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Guidelines

ESCMID rapid guidelines for assessment and management of long COVID

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Scope:
The aim of these guidelines is to provide evidence-based recommendations for the assessment and management of individuals with persistent symptoms after acute COVID-19 infection and to provide a definition for this entity, termed ‘long COVID’.

Methods:
We performed a search of the literature on studies addressing epidemiology, symptoms, assessment, and treatment of long COVID. The recommendations were grouped by these headings and by organ systems for assessment and treatment. An expert opinion definition of long COVID is provided. Symptoms were reviewed by a search of the available literature. For assessment recommendations, we aimed to perform a diagnostic meta-analysis, but no studies provided relevant results. For treatment recommendations we performed a systematic review of the literature in accordance with the PRISMA statement. We aimed to evaluate patient-related outcomes, including quality of life, return to baseline physical activity, and return to work. Quality assessment of studies included in the systematic review is provided according to study design.

Recommendations:
Evidence was insufficient to provide any recommendation other than conditional guidance. The panel recommends considering routine blood tests, chest imaging, and pulmonary function tests for patients with persistent respiratory symptoms at 3 months. Other tests should be performed mainly to exclude other conditions according to symptoms. For management, no evidence-based recommendations could be provided. Physical and respiratory rehabilitation should be considered. On the basis of limited evidence, the panel suggests designing high-quality prospective clinical studies/trials, including a control group, to further evaluate the assessment and management of individuals with persistent symptoms of COVID-19. Dana Yelin, Clin Microbiol Infect 2022;28:955

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Scope

Long COVID is an umbrella term referring to signs and symptoms that persist after acute SARS-CoV-2 infection. The prevalence of long COVID is highly heterogeneous among studies, probably reflecting the variability of definitions of this entity, the populations surveyed, and follow-up durations. According to the literature, 22% to 40% of convalescent patients are expected to experience one or more symptoms of long COVID [1,2]. The most common symptoms include fatigue, dyspnoea, cognitive impairment, and various pain symptoms (e.g. chest pain, headache, myalgia). Despite the mounting evidence, there are still significant gaps in our knowledge regarding pathogenesis, actual incidence,
potential risk factors, diagnosis, management, and long-term outcomes of long COVID.

**Context**

More than 300 million people are recovering from COVID-19 worldwide, and the public health impact of long COVID is expected to be profound [3]. There are no objective diagnostic criteria for long COVID, no consensus regarding an algorithm of investigation, and no evidence-based interventions [4]. Several guidelines/recommendations for the diagnosis and management of long COVID have been published, including those issued by the National Institute for Health and Care Excellence (published in December 2020 [5]), the CAMFIC Long COVID-19 Study Group from Spain [6], and French recommendations [7]. The WHO living guidance for the clinical management of COVID-19 also includes a section on the “Care of COVID-19 patients after acute illness” [8].

The current guidelines were not planned as evidence-based, but rather practical rapid guidelines/recommendations. In addition, although studies evaluating recovering patients are rapidly accumulating, up-to-date evidence-based guidelines are needed. The current guidelines are aimed towards physicians of any medical discipline who are taking care of patients after acute SARS-CoV-2 infection, with an emphasis on those who have not fully recovered after more than 12 weeks since diagnosis of acute illness, defined as having long COVID.

**Methods**

These guidelines were planned and developed by a group of infectious diseases experts and selected by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations for developing guidance documents. This expert panel reviewed the available literature, summarized the quality of evidence, and provided recommendations. The process was conducted via teleconferences. All panel members have experience in managing patients recovering from acute COVID-19.

**Literature search and data extraction**

We first browsed the following three ongoing initiatives for studies relevant for postdischarge and long-term follow-up: (a) Guidelines international network [9], (b) COVID-END of McMaster University [10], and (c) Cochrane library [11]. A search was also performed for existing guidelines from guideline institutes (http://www.guideline.gov/, http://www.nice.org.uk/, http://www.sumsearch.org, and http://www.sign.ac.uk/) and other health institutes (https://www.nih.gov/, https://www.cdc.gov/, and https://www.who.int/). We then performed a systematic search of the literature in PubMed, using the search term “COVID19 post-intensive care syndrome” OR “long-COVID” OR “long-haul COVID” OR “post-acute sequelae of SARS-CoV-2 infection” OR “chronic COVID syndrome” OR “post-acute COVID19 syndrome” OR “long hauler COVID” OR “long COVID” OR “long haul COVID” OR “post-acute COVID syndrome” OR “post COVID”. No language or publication year restrictions were applied. Only full-text articles were included. The last search was conducted on December 31, 2021.

In addition, we searched MedRxiv for relevant preprints (https://www.medrxiv.org/) and large relevant journal sites for early online publications (including The New England Journal of Medicine (https://www.nejm.org.proxy.tau.ac.il/coronavirus), The Lancet (https://www-thelancet-com.proxy.tau.ac.il/coronavirus), JAMA (https://jamanetwork-com.proxy.tau.ac.il/journals/jama/pages/coronavirus-alert), and Annals of Internal Medicine (https://annals-org.proxy.tau.ac.il/aim/pages/coronavirus-content).

The search hierarchy was to first identify systematic reviews and meta-analyses, followed by randomized controlled trials and observational comparative studies. Prospective cohort, retrospective cohort, and case-control studies, as well as case series were included. Case reports and case series including less than 20 participants were excluded, unless they provided an innovative finding. If a methodologically appropriate meta-analysis was identified to answer a specific question, we planned to end the search for additional studies.

Key questions were formulated in a PICO format (population/participant, intervention, comparator/control, outcome) when appropriate. Population/participant was defined as any adult patient (≥18 years) after the acute phase of COVID-19 (see definitions given in the following). Intervention was defined as any intervention for the assessment and management (pharmacological or other) of participants, and comparison/control as patients receiving a comparator intervention (studies comparing two interventions) or no intervention. Outcomes for management was defined as any outcome addressing improvement in physical, cognitive, or mental function, including quality-of-life measures. We did not attempt to contact the study authors for primary data.

Two independent panel members performed the search and screened for relevant studies. Any discrepancies were resolved through discussion with a third panel member. The process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [12].

**Search results**

The PubMed search yielded 13 881 titles (13 066 after exclusion of 815 duplicates). After inspection of titles and abstracts, 12 390 articles were excluded due to irrelevant study design, irrelevant population, or irrelevant topic. Subsequently, 676 articles were further inspected in full text, and 529 were excluded for similar reasons. Overall, we present data on 147 studies. Due to the paucity of comparative and/or randomized data, no recommendation could be based on evidence, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was not used.

**Quality of evidence scoring**

Quality assessment of included studies was performed by two panel members independently, and discrepancies were resolved through discussion with a third member. For systematic reviews and meta-analysis, we used the AMSTAR tool for quality assessment [13]. Studies were graded as having high, moderate, low, and critically low quality of evidence according to the AMSTAR critical appraisal tool [13]. For randomized controlled trials (RCTs), risk of bias was assessed using the domains recommended by the Cochrane handbook. Studies were graded as having low, high, or unknown risk of bias per the Cochrane handbook criteria [14]. For nonrandomized studies, the Newcastle Ottawa tool was used [15]. We planned to classify evidence certainty per question as high, moderate, low, or very low and recommendation strength as strong or conditional according to the GRADE system [16]. The panel also provided recommendations for research.

**Definitions of long COVID**

The WHO defines post-COVID-19 condition as persistent symptoms and/or signs, developing during or after an acute COVID-19 illness and lasting for at least 2 months and persisting beyond 12 weeks from the acute disease, that cannot be explained by an alternative diagnosis [17]. The CDC provides a similar definition,
with a different timeframe of beyond 4 weeks after the acute disease [18]. The Royal Society defines the same condition; however, no time frame is provided [17]. A similar term called post-acute sequela of SARS-CoV-2 infection has been termed by the National Institutes of Health [19]. A repository of published/available definitions of post-COVID-19 condition is maintained by the WHO [17].

Although no consensus regarding a single term for long COVID/post-COVID-19 condition has been obtained by a WHO Delphi process [17], we used the term long COVID in the current guidelines. Table 1 provides the definitions used for long COVID for the purposes of this document.

Long COVID is defined herein as one or more symptoms and/or signs (detailed in the following) persisting or relapsing/remitting for more than 12 weeks since an acute COVID-19 diagnosis, without an alternative explanation. This condition can affect all individuals who encountered COVID-19, regardless of the severity of the acute disease. The syndrome can be definite, probable, or possible, according to the level of certainty of the original acute COVID-19 infection (Table 1). We define post-acute COVID as one or more symptoms and/or signs persisting or relapsing/remitting from 4 to 12 weeks since a confirmed acute COVID-19 diagnosis, without an alternative diagnosis. This definition also includes several specific entities (thyroiditis, myocarditis, venous thromboembolism) that may appear during this period.

**Symptoms and risk factors of long COVID**

Across systematic reviews/meta-analyses, the most commonly observed symptoms among patients with long COVID are fatigue (31%–58%), dyspnoea (24%–40%), musculoskeletal pain (9%–19%), anosmia/dysgeusia (10%–22%), cognitive impairment (or brain fog: 12%–35%), sleep disturbances (11%–44%), cough (7%–29%), and chest pain (6%–17%) [20–26]. Table 2 provides a summary of reported symptoms and their respective prevalence ranges. Tables 3 and 4 provide symptom prevalence according to time intervals from the acute illness (1–3 months, 3–6 months, >6 months) and hospitalization status, respectively. Persisting symptoms seem to considerably affect patients’ quality of life and return to daily activities and work. A systematic review of 39 studies found that decreased quality of life was reported among 57% of patients with symptoms persisting beyond 12 weeks [27]. Follow-up studies report persistence of long-COVID symptoms up to 12 months after the acute disease [28,29].

The pathophysiologic mechanisms that underlie this disorder remain largely unknown, but available data implicate the multisystemic nature of COVID-19, immune dysregulation, autoimmune, and the neurotropism of SARS-CoV-2 [4,22,30]. Post-intensive care syndrome may provide an explanation for prolonged symptoms after critical COVID-19. This syndrome encompasses new or worsening abnormalities in physical, cognitive, and psychiatric domains after critical illness [31]. For patients who have long-COVID symptoms after critical care, it is difficult to distinguish whether persisting symptoms are caused by SARS-CoV-2 infection or post-intensive care syndrome.

Data on potential factors associated with an increased risk of developing specific long-COVID symptoms are accumulating in the literature, although the evidence is inconsistent. The two consistent risk factors for any long-COVID symptom are acute COVID-19 severity and sex (Table S1) [32–34]. Women have been shown to have an estimated two-fold risk of having long-COVID symptoms (OR: 1.3–5). Similarly, severe acute disease has been associated with an increased risk for long-COVID symptoms, with the strongest association with fatigue. Other risk factors, such as age, obesity, and the presence of comorbidities, have shown mixed results (Table S1).

**Recommendations**

We aimed to answer the following PICO questions: (a) Who should be assessed; (b) what assessment is needed for individuals with long COVID (subdivided according to systems and further subdivided by specific tests); and (c) how should individuals with long COVID be managed (also subdivided according to systems). Each section reports the main summary of evidence for each topic. Tables 5–8 provide details of the studies included.

**Who should be assessed for long COVID?**

In symptomatic patients, other serious/life-threatening conditions should be ruled out prior to considering long COVID. These include prior overlooked conditions (e.g. malignancy) or complications of acute COVID-19 (e.g. thromboembolic events, myocarditis, encephalitis). The investigation for other conditions should be guided by symptoms, signs, and other tests, performed according to the physician’s discretion. Long COVID is a diagnosis of exclusion.

**Recommendation**

As a first step, collecting specific clinical history is recommended to rule out previous underlying conditions, as well as iatrogenic causes or complications related to the acute episode. Hence, any patient with persisting or new symptoms that last more than 12 weeks after acute COVID-19 should be referred to medical care. For patients with symptoms 4 to 12 weeks after acute infection, assessment should be considered on a case-by-case basis, according to the severity and course of symptoms.

**General blood tests**

Few studies have assessed the use of routine blood tests in patients with long COVID. Huang et al., at a follow-up of 12 months after patients with COVID-19 were hospitalized, demonstrated low rates of laboratory abnormalities and no significant difference in rates of lymphocyte count <0.8 × 10⁹ per L or serum creatinine abnormality between recovering participants and controls. Nevertheless, as suggested, blood tests according to symptoms should be performed as part of an investigation to rule out other conditions. Some blood tests may be considered to identify possible complications after acute infection. These, however, should be interpreted with caution due to possible persistent abnormalities after

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**Table 1**

Summary of definitions for long COVID/post-acute COVID according to level of certainty of COVID-19 diagnosis

| Acute COVID-19 diagnosis/time from acute COVID-19 diagnosis | Typical symptoms of acute COVID-19, positive laboratory results | Typical symptoms, negative laboratory results, suggestive epidemiology | Typical symptoms, negative laboratory results and negative epidemiology |
|---|---|---|---|
| 4–12 wk | Confirmed post-acute COVID | Probable post-acute COVID | Possible post-acute COVID |
| >12 wk | Confirmed persistent long COVID | Probable persistent long COVID | Possible persistent long COVID |

* For asymptomatic patients: Confirmed acute COVID-19 diagnosis is considered a positive PCR test in a relevant epidemiological setting.
COVID-19. In one study evaluating 734 patients with severe disease 28 days after recovery, an increase in insulin dependency from 18% to 63% was noted, and 1.4% of new-onset diabetes cases were identified [35]. Two additional studies found an increase in new-onset diabetes in the months after recovery from COVID-19 [36,37]. This might be a result of surveillance bias in previously unknown diabetics or a real shift from prediabetes to diabetes caused by the acute disease or its treatment, although there is no evidence for the latter.

Elevated D-dimer can be observed at a median of >2 months after resolution of acute COVID-19, despite normalization of inflammatory markers and other coagulation parameters [38]. Similarly, detectable levels of high-sensitivity troponin T (>3 pg/mL) were reported in 71 of 100 patients evaluated at a median of 71 days (interquartile range [IQR], 64–92 days) after diagnosis of COVID-19, with 5 of 100 patients having significantly elevated high-sensitivity troponin T levels (>13.9 pg/mL) [39]. Increased NT-pro-BNP levels at a median follow-up of 71 days (IQR, 14–124 days) were reported from a systematic review in 10% of individuals tested (57 of 571) [40]. A systematic review accumulated data on 27 patients presenting with subacute thyroiditis after COVID-19 infection. Patients presented with typical features, including elevated FT4 and FT3, low thyroid stimulating hormone, and raised inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) [41].

**Recommendation**

As recommended by other guidelines [5–7], the following may be considered for symptomatic patients according to symptoms: C-reactive protein, blood count, kidney function, and liver function tests. Consider troponin, CKP-MB, and B-type natriuretic peptide for cardiac symptoms and complete thyroid function tests to rule out thyroiditis, if clinically suspected. For patients with decreased oxygen saturation, blood gases are recommended by some guidelines, although the benefit of this test is limited. D-dimer should not be used in patients without respiratory symptoms. Patients at increased risk for diabetes or impaired fasting glucose should be monitored for fasting glucose and glycated haemoglobin levels.

**What assessment is needed for individuals with long COVID?**

After ruling out other conditions, the following evaluations are suggested for individuals with suspected long COVID. First, the evaluation should include an interview with the patient to identify symptom severity and their impact on quality of life. Physicians should consider whether further assessment is needed for symptoms that are self-limited and without an effective and safe therapy. Options for therapy that can be considered in the context of clinical trials are discussed later in this article.

**Investigating individuals with dyspnoea**

In previous guidelines/recommendations [5–7], a diagnostic pathway is suggested for patients with dyspnoea persisting more than 4 to 12 weeks after acute COVID-19. Several studies used the modified Medical Research Council dyspnoea scale to assess severity of dyspnoea but did not provide a cut-off, thus necessitating further investigation [42,43].

**Pulmonary function testing**

Various rates of abnormal pulmonary function testing (PFT) have been reported in recovering patients, depending on definitions of abnormality, duration of follow-up, baseline (pre-COVID) pulmonary function, and mainly acute COVID-19 severity and the need for ventilatory support [44]. The most frequently impaired
pulmonary function test is diffusion capacity for carbon monoxide (DLCO), and the most frequent pattern observed is restrictive. DLCO impairment (<80% of predicted) has been found in varying proportions of patients, in correlation to disease severity. After critical disease and intensive care unit (ICU) admission, patients had up to 80% abnormal DLCO at discharge and 50% to 70% impairment at 3-month follow-up. After severe disease, patients had 30% to 68% impairment at 3 months [44,45]. At 3 months, higher computed tomography (CT) severity score and acute respiratory distress syndrome at acute disease were associated with impaired DLCO in one study including hospitalized patients [44]. Surprisingly, even among patients after mild-to-moderate disease, abnormal DLCO was demonstrated in approximately 10% [45].

Future progression to pulmonary fibrosis has been raised as a concern [46]. When tested at 6 months, patients exhibited somewhat lower rates of abnormalities than at 3 months, although the rates were still high (DLCO reduced in 29% for severe, 58% for critical) [47]. At a longer follow-up of 1 year, Huang et al. reported DLCO <80% in 23% to 54% of 243 patients with severe-critical acute COVID-19. Total lung capacity less than 80% of predicted decreased among critically ill patients from 39% at 6 months, but was still considerable at 29% at 12 months [29].

There is a paucity of data for patients with mild-to-moderate disease. Several studies included some patients after mild-to-moderate disease, mostly as a control group for the patients with severe disease [47,50,51]. These studies reported normal median PFTs and DLCO, but a considerable percentage of patients (10%—22%) still had abnormal results.

**Recommendation**

Evidence is insufficient to provide a recommendation for or against PFT. Considering that the test is simple and noninvasive and that future studies may suggest beneficial treatment for patients with abnormal PFT, the panel recommends considering routine PFT, including diffusion capacity, in all patients with severe and critical COVID-19 at 3 months from diagnosis, regardless of symptoms, as well as considering completing PFT with diffusion for patients with complete resolution [48,49].

### Table 3

| Symptom                          | 4–12 wk (%) | 3–6 mo (meta-analysis, % (95% CI) | 6–12 mo (%) |
|----------------------------------|-------------|----------------------------------|-------------|
| General                          |             |                                  |             |
| Fever/feverish                   | 1–51        | 1.1 (0.02–4.7)                   | 0.7         |
| Fatigue                          | 5–83        | 31 (23.9–39)                     | 4–35.8      |
| Headache                         | 4–36        | 4.9 (2.3–10)                     | 1.5–5       |
| Chest pain/tightness             | 3–35        | 6.4 (3.2–12.4)                   | 3–7         |
| Musculoskeletal                  |             |                                  |             |
| Joint pain/arthritis             | 10–48       | 9.4 (5.7–15)                     | 0.6–32.5    |
| Myalgia                          | 1–32        | 11.3 (6.2–19.8)                  | 0.6–9.2     |
| Respiratory                      |             |                                  |             |
| Dyspnoea                         | 2–64        | 2.5 (17.9–34)                    | 1.9–40.8    |
| Exertional dyspnoea              |             |                                  |             |
| Cough                            | 5–45        | 8.2 (4.9–13.4)                   | 3.2         |
| Sore throat                      | 1–17        | 4.7 (2.4–8.9)                    | 2–3         |
| Gustatory                        |             |                                  |             |
| Ageusia/dysgeusia                | 1–25        | 13.5 (9–19.9)                    | 3–15.1      |
| Anosmia                          | 2–21        | 15.2 (10.8–21)                   | 4–20.4      |
| Loss of appetite                 | 1–9         | 17.5 (4.1–51)                    | 0.3–3       |
| Neuropsychological               |             |                                  |             |
| Confusion/brain fog              | 9–14        | 17.9 (5.3–46.3)                  | 0.6         |
| Depression                       |             | 8 (4.1–15.1)                     | —           |
| Sleep disorder                   | 10–69       | 18.2 (9.5–31.6)                  | 1.5–41.3    |
| Posttraumatic stress disorder    |             | 9.1 (3.7–21)                     | 7           |
| Cardiovascular                   |             |                                  |             |
| Palpitations                     | 2–11        | 9.7 (6–15.3)                     | 0.6–9       |
| Skin                             | 8–15        | 2.8 (1–8.2)                      | 4           |

### Table 4

| Symptom                             | All patients (%) | Hospitalized (%) | Outpatients (%) |
|-------------------------------------|------------------|------------------|----------------|
| General                             |                  |                  |                |
| Fever/feverish                      | 0.05–6.8         | 10.4             | 1.41           |
| Fatigue                             | 4–73.2           | 17.5–54.5        | 24.6           |
| Headache                            | 0.05–47.4        | 24.6             | 8.8            |
| Chest pain/tightness                | 3.1–31.7         | 0.4–17.9         | 14.6           |
| Musculoskeletal                     |                  |                  |                |
| Joint pain/arthritis                | 9–37.3           | 5.9–28.6         | 9.3            |
| Myalgia                             | 2–44.9           | 37.4–47.8        | 10.8           |
| Respiratory                         |                  |                  |                |
| Dyspnoea                            | 21.8–39          | 5.5–59.7         | 13.7           |
| Exertional dyspnoea                 | 39–54.8          | 14.6–57.1        | —              |
| Cough                               | 3.2–23.4         | 2.5–35.1         | 6              |
| Sleep apnoea                        | 24–35.7          | 30.8–35.1        | —              |
| Throat pain                         | 4–19             |                  | 4.4            |
| Gustatory                           |                  |                  |                |
| Ageusia/dysgeusia                   | 7–16.1           | 9–21.6           | 16.8           |
| Anosmia                             | 11–45            | 4.6–26.1         | 22.2           |
| Loss of appetite                    | 8–10.2           |                  | —              |
| Neuropsychological                  |                  |                  |                |
| Confusion/brain fog                 | 3–63.3           |                  | 15.6           |
| Depression                          | 11–15.7          |                  | —              |
| Sleep disorder                      | 24–35.7          |                  | —              |
| Posttraumatic stress disorder       |                  |                  | —              |
| Cardiovascular                      |                  |                  |                |
| Palpitations                        | 3.9–40           |                  | 7.3            |
| Skin                                | 3–35.7           |                  | 1.6            |
Table 5
Studies addressing assessment of long COVID—Pulmonary function tests

| Systematic review identification | Timing of testing after COVID-19 | Severity of acute COVID-19 | FEV1 <80% predicted | PFC <80% predicted | FEV1/FVC <0.7 | DLCO <80% predicted | TLC <80% | AMSTAR quality assessment |
|---------------------------------|---------------------------------|---------------------------|---------------------|-------------------|---------------|---------------------|----------|--------------------------|
| Jennings et al., 2021 [27]      | >12 wk                          | Variable                  | 11% ± 6%            | 11% ± 9%          | 7% ± 1%       | 32% ± 11%           | —        | Low                      |
| Guo et al., 2021 [141]          | 3–6 mo                          | Hospitalized             | 33% (23%–44%)       | 10% (2%–18%)      | —             | 33% (23%–44%)       | —        | Critically low            |
| Guo et al., 2021 [141]          | >6 mo                           | Hospitalized             | 43% (22%–65%)       | 13% (8%–18%)      | —             | 43% (22%–65%)       | —        | Critically low            |
| Long et al., 2021 [24]          | 2–6 mo after admission (hospitalized patients) | Hospitalized | 7% (5%–9%) | 12% (1%–23%) | 20% (15%–26%) | 47% (32%–61%) | 14% (9%–18%) | Low |
| Sanchez-Ramirez et al., 2021 [26] | 3–6 mo                          | Variable                  | —                   | Obstructive pattern abnormalities: 8% (6%–9%) | — | Diffusion pattern abnormalities: 31% (24%–38%) | Restrictive pattern abnormalities: 12% (8%–17%) | Critically low |

AMSTAR, A MeaSurement Tool to Assess systematic Reviews; DLCO, carbon monoxide diffusing capacity; FEV1, forced expiratory volume; FVC, forced vital capacity; TLC, total lung capacity.

* Pooled prevalence (standard deviation).

Table 6
Studies addressing assessment of long COVID—Chest imaging

| Systematic review identification | Imaging type | Timing | Severity of acute COVID-19 | Abnormal pattern | Ground-glass opacity | Fibrosis | Reticulation | Bronchiectasis | Consolidation | AMSTAR quality assessment |
|---------------------------------|--------------|--------|---------------------------|------------------|----------------------|----------|-------------|----------------|--------------|--------------------------|
| Jennings et al., 2021 [27]      | Mix* CT      | >12 wk | Variable                  | 28% ± 17%        | 24% ± 17%            | 7% ± 9%  | 11% ± 12%   | —              | —            | Low                      |
| Sanchez-Ramirez et al., 2021 [26] | CT            | 3–6 mo | Variable                  | 59% (44%–73%)    | 39% (26%–52%)        | 31% (17%–44%) | 33% (13%–52%) | 26% (9%–43%) | 3% ± 3%     | Critically low             |
| Other studies                    |              |        |                           |                  |                      |          |             |                |              | Newcastle–Ottawa score |
| Huang et al., 2021 (Late follow up) [29] | CT            | 12 mo  | Hospitalized Severe and critical patients | 65/118 (55%) | 54/118 (46%) | — | 4/118 (4%) | 1/118 (0.8%) | 7 | 5 |
| D'Cruz et al., 2021 [53]        | Chest x-ray  | 6–8 wk | Variable                  |                   |                      |          |             |                |              | 4                        |
| Malia et al., 2021 [52]         |              |        |                           |                  |                      |          |             |                |              | 5                        |
| van den Borst et al., 2020 [51] |              |        |                           |                  |                      |          |             |                |              |                          |
| Raman et al., 2021 [63]         | Chest MRI    | 2–3 mo | Moderate to severe Low risk |                   |                      |          |             |                |              | 6                        |
| Dennis et al., 2021 [71]        | Chest MRI    | 3–4 mo | Low risk                  |                   |                      |          |             |                |              | 6                        |

AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CT, computed tomography; MRI, magnetic resonance imaging.

* CT, high-resolution CT, chest radiography, and/or MRI.
Table 7
Studies addressing assessment of long COVID—Others

| Who (severity of acute COVID-19) | When | Findings | References | Newcastle–Ottawa score |
|----------------------------------|------|----------|------------|------------------------|
| Cardiac Echocardiogram           | Mild to moderate (2–3 mo) | Evidence is variable. Different rates of abnormal findings (diastolic dysfunction, systolic dysfunction, elevated pulmonary artery pressure with or without pericardial disease). Rates are higher in patients hospitalized for analysis or referred to cardiology for ongoing cardiac symptoms (25%–27.5% overall abnormal findings). In one study, EF was normal in a cohort of 215 patients, but left ventricular global longitudinal strain was reduced in 29%. | Tudoran et al., 2021 [65] | 4 |
|                                 | Severe (3–4 mo) | High rates of diastolic dysfunction (55%). Lower rates of pericardial disease and pulmonary arterial hypertension and reduced left ventricular EF | Sonnweber et al., 2021 [67] | 5 |
|                                 | Mixed patient population (23–104 d) | Systematic review reporting reduced left ventricular EF in 0%–16%; left ventricular hypertrophy in 0%–0.5%; diastolic dysfunction in 0%–55%; pulmonary hypertension in 0%–10%; and pericardial effusion in 0%–6%. | Ramadan et al., 2021 [40] | AMSTAR grade: Low |
| Cardiac MRI                      | Asymptomatic to mild (Postacute period) | Abnormal MRI myocardial findings are common in the postacute period. A study of athletes showed abnormalities in 5 of 26 asymptomatic patients after mild disease (20%). In severe cases, abnormalities may be found in up to 70% of patients. No correlation was shown with ongoing symptoms. | Malek et al., 2021 [68] | 3 |
|                                 | Severe one third (2–3 mo) | Cardiac involvement in 78%, with ongoing myocardial inflammation in 60% | Puntmann et al., 2020 [39] | 7 |
|                                 | Moderate to severe (3–4 mo) | Findings suggestive of myocarditis (late gadolinium enhancement) in recovered patients were common in 26%–29% (13/50; 13/44) | Wang et al., 2021 [70] | 6 |
|                                 | Mild (6 mo) | Study of health care workers at 6 mo showing complete resolution of cardiac MRI findings in all patients | Denniss et al., 2021 [71] | 6 |
|                                 | Mixed patient population (14–180 d) | Systematic review reporting increased T1 in 0%–73%; increased T2 in 0%–46% and up to 100%. In four studies reporting formal diagnoses, myocarditis was reported in 0%–37%, myopericarditis in 0%–11%, pericarditis in 0%–3%, and myocardial infarction in 0%–2%. | Hassan et al., 2021 [73] | AMSTAR grade: Critically low |
| Functional (6MWT, STS, SPPB)     | Hospitalized, mostly severe to critical disease (1–12 mo) | 6MWT and SPPB were moderately/severely impaired in comparison with expected ranges for age and sex. Impairment is mostly dependent on disease severity, and patients after severe disease had lower SPO2 after testing. | Truffaut et al., 2021 [42] | 4 |
|                                 | Hospitalized After discharge | STS was severely impaired in patients after discharge, correlated with post-effort dyspnoea and desaturation | Shah et al., 2021 [77] van den | 4 |

(continued on next page)
| Who (severity of acute COVID-19) | When | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | References                                                                 | Newcastle–Ottawa score |
|----------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-------------------------|
| Cardiopulmonary stress testing (CPET) | All degrees 2–4 mo | Included individuals had relatively slightly lower than expected peak oxygen consumption (91.2% (19.4%)), lower probability of achieving anaerobic threshold, and higher probability of presenting symptoms during CPET. Compared with healthy controls, peak oxygen consumption was decreased (81%; SD: 23% of expected p < 0.0001). Of all recoverees, 28/51 (55%) had peak oxygen consumption <80% of predicted. Patients recovering from COVID-19 had symptoms associated with reduction in peak oxygen consumption; 8/71 (11%) had peak oxygen consumption <85% of predicted. Peak oxygen consumption is reduced to an average of 83% ± 15% of predicted. Exercise capacity is not associated with severity of COVID-19. Of the entire sample 6/31 (19%) had pulmonary-vascular limitations, 5/31 (16%) had pulmonary-mechanical limitations, 4/31 (13%) had deconditioning, and 1/31 (3%) had cardiac capacity limitation. Mean peak oxygen consumption was 73% of predicted. The main reason for dyspnoea is suspected to be muscular. | Barbagelata et al., 2021 [152] Raman et al., 2021 [63] Szekely et al., 2021 [153] Rinaldo et al., 2021 [154] Kersten et al., 2021 [155] Mohr et al., 2021 [156] | 6 5 6 5 5 5 |
| Moderate to severe | 2–3 mo | Higher rates vs. control group of higher T2 signal on susceptibility-weighted imaging in left and right thalamus; increased mean diffusivity in left posterior thalamic radiation and left and right averaged sagittal stratum. Compared with controls, volumetric and microstructural abnormalities were detected mainly in central olfactory cortices, partial white matter in right hemisphere. | Raman et al., 2021 [63] Lu et al., 2020 [162] | 6 7 |
| Severe | 2–4 mo | In patients recovering from COVID-19 pneumonia, physical deconditioning is the most common cause of impaired peak oxygen consumption (19/35 (54%) of sample had peak oxygen consumption <80% of predicted). | Jahn et al., 2021 [157] | 5 |
| All degrees | 6 mo | Patients with dysautonomia demonstrated objective functional limitations with significantly reduced work rate and peak oxygen consumption. Compared with asymptomatic recoverees, those with persistent dyspnoea had lower peak oxygen consumption (88% (76%–100%) of predicted). | Ladlow et al., 2021 [158] Aparisi et al., 2021 [159] | 5 6 |
| All degrees | 9 mo | Physiological abnormalities on CPET were mild (peak oxygen consumption was 86% (69%–100%) of predicted) and similar to matched historical controls with dyspnoea without antecedent COVID-19. Most (59%) had peak oxygen consumption <80% predicted (mean: 77% ± 21%) and circulatory limitation to exercise. Most of those with normal peak oxygen consumption had ventilatory abnormalities. | Alba et al., 2021 [160] Mancini et al., 2021 [161] | 6 5 |
| Brain imaging | PET CT | Any severity 3 mo | Increased number of functional complaints was correlated with hypometabolism of the brainstem and cerebellum cluster | Guedj et al., 2021 [79] | 5 |
| Brain MRI | Moderate to severe 2–3 mo | 6MWT, 6-minute walk test; AMSTAR, A MeaSurement Tool to Assess systematic Reviews; EF, ejection fraction; SPO2, peripheral capillary oxygen saturation; SPPB, short physical performance battery; STS, sit to stand.
| Study | Study design | Participants and setting | Timing | Number included | Intervention | Comparison | Outcome | Results | Quality assessment |
|-------|-------------|--------------------------|--------|-----------------|--------------|------------|---------|---------|-------------------|
| Reina-Gutierrez et al., 2021 [89] | SR and MA of RCTs | Patients with interstitial lung diseases, including those caused by coronaviruses. One trial post-COVID discharge (see Liu et al. [90]) | Any time | 11 RCTs with 637 patients | Pulmonary rehabilitation | Most noncomparative | Lung function, exercise capacity, health-related quality of life and dyspnoea | Significant improvement in all outcome (see text for details) | AMSTAR grade: Low |
| De sire et al., 2021 and Ceravolo et al., 2020 [91,92] | SR and MA | Patients with COVID-19, both acute and post-acute phases | Any time | 24 studies “post acute” phase, 10 studies “chronic” phase, including case reports and series | Rehabilitation | Most noncomparative (comparative studies included in this SR are presented separately in this table) | “All type of outcome measures” | “Sparse and low quality evidence concerning the efficacy of any rehabilitation intervention to promote functional recovery” | AMSTAR grade: Critically low |
| Liu et al., 2020 [90] | RCT | Elderly (age ≥65 y) recovering “with satisfying results” from COVID-19 | Hospital discharge | 72 (36 vs 36) | Respiratory rehabilitation (once daily 10 min for 6 wk, including (1) respiratory muscle training; (2) cough exercise; (3) diaphragmatic training; (4) stretching exercise; and (5) home exercise) | No intervention | 1. PFT (FEV1, FVC, FEV1/FVC, DLCO%) 2. 6MWT 3. Quality of life score (Short Form-36) 4. Anxiety score (SAS) 5. Activity of daily living (FIM) 6. Depression score (SDS) | Significant improvement in all PFT, 6MWT, quality of life score (SF36), and anxiety score SAS | Unclear risk of bias for concealment; low risk for generation; open |
| Sinha et al., 2020 [163] | Prospective cohort | Acute COVID-19 in ICU | ICU admission until 1 mo after discharge | 150 | Structured exercise protocol | None (comparison between start and end of intervention) | Functional status by FIM and POMA | Significant improvement in both FIM and POMA | NDCS: 2 |
| Hermann et al., 2020 [164] | Prospective cohort | Patients with postdischarge severe COVID-19 (most ICU), in inpatient rehabilitation clinic setting | >10 d of COVID onset, with 2 d asymptomatic | 28 | Cardiopulmonary rehabilitation (2–4 wk program) | None | Functional assessment by 6MWT and feeling thermometer | Significant improvement in both 6MWT and feeling thermometer | NDCS: 4 |
| Udina et al., 2021 [165] | Prospective cohort | Post-acute COVID-19 care facility, most after ICU | After discharge | 33 | Multicomponent therapeutic exercise protocol | None | Physical performance, including gait performance, exercise capacity (6MWT), ADL (Barthel index) | Significant improvement in all measures | NDCS: 4 |
| Piquet et al., 2021 [166] | Retrospective cohort | Inpatients with acute COVID-19 in specialized rehabilitation unit | Mean 20.4 ± 10.0 d from COVID-19 onset | 100 | Inpatient specialized rehabilitation unit | None | Barthel ADL Index; sit-to-stand frequency; and grip strength | Significant improvement in all measures | NDCS: 4 |
| Hameed et al., 2021 [94] | Prospective cohort | Discharged patients with COVID-19 with persisting symptoms | Outpatients after discharge | 106 | Three groups: 44 patients virtual rehabilitation program; 25 patients home physical therapy; 17 patients independent exercise program | 20 patients: No intervention | Sit-to-stand scores and step test | Significant improvement in both tests with virtual rehabilitation and home physical therapy | NDCS: 6 |
| Cucci et al., 2021 [167] | Retrospective cohort | Post-ICU patients with COVID-19 in inpatient rehabilitation setting | After ICU | 41 | Patient-tailored rehabilitation plan | None | Disability by Barthel index scale; resistance by 6MWT; and fatigue by Borg Rating of Perceived Exertion | Significant improvement in all measures | NDCS: 5 |
| Al Chikhanie et al., 2021 [95] | Prospective cohort | Post-ICU COVID-19 in a dedicated rehabilitation centre | After ICU | 42 | Pulmonary rehabilitation | Non-COVID-19 respiratory failure after ICU | 6MWT | Significant improvement in 6MWT between start and end of intervention in COVID-19 group and between this group and controls | NDCS: 6 |
| Study | Study design | Participants and setting | Timing | Number included | Intervention | Comparison | Outcome | Results | Quality assessment |
|-------|--------------|--------------------------|--------|-----------------|--------------|------------|---------|---------|-------------------|
| Bowles et al., 2021 [168] | Retrospective cohort | Discharged patients referred to home health care | After discharge | 1409 | Home health care | None | Symptoms and functional dependencies | Significant improvement in symptoms and function, as measured by frequency of pain, dyspnoea, cognitive function, anxiety, and functional status by ADL. | NCOS: 4 |
| Myall et al., 2021 [98] | Prospective cohort | Discharged patients with clinical, radiological and functional interstitial lung disease consistent with organizing pneumonia | 6 wk after discharge | 30 | Corticosteroids (maximum dose 0.5 mg/kg prednisolone) for 3 wk | None | Symptoms, lung function, radiological findings | Significant improvement in all measures | NCOS: 3 |
| Goel et al., 2021 [99] | Retrospective cohort | Abnormal chest computed tomography and desaturation (at rest <90% or decline of >4% during 6MWT) | At least 4 wk after acute COVID-19 | 24 | Equivalent of prednisolone 0.25–0.5 mg/kg and tapering for 6–8 wk | None | Symptoms, saturation, radiological findings | Significant improvement in all measures | NCOS: 2 |
| Addison et al., 2021 [108] | SR | Postinfectious olfactory dysfunction (non-COVID) | Not significant | 2352 | Any intervention (including olfactory training and various systemic and topical drugs) | Any control | Improvement in olfaction | No MA performed; authors conclusions supported olfactory training, and consider steroids (nasal or systemic), theophylline, and sodium citrate | AMSTAR grade: Low |
| Abdelalim et al., 2021 [109] | RCT | Patients recovering from COVID-19 (70% mild) | Recovering or discharged with 2 negative PCR tests | 108 randomized, 100 evaluated (50 per group) | Topical corticosteroid nasal spray (mometasone furoate) for 3 wk with olfactory training | Olfactory training alone | Number with recovered smell sense at 3 wk, change in smell score according to patient-reported degree of anosmia/hypoaosmia (subjectively with visual analogue scale) | Number recovered: 31 (625 intervention, 26 (532) control (p = 0.31) | Unclear risk of bias for concealment and generation; open |
| Mohamad et al., 2021 [110] | RCT | "Post COVID-19" patients with olfactory loss | "Post COVID" | 40 randomized (20 evaluated in intervention group, 16 in control) | Insulin fast-dissolving film for intranasal delivery | Placebo (insulin-free fast-dissolving film) | Smell sensation improvement at 4 wk (using olfactory detection score) | Significantly higher olfactory detection scores with intervention (p = 0.0163) | Unclear risk of bias for concealment and generation; double blind |

6MWT, 6-minute walk test; ADL, activity of daily living; AMSTAR, A MeaSurement Tool to Assess systematic Reviews; DLCO, diffusing lung capacity for carbon monoxide; FEV1, forced expiratory volume at 1 second; FIM, functional independence measure; FVC, forced vital capacity; ICU, intensive care unit; MA, meta-analysis; NCOS, Newcastle–Ottawa score; PFT, pulmonary function test; POMA, performance-oriented mobility assessment; RCT, randomized controlled trial; SDS, self-rating depression score; SR, systematic review.
reporting persistent dyspnoea 3 months after acute disease and those with known prior lung disease.

Chest imaging

Chest X-ray. Two observational studies investigating follow-up chest x-ray in patients with COVID-19 at 6 to 8 weeks concluded that it is a poor marker for recovery, demonstrating correlation to severity of initial disease but not to ongoing symptoms [52,53]. Three additional small observational studies reported conflicting findings. One study found reticulat opacity/peripheral atelectasis in 88% and ground-glass opacities in 61% of x-rays performed at 8 to 12 weeks, and the other two studies found only 12% and 7% abnormalities, respectively [Tables 5–7] [51,54,55]. Long-term follow-up data are lacking. Among survivors of SARS and Middle East respiratory syndrome severe illness, chest x-ray was found to have residual abnormalities in approximately a third of patients at 3 and even 6 months [56,57]. No studies had correlated abnormal chest x-ray with clinical outcomes.

Recommendation. Evidence is insufficient to provide a recommendation for or against chest x-ray. Chest x-ray may be considered in patients with long COVID and persistent respiratory symptoms at 3 months to rule out other diagnoses and for a possible early diagnosis of pulmonary fibrosis.

Chest computed tomography/magnetic resonance imaging. Chest CT in patients after severe and critical disease frequently shows abnormalities, mainly ground glass opacities (GGOs), consolidations, and fibrotic changes. These changes are reported in approximately 60% to 75% of patients at 3 months [42,54,58–60].

A systematic review summarizing chest CT findings at 3 to 6 months after COVID-19 of any severity, rates of polled CT abnormalities were 59% (IQR, 44–73%), with GGO being the most prevalent pattern (39%; IQR, 26–52%), followed by fibrosis and reticulation (each approximately 30%) [26]. According to two studies including around 500 patients, approximately 60% still had parenchymal findings at 6 months [61,62]. In one of these studies, fibrotic-like changes were reported in 35% of patients [40 of 114] [62]. These findings correlated with older age and severity of acute disease and were reported regardless of ongoing symptoms. It is still unknown whether these findings predict future lung impairment. Later chest CT follow-up results were reported by Huang et al. for hospitalized patients 12 months after acute COVID. This study reported abnormal CT findings at 1 year for 55% of patients (65 of 118), with GGOs in 46%, mainly derived from critically ill patients, who had abnormalities in 87% of examinations [29]. Chest magnetic resonance imaging (MRI) was performed on 53 recovering patients at 2 to 3 months, showing parenchymal abnormalities in 60% (n = 32), without clear clinical correlation [63].

Limited data are available to report the long-term chest CT findings in mild-to-moderate patients, with some data showing similar rates of abnormalities as for severe patients and some showing lower rates. In the Huang et al. cohort, at 6 months, hospitalized patients with mild-to-moderate disease had CT abnormalities in approximately 50% of patients, which was similar to patients with more severe disease; however, at 1 year, rates were significantly lower among patients with mild-to-moderate disease (39%) [29,47] Another study reported similar rates of chest CT abnormalities among 51 patients recovering from moderate COVID-19 compared with those with severe disease. Signs of fibrosis specifically were significantly less common among patients with moderate disease [51]. In another study, CT abnormalities at 6 months were significantly less common among patients with moderate (~3%) compared with severe (53%) disease [43].

Recommendation. Evidence is insufficient to provide a recommendation for or against chest imaging. Chest CT should be considered at 3 to 6 months in patients with dyspnoea or abnormal PFTs, regardless of symptoms, to rule out other causes and identify fibrotic changes.

Investigating patients with dyspnoea, cardiac complaints, and fatigue

Cardiac imaging. Reports on severe cardiac complications (pericarditis, myocarditis, heart failure, and cardiac arrhythmias) after COVID-19 have been published, although causality is not always evident. One observational study showed that 27.5% of patients (14 of 51) admitted for evaluation of cardiac symptoms (chest pain, palpitations, effort dyspnoea, oedema) 2 months after acute COVID-19 were diagnosed with severe cardiovascular complications [64]. However, this reflects the most severe end of the spectrum, due to selection bias. Another study assessed patients referred to outpatient cardiology evaluation in the first 3 months after mild-to-moderate disease and reported transthoracic echocardiographic (TTE) abnormalities in 25% of patients (38 of 150), mostly reduced ejection fraction (EF), elevated pulmonary artery pressure, diastolic dysfunction, and thickened pericardium [65]. Additional studies demonstrated considerable rates of TTE findings in asymptomatic people 30 to 100 days after COVID-19, including a reduction in the left ventricular global longitudinal strain, diastolic dysfunction, and pulmonary hypertension [66,67]. At a similar follow-up duration, a systematic review reported echocardiographic findings for symptomatic patients with variable severity, including diastolic dysfunction in up to 55% of individuals tested, reduced left ventricular EF in up to 16%, and pulmonary hypertension in up to 10% [40].

Cardiac MRI studies have shown common abnormalities ranging from 19% to 71% in recovering patients at 1 to 4 months [63,68–71]. These findings usually did not correlate with symptoms and were temporary, as suggested by joy et al., and demonstrated resolution of abnormalities at 6 months after diagnosis [72]. In data from systematic reviews, including variable severity of an acute COVID-19 population at a follow-up of 14 to 180 days, cardiac MRI abnormalities were reported with wide variability, and in up to 60% of 73% of tested patients. In four studies reporting formal diagnoses using cardiac MRI, myocarditis was reported in 0% to 37%, myopericarditis in 0% to 11%, pericarditis in 0% to 3%, and myocardial infarction in 0% to 2% of patients [40,73].

Recommendation. Evidence is insufficient to provide recommendations for or against any of the aforementioned cardiac tests. Considering TTE is noninvasive, it may be offered for patients presenting with persistent symptoms suggestive of perimyocardial injury (chest pain, palpitations, signs and symptoms of heart failure). It is reasonable that for patients who had cardiac abnormalities during acute disease (myocarditis, pericarditis, heart failure), a repeat TTE would be performed at 2 to 3 months. Further investigation for cardiac abnormalities should be performed according to symptoms in patients presenting with cardiac symptoms. Cardiac MRI should only be performed on a case-by-case basis with a specific clinical question in mind (e.g. athletes returning to physical activity).

Functional testing. There are several functional tests aimed at evaluating physical performance in frail and post-illness patients. The 6-minute-walk test (6MWT) includes measurement of distance walked during 6 minutes and SpO2 before and after. The sit-to-stand test measures the number of repeats during a certain time period (15–30 seconds, usually). The Short Physical Performance Battery includes balance assessment in a standing position, walking speed for 4 minutes, and standing up from a chair with five repetitions. Several studies assessed discharged patients with acute or long COVID using these methods and mostly found moderate-to-
severe impairment that correlated with acute disease severity [42,47,50,51,74–77].

Specifically, for the 6MWT, individuals recovering from COVID-19 exhibited inconsistent results in this test, depending on disease severity. In general, a mild-to-moderate limitation that was evident during the first few months after acute illness abated with time. A small comparative study found pulmonary rehabilitation to be effective in improving the physical capacity of recoverees, as reflected by the 6MWT [78]. For the 6MWT according to disease severity in individual studies, refer to Table S2. Cardiopulmonary stress testing (CPET) can potentially reveal the mechanisms leading to subjective symptoms in individuals with long COVID. This has the potential to guide rehabilitation efforts. Although most studies assessed previously hospitalized individuals and found at least mild impairment months later, data gathered thus far have yielded conflicting results with respect to the pathophysiological mechanism contributing to dyspnoea and effort intolerance (see Tables 5–7 for relevant studies). Further research with appropriate control arms is warranted.

Recommendation. Evidence is insufficient to provide recommendations for or against any of the aforementioned functional tests. Consider performing them at the beginning of an intervention/rehabilitation program to assess progress.

Investigating patients with neurocognitive complaints

Brain imaging. Few small studies have assessed brain imaging in patients with long COVID (Tables 5–7). Guedj et al. [79] conducted positron emission tomography/CT in 35 patients at a mean of 95.5 ± 30 days after acute COVID-19 and compared the findings with age- and sex-matched historical uninfected controls. They found specific areas of hypometabolism that were associated with symptoms of hyposmia/anosmia, memory/cognitive impairment, pain, and insomnia and that were significantly distinguished from the control group [79]. These findings were also demonstrated in smaller studies [80]. Raman et al. conducted a prospective study including 58 participants 2 to 3 months after acute moderate-to-severe COVID-19 compared with matched controls. Of the study cohort, 53 underwent brain MRI, with 32 showing abnormalities and higher rates of pathology in the thalamus and sagittal stratum compared with controls. Periventricular white matter hyper-intensities in the study group did not correlate with cognitive impairment [63].

Recommendation. Limited evidence does not support the use of brain imaging to investigate long-COVID complaints, other than to rule out other causes or for research purposes.

Psychological/psychiatric evaluation. Anxiety, depression, and post-traumatic stress disorder were reported in 16% to 47% of patients hospitalized for COVID-19 within 2 to 3 months of discharge, with no comparison to a control group [81,82]. In a large retrospective cohort of 236 379 patients followed for 6 months after COVID-19, the estimated incidences of mood, anxiety, or psychotic disorders were higher compared with patients after other respiratory infections. Substance use disorders and insomnia were more common as well. Incidences of anxiety and psychotic disorder were 17% and 1.2%, respectively, for the entire cohort, but were higher in hospitalized patients and specifically those admitted to the ICU [83].

Recommendations regarding psychological/psychiatric assessment are beyond the scope of these guidelines. Nevertheless, healthcare practitioners should be aware of the substantial incidence of psychological sequelae of COVID-19 of any severity, and, whenever relevant, refer patients for assessment and therapy.

Management of patients with long COVID

The studies included are summarized in Table 8.

Should post-discharge (extended) thromboprophylaxis be administered to patients with COVID-19?

Recommendations from several societies do not support routine use of post-discharge (extended) thromboprophylaxis based on low rates of post discharge venous thromboembolism (VTE) among patients with COVID-19 and studies addressing other hospitalized populations. All recommend individualized risk assessment and decisions. Extended prophylaxis refers to up to 45 days. The types of anticoagulation recommended include low-molecular-weight heparin or direct oral anticoagulants [84–87]. One randomized controlled trial suggested a benefit of rivaroxaban 10 mg daily compared with no anticoagulant after discharge in high-risk individuals [88]. Other than this study, the recommendations are not based on comparative studies, but on considerations of risk and benefit.

Recommendation

Evidence is insufficient to provide a recommendation for or against the intervention. It is advisable to perform individualized risk stratification of the risk for thrombotic events vs. haemorrhagic events. Consider extended anticoagulation prophylaxis for patients with a low risk of bleeding and elevated risk for VTE (active malignancy, immobility, history of VTE, recent major surgery, thrombophilia).

Should physical or pulmonary rehabilitation be offered to patients, and when?

A meta-analysis and systematic review of RCTs was conducted to evaluate the effectiveness of pulmonary rehabilitation in interstitial lung disease in general, including COVID-19. This meta-analysis demonstrated improved walking distance in the 6MWT with the intervention (pooled effect size estimate for pulmonary rehabilitation: 44.55; 95% CI, 32.46–56.64), improved quality of life (effect size: 0.52; 95% CI, 0.22–0.82), improved dyspnoea (effect estimate: 0.39; 95% CI, −0.08 to 0.87), and significant improvement in lung function as evaluated by forced vital capacity (effect size: 0.37; 95% CI, 0.02–0.71) [89]. One small RCT included in the meta-analysis evaluated elderly patients discharged from the hospital after COVID-19 and demonstrated significant improvement in PFT, 6MWT, quality of life scale, and anxiety score with the intervention (Table 8) [90].

A living systematic review evaluated rehabilitation specifically in COVID-19, both acute and post-acute phases, with one of the addressed questions being “what is the evidence for effect of intervention for limitation(s) of functioning?” [91,92]. Only three comparative studies were available for this question, addressing different patients and comparisons (Table 8). One of these studies is the RCT by Liu et al. described earlier [90,93,94]. Additional studies presented in this systematic review included noncomparative studies, all reporting significant improvement in symptoms and respiratory and general function in response to the intervention (Table 8).

Explicit timing of starting rehabilitation was not provided in the literature. The British Society of Rehabilitation Medicine recommends that rehabilitation start on patient admission and be continued throughout hospitalization and then after discharge [95]. Other guidelines for rehabilitation after critical illness in general recommend initiating rehabilitation programs within the first 30 days (at the post-acute phase) [96]. Rehabilitation programs
should include (according to the individual patient) exercise, pulmonary, cardiac, musculoskeletal, neurological, and psychological rehabilitation [95,97].

**Recommendation**

Evidence is insufficient to provide a recommendation for or against the intervention specifically for COVID-19. No data regarding persistent long COVID were identified. Until further evidence accumulates, it is reasonable that clinicians follow available consensus statements regarding multidisciplinary rehabilitation in the post-acute stage [97].

**How should persistent pulmonary symptoms/signs be managed?**

In one small, noncomparative, prospective study, 30 patients diagnosed with interstitial lung disease consistent with organizing pneumonia 6 weeks after discharge (persistent symptoms, functional or physiological abnormalities, and parenchymal abnormality on CT) were treated with corticosteroids (maximum initial dose of 0.5mg/kg prednisolone) for 3 weeks. All patients demonstrated significant symptomatic improvement, significant increase in gas transfer and forced vital capacity, and radiologic improvement [98]. In another small study, the authors retrospectively reviewed the routine management of patients with abnormal CT findings over 4 weeks after COVID-19 and desaturation, treated with corticosteroids. At a follow-up at 12 to 14 weeks, 24 patients demonstrated improved fatigue, breathlessness, and cough, as well as improved modified Medical Research Council score, saturation at rest, 6MWT results, and imaging findings [99]. However, others reported significant spontaneous recovery within 12 weeks for similar patients, raising the question of whether steroids are beneficial [100]. Continuing steroids for patients with persistent hypoxemia and abnormal CT at discharge and/or follow-up has been suggested based on clinical experience but not tested in comparative clinical studies [101,102].

Few cases of treatment of long-COVID lung fibrosis with antifibrotic agents have been reported [103]. This therapeutic option is currently being tested in clinical trials. Trials are ongoing to evaluate the use of the antifibrotic nintedanib and pirfenidone, as well as other drugs [104–106].

**Recommendation**

Evidence is insufficient to provide a recommendation for or against any intervention.

**How should persistent cough be managed?**

There are no clinical studies evaluating the management of persistent cough after acute COVID-19. In a review discussing the possible pathophysiology and management of cough in patients with COVID-19, further investigation into the role of gabapentin and pregabalin, antimuscarinic drugs, and other novel drugs that interfere with the neuroinflammatory pathways has been suggested [22].

**Recommendation**

Evidence is insufficient to provide a recommendation for or against any intervention.

**How should smell and taste disturbances be managed?**

A Cochrane systematic review aimed to assess interventions to treat persistent COVID-19–related olfactory dysfunction. The search for RCTs for inclusion resulted in only one small trial comparing prednisone plus nasal irrigation (intranasal steroids with mucolytic and decongestant agents) for 15 days versus no treatment. The study included nine patients in each arm but was graded as high risk of bias, and the results were reported only up until 40 days, limiting the ability to draw conclusions [107].

Addison et al. conducted a systematic review evaluating the management of any postinfectious olfactory dysfunction. In total, 15 studies addressing this entity directly were included, but none specifically evaluated patients with COVID-19. The interventions tested included olfactory training and various topical and systemic treatments. All 11 studies evaluating olfactory training (not all comparative) showed a benefit of the intervention [108]. The manuscript included a consensus statement by the clinical olfactory working group, which recommended routine use of olfactory training, but was controversial regarding pharmacologic therapy with a recommendation to consider steroids (nasal or systemic), theophylline, and sodium citrate.

A role of smoking and olfactory dysfunction in general has been discussed. The consensus document states that the benefit of smoking cessation in patients with long-COVID anosmia/ageusia is not clear, but an overall benefit justifies the recommendation. Other therapies described that need further study include oral and intranasal corticosteroids, theophylline, sodium citrate, N-methyl D-aspartate antagonist (caroverine), traditional Chinese acupuncture, a-lipoic acid, vitamin A, minocycline, and zinc sulphate [108].

One low-quality RCT including 100 patients recovering from COVID-19 evaluated topical corticosteroid nasal spray (mometasone furoate) for 3 weeks combined with olfactory training versus olfactory training alone. In this study, no difference between groups was demonstrated in rates or patients with olfactory recovery or duration of anosmia/hyposmia [109]. An additional small, low-quality RCT evaluated insulin fast-dissolving film for intranasal delivery versus placebo in 40 post-COVID patients with olfactory loss. In this study, significantly higher olfactory detection scores were demonstrated with intervention (p = 0.0163) [110].

**Recommendation**

Evidence is insufficient to provide a recommendation for or against any intervention. Due to its simplicity and safety, olfactory training should probably be suggested for all patients. Physicians should discuss the likelihood for spontaneous recovery with patients, and other interventions should be suggested only in clinical trials. Smoking cessation should be recommended.

**How should fatigue be managed?**

Clinical overlap has been suggested between long COVID and postviral fatigue syndromes/postinfectious myalgia encephalomyelitis/chronic fatigue syndrome. For the latter, various interventions have been suggested [5,111]. Systematic reviews of such interventions included various medications, complementary and alternative medicine, cognitive behavioural therapy, and exercise. The included studies were heterogeneous and data were limited, although the drug rintatolimod, counselling therapies, and graded exercise therapy suggested a benefit [112,113]. No evidence is available to support interventions for the management of fatigue in patients with long COVID. Graded exercise and cognitive behavioural therapy are controversial for the management of myalgia encephalomyelitis/chronic fatigue syndrome and should be further investigated for patients with long COVID prior to any recommendation [113,114].

**Recommendation**

Evidence is insufficient to provide a recommendation for or against any intervention.
How should neurological/cognitive long-COVID sequelae be managed?

There are no clinical studies evaluating any pharmacological treatment for neurological sequelae of long COVID. The flavonoid luteolin has been suggested as a potential treatment, by inhibiting a proinflammatory cascade of mast cells and microglia activation in the hypothalamus. However, no studies have evaluated this intervention [115]. The cannabis derivatives cannabidiol and cannabivarin have been suggested to have the potential to bind to and downregulate central nervous system proteins related to long-COVID symptoms. These compounds have not been tested in clinical studies [116]. Methylene blue has been suggested as a possible therapy for neurocognitive impairment in long COVID due to its mitochondrial protective effects [117]. The therapeutic potential is theoretical, however, and without clinical evidence.

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

How should emotional/psychiatric long COVID sequelae be managed?

Clomipramine, a tricyclic antidepressant with anti-inflammatory action and penetration to the central nervous system, has been suggested as a potential drug to prevent post-infectious mental complications. Further studies are needed [118].

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

Recommendations for future studies on long COVID

As reflected in these guidelines, studies on long COVID are limited by the lack of a consistent definition of long COVID in terms of symptoms and timeframes, the absence of typical laboratory findings/diagnostic tests, and the absence of a comparison group in most studies. Selection bias might be pronounced due to the considerable portion of online recruitment studies [119]. In addition, the study design is usually retrospective, including symptomatic patients (rather than all recovering patients), thus limiting the ability to measure the scope of the problem and evaluate risk factors.

Additional studies are needed, including studies following consecutive patients recovering from COVID-19, with various severities of the acute disease. Such studies should be designed to evaluate the incidence of long COVID and to identify risk factors for its development. The first priority should be to evaluate healthy, community-treated persons and to evaluate the scope of the problem in this population and the need for follow up. Considering the toll of a stressful pandemic, quarantine, and unemployment, Amin-Chowdhury et al. suggested prospective longitudinal cohort studies using a noninfected control group [119].

Clustering of symptoms may assist in evaluating the scope of illness compared with noninfected people, as well as risk factors. Amin-Chowdhury et al. described the following clusters in a large prospective cohort: sensory (ageusia, anosmia, loss of appetite, and blurred vision), neurological (forgetfulness, short-term memory loss, and confusion/brain fog), and cardiorespiratory (chest tightness/pain, unusual fatigue, breathlessness after minimal exertion/ at rest, and palpitations) [120]. Patients after ICU hospitalization should be addressed separately in studies, including studies assessing rehabilitation starting in the hospital and different interventions to prevent and treat lung injury. Patients with less severe disease should be investigated for interventions to resolve their leading symptom/cluster of symptoms (as described). Outcomes addressed should include return to work and return to previous activity level, including sports. Further research is also needed to elucidate the pathophysiology of various long-COVID symptoms. Additional studies should assess long-COVID prevalence and symptoms after different SARS-CoV-2 variants and vaccination.

Long-term follow-up studies of symptomatic patients are needed to evaluate the assessment and management of interventions, using predefined patient-related outcomes, including quality of life, time to return to work and baseline physical activity, and cognitive and functional assessments. These studies should be in the form of RCTs.

Author contributions

These guidelines were developed by a group of infectious diseases specialists who care for patients recovering from acute COVID-19. All members formulated the questions and aims of these guidelines. DYa, DYe, and IM performed the literature search, and all members were involved in the data extraction and writing of the manuscript. All panel members reviewed the last version of the manuscript. The guidelines were written under the guidance and support of LS (ESCMID Guidelines Director).

Transparency declaration

All authors declare no conflicts of interest. No funding sources.

Updating

These are rapid guidelines aimed to capture current evidence on the topic. However, due to the rapid evolution of the literature, the authors plan to conduct these as living guidelines to be modified with upcoming new evidence. The panel will meet monthly regarding the need for updates. The panel members will perform an updated search every 3 months and will update the guidelines once substantial evidence for changing any recommendation is observed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.018.

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