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].
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 another 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:

\[
\#1: \text{“COVID-19” OR “SARS-CoV-2”} \\
\#2: \text{“sequelae” OR “persistence” OR “persitant” OR “long-COVID” OR “long-haul COVID” OR “post-acute COVID” OR “persistent COVID-19” OR “long-hauler COVID” OR “post-acute sequelae” of “SARS-CoV-2 infection” OR “chonic COVID syndrome”} \\
\#3: \#1 \text{AND} \#2
\]

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](image-url)
| 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”                                             |
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 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, 29, 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].

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| 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 |

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Table 1 (continued)
| Reference | Study design and period | Country and setting | COVID-19 patient numbers and status at enrolment | Comparison group | Age (years) of COVID-19 patients | Female (%) | Duration of follow-up (days) | Lost to follow-up (%) | Proportion of COVID-19 patients with persisting symptoms at the end of follow-up (%) | Main risk factors for persisting symptoms | Main risk factors for persisting symptomsoverall | Remarks Limitation |
|-----------|-------------------------|---------------------|-------------------------------------------------|-----------------|-------------------------------|------------|-----------------------------|----------------------|-------------------------------------------------|-----------------------|------------------------------------------|---------------------|
| Jacobs [43] | Prospective cohort (telephone interviews) | US, one hospital | 183 in-patients requiring oxygen support during hospitalization, 15 requiring mechanical ventilation | None | 57 (range 45-60) | 48 | 35 days (1 months) | 38 | 30 | Arthralgia (55), fatigue (44), dyspnea (32), cough (25), myalgia (21), sputum (15), headache (10), disorder (9), constipation (4), diarrhea (4), fever (1), ulcer (1) | | 48 Female sex and older age associated with persisting symptoms overall | Single center, small sample, no control group, based on self-reported, not available data for pulmonary function and 6-min walking test, some symptoms were persistent following COVID-19 infection or occurred post-discharge, not evaluate the mild COVID-19 |
| 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 (%) 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 |
|-----------|---------------------|-------------------------------------|-----------------------------------------------|-----------------|-----------------------------|-----------------------------|----------------------------|-------------------------------------------------|-----------------|----------------------------------|---------|-----------|
| Cellai [46] | US, 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 | – | Small sample size, no control group, based on self-reported by telephone |
| 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 |
|----------------|---------------------|-------------------------------------|--------------------------------------------------|------------------|---------------------------------|-----------------------------|------------------------|-----------------------------------------------------------------|----------------------|------------------------------------------|----------|------------|
| Graham's [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 (diabetes, nausea, vomiting, gastroparesis, 28), hearing problems (19), vision problems (18), seizure (1), dysphagia (2), ... (diarrhea, nausea, vomiting, gastroparesis, 28), dysphagia (2), ... (diarrhea, nausea, vomiting, gastroparesis, 28), dysphagia (2), ... (diarrhea, nausea, vomiting, gastroparesis, 28), 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 |
| 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 |
|---------------|---------------------|-------------------------------------|-----------------------------------------------|---------------|-------------------------------|--------------------------|-------------------------|-----------------------------------------------------------------|------------------|------------------------------------------|---------|------------|
| 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 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 (46), cough (46), pain (22), dysphonia (20), sore-throat (17), constipation 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-Castillo [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 (3), dyspnea (3), 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 |
| 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 |
|------------------|---------------------|-------------------------------------|-------------------------------------------------|------------------|---------------------------------|-----------------------------|------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------------|----------|------------|
| Carfì [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), dyspea (43), arthralgia (27), thoracic pain (22), cough (18), smell disorder (17), Sjögren’s syndrome (16), rhinitis (15), conjunctivitis (10), taste disorder (10), headache (9), sputum (8), anorexia (8), sore-throat (7), vertigo (6), myalgia (6), diarrhea (3) | 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 |          |            |
| Carvalho-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, headache, and/or fatigue (22), weight loss (17), arthralgia (16), chest pain (13), diarrhea and/or vomiting (12), skin symptoms (12), palpitation (11), dyspea (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 |          |            |
| 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 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 exanethromycin 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, 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, 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%), palpitiation (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 (%) | 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), diarrhoea (2), anosmia (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), diarrhoea (26), fever (20) | 44 | Troponin I levels during acute illness associated with fatigue at follow-up | – | Single center, small sample size, no control group |
| 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 |
|-----------|---------------------|-------------------------------------|-----------------------------------------------|-----------------|----------------------------------------|----------------------------|----------------------|-----------------------------------------------|---------------------|------------------------------------------|---------|-----------|
| 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 ≥ 60 years (45.3) | 44 | 3 months | Gastrointestinal symptoms overall (44), anorexia (24), nausea (18), acid reflux (18), diarrhea (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±15.49 | 42 | 3 months | Gastrointestinal symptom (31), headache (18), fatigue (16), dysgeusia (15), taste disorder (4), cough (2) | 29 | Not evaluated | – | Small sample size, no control group, not evaluate the critical patients |
| 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 |
| Sonnweber [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: 3, invasive ventilation: 3, non-invasive ventilation: 3, invasive ventilation: 29) | None | 57 ± 14 | 43 | 100 days (3 months) | Dyspnea (36), pain (24), night sweats (24), smell 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 |
| 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 (%) | 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), wheez (3), nausea/vomiting (2), diarrhea (2), conjunctivitis (2), seizure (1), skin rash (1), ear pain (1), enlarged lymph nodes (1), chills (1), fever (< 1) | 52 | Number of comorbidities and of 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 |
| 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 |
|-----------|---------------------|-------------------------------------|-----------------------------------------------|-----------------|------------------------------------------|-----------------------------|----------------------|-----------------------------------------------------------------------------------|-----------------|------------------------------------------|---------|
| 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 ± 12.8 | 40 | 3 to 6 months | Impaired mobility as assessed by 2 min walking test (32); impaired lower extremity functional performance as assessed by Short Physical Performance Battery (14) | 73 | ICU and mechanical correlate with physical impairment | Remarks – | Limitation: 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 ± 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 – | Remarks: Single center, small sample size |
| 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 (%) | 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  | 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 ± 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) | 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  | 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 ± 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 ± 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 |
|------------|---------------------|-------------------------------------|-----------------------------------------------|------------------|------------------------------------------|-----------------------------|---------------------|-----------------------------------------------------------------|----------------------|---------------------------------|----------|------------|
| Kayasslan  | Turkey, one hospital| Prospective cohort (self-questionnaire), 1/8/2020–31/10/2020 | 1007 patients (416 in-patients, ICU: 58) | None             | 45.0 ± 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    | Italy, one hospital | Cross-sectional (follow-up consultation and online-survey), March to November 2020 | 129 patients ≤ 18 years (out-patients: 123, in-patients: 6, ICU: 3) | None             | 11 ± 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 | –                                      | –       | Single center, small sample size, no control group |

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| 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 |
|-----------|---------------------|-------------------------------------|-----------------------------------------------|-----------------|------------------------------------------|--------------------------|--------------------|-------------------------------------------------|-------------------|--------------------------------------------|---------|------------|
| 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 |
| Ghosn [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 admission, transfer to ICU during acute phase | No control group |
| 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 |
| 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 (%) | 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), 2/2/2020–20/4/2020 | 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 |
| 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 | 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), sore throat (5), weight gain (5), anorexia (4), taste disorder (3), diarrhea (3), abdominal pain (3) | 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 |
| 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 |
|-----------|---------------------|-----------------------------------|-----------------------------------------------|-----------------|------------------------------------------|-----------------|---------------------|------------------------------------------------|----------------|---------------------------------|---------|-----------|
| Fernández-de-Las-Peñas [23] | Spain, four hospitals | Prospective cohort (telephone interview), 01/09/2020–30/11/2020 | 1142 inpatients (ICU: 80) | None | 61 ± 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 |
| 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 |
|------------|----------------------|-------------------------------------|-----------------------------------------------|-----------------|-----------------------------------------|-----------------------------|------------------------|----------------------------------------------------------------|------------------|-------------------------------------------|---------|-----------|
| 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 outpatients | 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 |
| 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 (%) | 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 | ≥ 1 symptoms (64), Fatigue (34), reduced exercise capacity (32), dizziness (16), palpitation (12), body aches (10), smell disorder (10), taste disorder (8), headache (4), sore throat (2), cough (2), diarrhea (2) | 34.3 | Not evaluated |         |           |
| 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 |

*HFNC 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* (7017 patients) | > 6 months (2112 patients) |
| **Inpatients only** | 8 studies | 9 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 |

*One 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 tachycardia 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].

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