hospital	Prospective cohort (telephone interview), 03/03/2020–27/4/2020	125 discharged patients with smell or taste disorder at onset (nearly all non-severe)	None	36 (range 16–85)	55	7 months	Smell disorder (24), taste disorder (21) at 7 months	38	Being female associated with persistence of symptoms	Single center, small sample size, no control group, self-report by telephone interview	

Table 4 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrollment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) of COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Soraas [26]	Norway, four laboratories	Prospective cohort (self-questionnaire), 01/02/2020–15/04/2020	588 adults out-patient (nearly all symptomatic)	5225 SARS-CoV-2 PCR negative patients and 3189 randomly selected non-tested individual from the Norwegian population	47.3 ± 13.9	57	248 days (8 months)	Fatigue (31), taste or smell disorders (18), dyspnea (14), cough (13), fever (8)	26–35	Not evaluated		Single center, self-reported by questionnaire, response bias at follow-up (patient with SARS-Cov-2 status at baseline could lead to participant)
Boscolo-Rizzo [20]	Italy, one hospital	Prospective cohort (telephone interview), 1/3/2020–31/3/2020	161 out-patients	None	47 (range: 18–76)	61	12 months	Fatigue (27), smell and/or taste disorder (22), smell disorders (21), taste disorder (15), dyspnea (13), myalgia (9)	14	Female, aged 40–54, BMI ≥ 25 are associated with higher risk of long COVID		Single center, no control group, based on self-reported by telephone

Table 4 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean \pm SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Seeblee [31]	Germany, one hospital	Prospective cohort (follow-up consultation), 22/2/2020–18/04/2020	96 patients (hospitalized: 21, invasive ventilation: 4)	None	57 (range: 50–63)	55.2	12 months	34.3	34.3	Not evaluated		

Table 4 (continued)

Reference	Country and setting	Study design and period of inclusion	COVID-19 patient numbers and status at enrolment	Comparison group	Age mean ± SD (years) of COVID-19 patients	Female (%) COVID-19 patients	Duration of follow-up	Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%)	Lost to follow-up (%)	Main risk factors for persisting symptoms	Remarks	Limitation
Asadi-Pooya [49]	Iran, 55 centers	Prospective cohort (telephone interview), 19/02/2020–20/11/2020	2915 discharged patients (ICU: 344)	None	52 ± 15	49						
							6–12 months:		Not documented	Females, respiratory symptoms at admission and severity of the illness was associated with symptoms persistence		No control group, based on self-reported by telephone
							Fatigue (25), exercise intolerance (20), dyspnea (17), myalgia (15), joint pain (15), weakness (14), headache (10), chest pain (9), weight loss (9), palpitation (8), dizziness (6), sweating (7), cough (7), sputum (6), smell disorder (5), weight gain (5), sore throat (4), anorexia (4), taste disorder (3), diarrhea (3), abdominal pain (3),					

^aHFNC high-low nasal cannula, NIV non-invasive mechanical ventilation, ICU intensive care unit

Discussion

Eighteen studies were conducted in hospitalized patients with large variations in the prevalence of persisting symptoms, which is likely to be due to the heterogeneity in terms of patient demographics, disease severity at the acute phase, and the care provided. Fatigue (16–64%), dyspnea (15–61%), arthralgia (8–55%), cough (2–59%), and thoracic pain (5–62%) were the most frequent persisting symptoms. In nineteen studies conducted in outpatients or in population with a majority of outpatients, the persistence of these symptoms was less prevalent and 3–24% of patients reported prolonged smell and taste disorders (Table 5).

Risk factors were evaluated in twenty-one studies. The most common risk for symptom persistence were being female, older age, chronic respiratory disease, high body mass index (BMI), cancer, and the severity of COVID-19 at the acute phase.

Common limitations among the studies reviewed here include their small sample size and the risk of bias recall, notably during telephone interviews. Symptoms were frequently assessed without any validated objective scale or score. As an example, most of the articles assess dyspnea but do not mention its pulmonary or cardiac origin. Thus, there is a confounding factor between functional capacity, which could be fixed with rehabilitation programmes, and the presence of true impairment [41, 51, 52]. In addition, we could not conduct a meta-analysis to compare the characteristics of patients at baseline and at follow-up time due to heterogeneity of the data. Despite this limitation, the range of clinical signs that make up post-COVID syndrome seems to exist in substance, as shown by this comparative study evaluating general symptoms in 538

COVID-19 survivors compared to general symptoms in 184 patients without COVID, finding significant differences in post-COVID cardinal signs [40]. In addition, we excluded case reports which may have emphasized the occurrence of rare events, including stroke and dermatological symptoms.

Given the diversity of symptoms that could be attributed to long COVID, patients should have access to dedicated multidisciplinary healthcare allowing a holistic approach to be taken. The first step would be a robust assessment of the persistent symptoms reported by the patients, using screening questionnaires. Ideally, such questionnaires should be standardized so that the medical community could use the same tools making the results of the studies comparable. They should also be linked to a standardized physical screening evaluation.

Infectious disease specialists are not necessarily well-trained in evaluating subjective symptoms such as fatigue or insomnia, and would benefit from using clinical tools allowing such symptoms to be classified and quantified. Similarly, symptoms such as dyspnea, thoracic pain, or smell and taste disorders should be quantified using existing validated scales. In addition, depending on the symptoms, the standardized investigation of respiratory, cardiac, olfactory, and gustatory functions should be proposed to the patients including a full blood count, kidney and liver function tests, C-reactive protein tests, exercise tolerance tests, and imagery. The NICE guideline [<https://www.nice.org.uk/guidance/NG188>] proposes such an approach and could serve as a basis for such an approach. Other authors have proposed a potential approach to categorizing post-acute COVID-19 into three domains (persistent symptoms,

Table 5 Top persisting symptoms in patients with long COVID-19

	< 12 weeks (2719 patients)	12 weeks–6 months ^a (7017 patients)	> 6 months (2112 patients)
Inpatients only	8 studies	Nine studies	1 study
Fatigue	31–64%	16–63%	61%
Dyspnea	31–54%	15–61%	48%
Arthralgia	22–55%	8–9%	15%
Cough	5–46%	2–59%	7%
Thoracic pain	18–22%	5–62%	9%
Smell and taste disorders	2–17%	4–13%	5
Majority of outpatients	4 studies	Eleven studies	5 studies
Fatigue	12–84%	11–42%	25–34%
Smell and/or taste disorders	4–74%	3–24%	3–24%
Cough	5–54%	4–17%	2–13%
Dyspnea	8–50%	8–37%	13–22%
Thoracic pain	13–42%	3–14%	9
Arthralgia	16–31%	7–18%	15

^aOne study observed at two-time follow-up: 3–6 months and 6–12 months after the acute phase

organ dysfunction, and multisystem inflammatory syndrome), recognizing the potential interplay between organ pathology and symptomatology [53]. The pathophysiology and management of long COVID is currently an emerging field with little information available [8, 54]. Autonomic dysfunction, a chronic inflammatory and autoimmune response, has been proposed as a possible mechanism for long COVID [55], together with means of management [56] and pathological proof of SARS-CoV-2 presence in the vagus nerve structure [57]. Other authors propose that cognitive behavioral therapy may be an effective treatment for post-COVID fatigue syndrome [58]. Some authors proposed increasing fluid and salt, physical countermeasures, and adapted lifestyle for the postural orthostatic tachycardiac syndrome [55, 59]. Effective outpatient care for patients with long COVID-19 requires coordination across multiple subspecialties, which can be proposed in specialized post-COVID units [60]. Furthermore, sub-clinical or non-clinical assessment of multiple organ damage is now available with the help of 18F-FDG PET scans tools, which represent a relevant and modern technique to preventing unsuspected problems and explaining post-COVID or long COVID syndrome [61].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10096-022-04417-4>.

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