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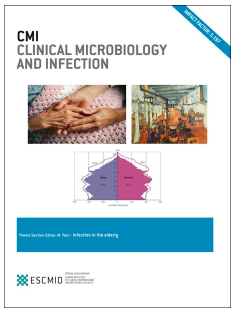

ESCMID rapid guidelines for assessment and management of long COVID

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ESCMID rapid guidelines for assessment and management of long COVID

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Abstract

Scope: The aim of these guidelines is to provide evidence-based recommendations for assessment and management of individuals with persistent symptoms after acute COVID-19 infection, and 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 functions 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 assessment and management of individuals with persistent symptoms of COVID-19.

Scope

Long COVID is an umbrella term referring to signs and symptoms that persist after acute severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The prevalence of long COVID is highly heterogeneous among studies, probably reflecting the variability of definitions of this entity; populations surveyed and follow-up durations. According to the literature, 22-40% of convalescent patients are expected to experience one or more symptoms of long COVID. [1,2] The most common symptoms include fatigue, dyspnea, cognitive impairment, and various pain symptoms (chest pain, headache, myalgia, etc). 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

Over 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 algorithm of investigation, and no evidence-based interventions. [4] Several guidelines/recommendations for diagnosis and management of long COVID have been published, including those issued by the National Institute for health and Care Excellence (NICE), [5] published in December 2020; the CAMFiC long COVID-19 Study Group from Spain; [6] and French recommendations. [7] The World Health Organization (WHO) Living guidance for clinical management of COVID-19 also include a section on "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, while 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 following acute SARS-CoV-2 infection with emphasis on those who have not fully recovered after over 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, 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 by 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 post-discharge and long-term follow up: 1) Guidelines international network [9]; 2) COVID-END of McMaster University [10]; 3) 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/, 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 Dec 31st 2021. In addition, we searched MedRxiv for relevant preprints (https://www.medrxiv.org/), and large relevant journal sites for early online publications (including: T*he New England Journal of Medicine* (https://www-nejm-org.rproxy.tau.ac.il/coronavirus), *The Lancet* (https://www-thelancet-com.rproxy.tau.ac.il/coronavirus), *JAMA* (https://jamanetwork-com.rproxy.tau.ac.il/journals/jama/pages/coronavirus-alert), and *Annals of Internal Medicine* (https://annals-org.rproxy.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, case-control studies and 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: any adult (≥18 years) patient following the acute phase of COVID-19 (see definitions below); intervention: any intervention for the assessment and management (pharmacological or other) of participants; comparison/control: patients receiving a comparator intervention (studies comparing two interventions) or no intervention; outcomes: for management - 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 (PRISMA) statement. [12]

Search results

Our PubMed search yielded 13,881 titles (13,066 after exclusion of 815 duplicates). After inspection of titles and abstracts, 12,390 were excluded due to irrelevant study design, irrelevant population, or irrelevant topic; 676 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 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 high, moderate, low, and critically low quality of evidence according to 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 low, high or unknown risk of bias, according to the Cochrane handbook's criteria. [14] For non-randomized 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 Grading of Recommendations Assessment, Development and Evaluation (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, lasting for at least 2 months and persisting beyond 12 weeks from the acute disease and cannot be explained by an alternative diagnosis [17] . The CDC provides a similar definition, with a different timeframe of beyond 4 weeks post the acute disease. [18] The Royal Society defines the same condition, however no time frame is provided. [17] A similar term called post-acute sequelae of SARS-CoV-2 infection (PASC) has been termed by the National institute of Health (NIH). [19] A repository of published/available definitions of post COVID-19 condition is maintained by the WHO. [17]

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

Long COVID is defined here as one or more symptoms and/or signs (as described below) 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 (see Table 1). Post-acute COVID: We define post-acute COVID as one or more symptoms and/or signs (as described below) persisting or relapsing/remitting from 4 to 12 weeks since 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 long COVID patients are fatigue (31-58%), dyspnea (24-40%), musculoskeletal pain (9-19%), anosmia/dysgeusia (10-22%), cognitive impairment ('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 & 4 provide symptom prevalence according to time intervals from the acute illness (1-3m, 3-6m, >6m) and hospitalization status, respectivelyPersisting symptoms seem to considerably affect the 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, autoimmunity and the neurotropism of SARS-CoV-2. [4,22,30] Post-intensive care syndrome may provide an explanation for prolonged symptoms following 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 increased risk of developing specific long COVID symptoms are accumulating in the literature though the evidence is inconsistent. The two consistent risk factors for any long COVID symptom are acute COVID-19 severity and gender. [32–34] (See Supplemental Table 1) Women have been shown to have an estimated two-fold risk of having long COVID symptoms (odds ratios between 1.3 and 5). Similarly, severe acute disease has been associated with increased risk for long COVID symptoms, with

strongest association with fatigue. Other risk factors such as age, obesity and presence of comorbidities have shown mixed results. (Supplemental Table 1).

Recommendations

We aimed to answer the following PICO questions: 1) Who should be assessed?; 2) What assessment needed for individuals with long COVID ? (sub-divided according to systems and further subdivided by specific tests); 3) How to manage individuals with long COVID? (also sub-divided according to systems). Each section reports the main summary of evidence for each topic. Tables 5-6 provide details of the studies included.

1. 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, myopericarditis, 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, it is suggested to collect specific clinical history 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 over 12 weeks after acute COVID-19, should be referred to medical care. For patients 4-12 weeks following 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 COVID-19 hospitalized patients, demonstrated low rates of laboratory abnormalities, and no significant difference in rates of lymphocyte count < $0{\cdot}8 \times 10^{9}$ per L or serum creatinine abnormality between recovering participants and controls. Nevertheless, as suggested above, blood tests according to symptoms, should be collected as part of an investigation to rule out other conditions.

Some blood tests may be considered in order to identify possible complications following acute infection. These however, should be interpreted with caution, due to possible persistent abnormalities following COVID-19. In one study evaluating 734 severe patients 28 days post recovery, an increase in insulin dependency from 18% to 63%, and 1.4% of new onset diabetes were identified. [35] Two additional studies found an increase in new onset diabetes in the months following recovery from COVID-19. [36,37] This might be a result of surveillance bias in previously unknown diabetics or a real shift from pre-diabetes to diabetes, caused by the acute disease or by its' treatment, although there is no evidence for the latter. Elevated D-dimer can be observed at a median of over 2 months following resolution of acute COVID-19, despite normalization of inflammatory markers and other coagulation parameters. [38] Similarly, detectable levels of high-sensitivity troponin T (hsTnT, greater than 3 pg/mL) were reported in 71/100 patients evaluated at a median of 71 days (IQR 64-92) after diagnosis of COVID-19; with 5/100 patients having significantly elevated hsTnT (greater than 13.9 pg/mL). [39] Increased NT-pro-BNP levels at median follow up of 71 (14-124 days) were reported from a systematic review in 10% of individuals tested (57/571). [40] A systematic review accumulated data on 27 patients presenting with subacute thyroiditis following COVID-19. Patients presented with typical features, including elevated fT4 and fT3, low TSH and raised inflammatory markers (CRP and ESR). [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, CPK-MB, and B-type natriuretic peptide (BNP) 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, though 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 hemoglobin levels.

2. What assessment is needed for individuals with long COVID?

After ruling out other conditions, the followings are suggested to evaluate individuals with suspected long COVID. First, the evaluation should include an interview with the patient to identify symptoms' 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 (See below options for therapy that can be considered in the context of clinical trials).

Investigating individuals with dyspnea:

In previous guidelines/recommendations, [5–7] a diagnostic pathway is suggested for patients with dyspnea persisting more than 4-12 weeks after acute COVID-19. Several studies used the Modified medical research council (mMRC) dyspnea scale to assess severity of dyspnea, however without providing a cut-off necessitating further investigation. [42,43]

Pulmonary function testing (PFT)

Various rates of abnormal 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 need for ventilatory support. [44] . The most frequently impaired pulmonary function test is diffusion capacity (DLCO), and the most frequent pattern observed is restrictive. DLCO impairment (below 80% of predicted) has been found in varying proportions of patients, in correlation to disease severity. Patients following critical disease and ICU admission had up to 80% abnormal DLCO at discharge and 50-70% impairment at 3 months follow-up. Patients following severe disease had 30-68% impairment at 3 months. [44,45] At 3 months, higher CT severity score and ARDS at acute disease were associated with impaired DLCO in one study including hospitalized patients. [44] Surprisingly, even among patients following mild-moderate disease, abnormal DLCO was demonstrated in ~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 then at 3 months, though still high (DLCO reduced in 29% for severe 58% for critical). [47] This correlates with the finding that on serial testing of patients with restrictive pattern, tested individuals demonstrated overall improvement at 6 months compared to 10 weeks but not complete resolution. [48,49] At a longer follow up of one year, Huang et al. reported DLCO<80% in 23%-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, 29%, at 12 months. [29]

There is a paucity of data for mild-moderate patients. Several of the studies included some patients following mild-moderate disease, mostly as a control group for the severe patients.

[47,50,51] These studies reported normal median PFTs and DLCO but a considerable percentage (10-22%) of patients still had abnormal results.

Recommendation: Evidence is insufficient to provide a recommendation for or against PFT. Considering that the test is simple and non-invasive, and that future studies may suggest beneficial treatment for patients with abnormal PFT, the panel recommends considering routine PFT including diffusion capacity in all severe and critical COVID-19 patients at 3 months from diagnosis, regardless of symptoms; as well as considering completing PFT with diffusion for patients complaining of persistent dyspnea at 3 months following the acute disease and for patients with known prior lung disease.

Chest imaging

- Chest X-ray

Two observational studies investigating follow-up chest X-ray in COVID-19 patients at 6-8 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 found reticular opacities/peripheral atelectasis in 88% and ground-glass opacities in 61% of X-rays performed at 8-12 weeks; the other two studies found only 12% and 7% abnormalities. [51,54,55] (Table 5) Long follow up data are lacking. Among survivors of SARS and MERS severe illness, chest X-ray was found to have residual abnormalities in about a third of patients at 3 and even 6 months. [56,57]

No studies have 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 long COVID patients with persistent respiratory

symptoms at 3 months to rule out other diagnoses and for possible early diagnosis of pulmonary fibrosis.

- Chest CT/MRI

Chest CT in patients post severe and critical disease frequently shows abnormalities, mainly ground glass opacities (GGO), consolidations and fibrotic changes. These changes are reported in ~60-75% at 3 months. [42,54,58–60]

A systematic review summarizing chest CT findings at 3-6 month after COVID-19 with any severity, rates of polled CT abnormalities were 59% (IQR 44–73%), with GGO being the most prevalent pattern (39%, IQR 26–52%), flowed by fibrosis and reticulation (each ~30%). [26] According to two studies including ~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% (40/114) of patients. [62] These findings correlated with older age and severity of the 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 at 12-month post acute COVID. This study reported abnormal CT finding at 1year for 55% (65/118) of patients, with GGO in 46%, mainly derived from critically ill patients, who had abnormalities in 87% of exams. [29] Chest MRI was performed on 53 recovering patients at 2-3 months, showing parenchymal abnormalities in 60% (32/53), without clear clinical correlation. [63]

Limited data are available to report the long-term chest CT findings in mild-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-moderated disease had CT abnormalities in ~50%, similar to more severe patients; however, at 1 year, rates were significantly lower among mild-moderate patients (39%). [29,47] Another study reported similar rates of chest CT abnormalities among 51 moderate COVID-19 recovering patients compared to more severe patients. Signs of fibrosis specifically were significantly less common among moderate patients. [51] In another study, CT abnormalities at 6 months were significantly less common among moderate (~3%) compared to severe patients (53%). [43]

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

Investigating patients with dyspnea, cardiac complains, and fatigue:

- Cardiac imaging

Reports on severe cardiac complications (pericarditis, myocarditis, heart failure and cardiac arrhythmias) post-COVID-19 have been published, though causality is not always evident. One observational study showed that 27.5% (14/51) of patients admitted for evaluation of cardiac symptoms (chest pain, palpitations, effort dyspnea, edema) 2 months after acute COVID-19 were diagnosed with a 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 following mild-moderate disease and reported echocardiographic (TTE) abnormalities in 25% (38/150), 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 30-100 days post COVID-19, including reduction in left ventricular global longitudinal strain (LVGLS), diastolic dysfunction, and pulmonary hypertension. [66,67] At a similar follow up duration, for symptomatic patients with variable severity, a systematic review reported echocardiographic findings including diastolic dysfunction in up to 55% of individuals tested; reduced left ventricular ejection fraction in up to 16%; and pulmonary hypertension in up to 10%. [40]

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

Recommendation: Evidence is insufficient to provide recommendations for or against any of the above cardiac tests. Considering TTE is a non-invasive test, it may be offered for patients presenting with persistent symptoms suggestive of peri-myocardial injury (chest pain, palpitations, signs and symptoms of heart failure). It is reasonable that for patients who had cardiac abnormalities during the acute disease (myocarditis, pericarditis, heart failure) a repeat TTE would be performed at 2-3 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 six-minute-walk test (6MWT) includes measurement of distance walked during 6 minutes, and SpO2 before and after. Sit-to-stand test measures the number of repeats during a certain time period (15-30 seconds usually). Short Physical Performance Battery (SPPB) includes balance assessment in standing position, walking speed for 4 minutes, and standing up from a chair with 5 repetitions. Several studies assessed discharged acute COVID and long COVID patients 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, the mild to moderate limitation that was evident during the first few months following the 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 6MWT according to disease severity in individual studies see Supplemental Table 2. 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 reached conflicting results with respect to the pathophysiological mechanism contributing to dyspnea and effort intolerance (see Table 5 for relevant studies). Further research with appropriate control arms is warranted.

Recommendation**:** Evidence is insufficient to provide recommendations for or against any of the above functional test. Consider performing at the beginning of an interventional/rehabilitation program to assess progress.

Investigating patients with neurocognitive complains:

Brain imaging

Few small studies have assessed brain imaging in long COVID patients. (See Table 5 for details) Guedj et al. conducted PET/CT in 35 patients at mean 95.5+-30 days post-acute COVID-19 and compared the findings to 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 2-3 months after acute moderate-severe COVID-19, with matched controls. Of the study cohort, 53 performed brain MRI, with 32 showing abnormalities and higher rates of pathology in thalamus and sagittal stratum compared to controls. Periventricular white matter hyperintensities demonstrated in the study group did not correlate with cognitive impairment. [63]

Recommendation**:** Limited evidence does not support use of brain imaging for investigating long COVID complaints, other than for ruling out other causes or for research purposes.

Psychological/psychiatric evaluation

Anxiety, depression, and post-traumatic stress disorder were reported in 16-47% of hospitalized COVID patients within 2-3 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 post COVID-19, the estimated incidences of mood, anxiety, or psychotic disorders were higher compared to patients following other respiratory infections. Substance use disorders and insomnia were more common as well. Incidences of anxiety and psychotic disorder were 17% an 1.2%, respectively, for the entire cohort, but were higher in hospitalized and specifically ICU patients. [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 relevant assessment and therapy.

3. Management of patients with long COVID

The studies included are summarized in Table 6.

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

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 COVID-19 patients 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 (LMWH) or direct oral anticoagulants (DOACs). [84–87] One randomized controlled trial suggested benefit of rivaroxaban 10 mg daily compared to no anticoagulant post-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 risk for thrombotic event vs hemorrhagic event. Consider extended anticoagulation prophylaxis for patients with 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 coronavirus diseases. This meta-analysis demonstrated improved walking distance in the 6-minute walk test 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 dyspnea (effect estimate 0.39, 95% CI: -0.08; 0.87); and significant improvement in lung function, evaluated by forced vital capacity (FVC) (effect size 0.37; 95% CI: 0.02; 0.71). [89] One small RCT included in the meta-analysis evaluated elderly patients discharged from hospital following COVID-19, and demonstrated significant improvement in pulmonary function test, 6MWT, quality of life scale and anxiety score with the intervention [90] (Table 6).

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. (See Table 6) One of these studies is the RCT by Liu et al. described above. [93–95] Additional studies

presented in this SR included non-comparative studies, all reporting significant improvement in symptoms, respiratory and general functional in response to the intervention. (Table 6)

Explicit timing of starting rehabilitation could not be provided from the literature. The British Society of Rehabilitation Medicine recommends that rehabilitation start on patient's admission, and continued throughout hospitalization and then following discharge. [96] Other guidelines for rehabilitation after critical illness in general recommend initiating rehabilitation programs within the first 30 days (at the post-acute phase). [97] Rehabilitation program should include, according to individual patient, exercise rehabilitation, pulmonary, cardiac, musculoskeletal, neurological, and psychological rehabilitation. [96,98]

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. [98]

How should persistent pulmonary symptoms/signs be managed?

In one small non-comparative prospective study, 30 patients who were diagnosed as having interstitial lung disease consistent with organizing pneumonia at 6-weeks post-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 three weeks. All patients demonstrated significant symptomatic improvement, significant increase in gas transfer and FVC, as well as radiologic improvement. [99] In another small study, authors retrospectively reviewed their routine management of patients with abnormal CT findings at over 4 weeks following COVID-19 and desaturation, treated with corticosteroids. At a follow up at 12-14 weeks, 24 patients demonstrated improved fatigue, breathlessness and cough, as well as improved MMRC score,

saturation at rest and on 6MWT, and imaging findings. [100] However, others reported significant spontaneous recovery within 12 weeks for similar patients, raising the question whether steroids are beneficial. [101] Continuing steroids for patients with persistent hypoxemia and abnormal CT at discharge and/or at follow up has been suggested based on clinical experience, though not tested in comparative clinical studies. [102,103]

Few cases of treatment of long COVID lung fibrosis with antifibrotic agents have been reported. [104] 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 [105–107]

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 following acute COVID-19. In a review discussing possible pathophysiology and management of cough in patients with COVID-19, it has been suggested to further investigate the role of gabapentin and pregabalin, antimuscarinic drugs, and other novel drugs that interfere with the neuroinflammatory pathways. [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 COVID-19 persisting olfactory dysfunction. The search for randomized controlled trials for inclusion resulted in

only one small trial comparing prednisone plus nasal irrigation (intranasal steroids with mucolytic and decongestant agents) for 15 days, compared to no treatment. The study included nine patients in each arm. This study was graded as high risk of bias, and results were reported only up till 40 days, limiting to ability to draw conclusions. [108] Addison et al. conducted a systematic review evaluating management of any postinfectious olfactory dysfunction. In total, 15 studies addressing this entity directly were included, none evaluated specifically COVID-19 patients. Interventions tested included olfactory training and various topical and systemic treatments. All 11 studies evaluating olfactory training (not all comparative) showed benefit of the intervention. [109] The manuscript included a consensus statement by the clinical olfactory working group, who recommended routine use of olfactory training, and were 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. In this consensus document, it is stated that benefit of smoking cessation in long COVID anosmia/ageusia is not clear, but 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 sulfate. [109]

One low quality RCT including 100 recovering COVID-19 patients 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. [110] An additional small, low quality RCT evaluated insulin fast-dissolving film for intra-nasal delivery vs. placebo in 40 post-COVID patients with olfactory loss. In this study,

significantly higher olfactory detection scores were demonstrated with intervention (P=0.0163). [111]

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 overlaps have been suggested between long COVID and post-viral fatigue syndromes / post-infectious myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS). For the latter, various interventions have been suggested. [5,112] Systematic reviews of such interventions included various medications, complementary and alternative medicine, cognitive behavioral therapy, and exercise. The included studies were heterogeneous and data were limited, although the drug rintatolimod, counselling therapies, and graded exercise therapy suggested benefit. [113,114] No evidence is available to support interventions for managing fatigue in long COVID patients. Graded exercise and cognitive behavioral therapy are controversial for the management of ME/CFS and should be further investigated for long COVID patients prior to any recommendation. [114,115]

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 pro-inflammatory cascade of mast cells and microglia activation in the

hypothalamus. However, no studies have evaluated this intervention. [116] The cannabis derivatives cannabidiol and cannabivarin have been suggested to have the potential to bind to central nervous system proteins related to long COVID symptoms and downregulate them. These compounds have not been tested in clinical studies. [117] Methylene blue has been suggested as a possible therapy for neurocognitive impairment in long COVID due to its mitochondrial protective effects. [118] The therapeutic potential is theoretical, however, 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 penetrance to central nervous system, has been suggested as a potential drug to prevent post-infectious mental complications. Further studies are needed. [119]

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; absence of typical laboratory findings/diagnostic tests; and absence of a comparison group in most studies. Selection bias might be pronounced due to the considerable portion of online recruitment studies. [120] In addition, 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 would be to evaluate healthy, community treated persons, to evaluate the scope of the problem in this population and the need for follow up. Considering the toll of stressful pandemic, quarantine and unemployment, Amin-Chowdhury et al. suggested prospective longitudinal cohort studies using a non-infected control group. [120]

Clustering of symptoms may assist in evaluating the scope of illness, compared to non-infected people, and evaluate risk factors. Amin-Chowdhury et al. described the following clusters in a large prospective cohort: sensory cluster (ageusia, anosmia, loss of appetite and blurred vision), neurological cluster (forgetfulness, short-term memory loss and confusion/brain fog), and cardiorespiratory cluster (chest tightness/pain, unusual fatigue, breathlessness after minimal exertion/at rest, palpitations). [121] Patients following ICU hospitalization should be addressed separately in studies, including studies assessing rehabilitation starting in hospital, and different interventions to prevent and treat lung injury. Less severe patients should be investigated for interventions to resolve their leading symptom / cluster of symptoms (as descried above). 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 long COVID various symptoms. Additional studies should assess long COVID prevalence and symptoms following different SARS-CoV-2 variants, and following vaccination.

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

Description of the developing group

These guidelines were developed by a group of infectious diseases specialists, caring 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; all members were involved in 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.

Conflict of interest

All authors declare none.

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among ESCMID members; we thank Virginie Prendki, Miriam Weinberger, and Petar Velikov, for critical review of the draft guideline.

Updating

These are rapid guidelines aimed to capture current evidence on the topic. However, due to the rapid evolvement of the literature, we 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 three months and will update the guidelines once substantial evidence for changing any recommendation will be observed.

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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 lab result**	**Typical symptoms, negative lab results, Suggestive epidemiology**	**Typical symptoms, negative lab results and negative epidemiology**
4-12 weeks	Confirmed post-acute COVID	Probable post-acute COVID	Possible post-acute COVID
>12 weeks	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.

Table 2. Prevalence of most common long-COVID / Post COVID-19 condition symptoms according to systematic reviews/meta-analyses.

Meta-analysis	Included studies	Max follow-up duration (days)	Inclusion criteria	Quality assessment	Statistical analysis	Fatigue	Dyspnoea	Chest Pain	Cough	Anosmia	Dysgeusia	Sleep disorders	Headache	Depression	Joint pain
Cares-Marambio et al. [21]	10	110	hospitalized, adult patients, follow-up >30 days after COVID-19 diagnosis	NHLBI (Study Quality Assessment Tools)	random-effect model, I^2	0.52 (0.38-0.66)	0.37 (0.28-0.48)	0.16 (0.10-0.23)	0.14 (0.06-0.24)						
Lopez-Leon et al. [20]	15	110	follow up >2 weeks after COVID -19 diagnosis	MetaXL Guidelines	random-effect model, I^2, sensitivity analysis	0.58 (0.42-0.73)	0.24 (0.14-0.36)	0.16 (0.10-0.22)	0.29 (0.07-0.34)	0.21 (0.12-0.32)	0.23 (0.14-0.33)	0.11 (0.08-0.24)	0.44 (0.13-0.78)	0.12 (0.03-0.23)	0.19 (0.07-0.34)
Iqbal et al. [23] (1)	24	90	symptoms <12 weeks post-COVID-19	Risk of Bias Tool (Hoy et al, 2012)	meta-analysis of proportion, I^2	0.37 (0.20-0.56)	0.35 (0.16-0.56)	0.15 (0.04-0.31)	0.07 (0.03-0.11)	0.22 (0.11-0.36)	0.21 (0.06-0.42)		0.24 (0.15-0.35)	0.20 (0.09-0.33)	
Iqbal et al. [23] (2)	15	180	symptoms >12 weeks post-COVID-19	Risk of Bias Tool (Hoy et al, 2012)	meta-analysis of proportion, I^2	0.48 (0.23-0.73)	0.39 (0.16-0.64)	0.17 (0.05-0.35)	0.11 (0.07-0.17)	0.17 (0.10-0.25)	0.18 (0.10-0.28)	0.44 (0.08-0.85)	0.12 (0.00-0.44)		
Hoshijima et al. [122]	35	210	adults with symptoms >1 month of disease onset or hospital discharge	Newcastle-Ottawa scale	inverse variance with logit transformation, I^2, meta-regression	0.45 (0.32-0.59)	0.25 (0.15-0.38)	0.17 (0.12-0.25)	0.19 (0.13-0.26)	0.19 (0.13-0.27)	0.14 (0.09-0.20)	0.26 (0.09-0.57)	0.16 (0.09-0.27)	0.12 (0.06-0.21)	0.13 (0.07-0.24)
Song et al. [22]	14	180	persistent cough in hospitalized COVID-19 patients	NA	random-effect model, I^2				0.18 (0.12-0.24)						

Sanchez-Ramirez et al. [26])	24	>3 months	follow up >3 months after COVID -19 diagnosis	NHLBI (Study Quality Assessment Tools)	random-effect model, I^2	0.38 (0.27-0.49)	0.32 (0.24-0.40)	0.16 (0.12-0.21)	0.13 (0.09-0.17)						
Michelen et al. [25]	32	>12 weeks	follow up >12 weeks after COVID -19 diagnosis	Risk of Bias Tool (Hoy et al, 2012)	random intercept logistic regression, I^2, subgroup analysis	0.31 (0.24-0.39)	0.25 (0.18-0.34)	0.06 (0.03-0.12)	0.08 (0.05-0.13)	0.15 (0.11-0.21)	0.14 (0.09-0.20)	0.18 (0.10-0.32)	0.05 (0.02-0.10)	0.08 (0.04-0.15)	0.26 (0.21-0.36)
Long et al. [24]	16	> 1 month > 2 months post-admission	hospitalized. > 1 month post-discharge or > 2 months post-admission	Newcastle-Ottawa scale	fixed-effect or random effect depending on I^2, sensitivity analysis	0.47 (0.36-0.59)	0.33 (0.22-0.43)	0.07 (0.01-0.13)	0.17 (0.11-0.22)	0.11 (0.08-0.14)	0.10 (0.06-0.13)	0.27 (0.21-0.32)	0.15 (0.03-0.26)		0.35 (0.21-0.48)

Numbers indicate pooled prevalence of specific symptoms (effect size, 95% confidence interval)

Table 3. Prevalence of symptoms by time from acute diseases

	Symptom	4-12 weeks[#] (range)	3-6 months[$] (meta-analysis, %, 95%CI)	6-12 months[§] (range)
General	Fever/feverish	1-51%	1,1 (0,2-4,7)	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/arthralgia	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	Dyspnea	2-64%	25 (17,9-34)	1,9-40,8%
	Exertional dyspnea			
	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%
Neuro-psychological	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)	1,5-43,3%
	PTSD	-	9,1 (3,7-21)	7%
Cardiovascular	Palpitations	2-11%	9,7 (6-15,3)	0,6-9%
Skin	Rash	8-15%	2,8 (1-8,2)	4%

Reference: [27]

$ Reference: [25]

§ Reference: [28,29,123–125]

Table 4. Prevalence of long COVID symptoms in studies investigating patients regardless of disease severity and in studies in hospitalized patients. [23,25,28,47,55,74,123,124,126–141].

	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/arthralgia	9-37,3%	5,9-28,6%	9,3%
	Myalgia	2-44,9%	37,4-47,8%	10,8%
Respiratory	Dyspnea	21,8-39%	5,5-59,7%	13,7%
	Exertional dyspnea	39-54,8%	14,6-57,1%	
	Cough	3,2-23,4%	2,5-35,1%	6%
	Sleep apnea	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%	-	-
Neuro-psychological	Confusion / 'brain fog'	3-63,3%	-	15,6%
	Depression	11-15,7%	-	-
	Sleep disorder	24-35,7%	-	-
	PTSD	-	5,8-10,4%	7%
Cardiovascular	Palpitations	3,9-40%	-	7,3%
Skin	Rash	3-35,7%	-	1,6%

Table 5. Studies addressing assessment of long COVID

A. Pulmonary

I. Pulmonary function tests

Systematic review identification	Timing of testing after COVID-19	Severity of acute COVID-19	FEV1 < 80% predicted	FVC < 80% predicted	FEV1/FVC < 0.7	DLCO < 80% predicted	TLC < 80%	AMSTAR quality assessment
Jennings 2021 [27]	>12w	Variable	11+-6%	11+-9%	7+-1%	32%+-11%	-	Low
Guo 2021 [142]	3-6m	Hospitalized	33% (23-44%)	10% (2-18%)		33% (23–44%)	-	Critically low
Guo 2021 [142]	>6m	Hospitalized	43% (22-65%)	13% (8-18%)	-	43% (22–65%)	-	Critically low
Long 2021 [24]	2-6m post admission (hospitalized patients)	Hospitalized	7% (5-9%)	12% (1-23%)	20% (15-26%)	47% (32-61%)	14% (9–18%)	Low
Sanchez-Ramirez 2021 [26]	3-6 months	Variable	-	Obstructive pattern abnormalities - 8% (6–9%)	-	Diffusion pattern abnormalities - 31% (24–38%)	Restrictive pattern abnormalities - 12% (8–17%)	Critically low

[1] Pooled Prevalence (SD)

[2] Pooled Prevalence (95% confidence interval [CI])

FEV1 – Forced expiratory volume; FVC - Forced vital capacity; DLCO - Carbon monoxide diffusing capacity; TLC - Total lung capacity;

AMSTAR - A MeaSurement Tool to Assess systematic Reviews

II. 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 2021 [27]	Mix*	>12w	Variable	28+-17%	24+-26%	7+-9%	11+-12%	-	3+-3%	Low
Sanchez-Ramirez 2021 [26]	CT	3-6m	Variable	59% (44–73%)	39% (26–52%)	31% (17–44%)	33% (13–52%)	26% (9–43%)	6% (2–11%) 89 <	Critically low
Other studies										**NCOS**
Huang 2021 Late follow up [29]	CT	12m	Hospitalized	65/118 (55%)	54/118 (46%)	-	4/118 (4%)	-	1/118 (0.8%)	7

D'Cruz 2021[53]; Mallia 2021; [52] van den Borst 2020 [51]	Chest x-ray	6-8 weeks	Severe and critical patients	Most patients (up to 87%) showed improvement to complete resolution of follow-up CXR, related to disease severity but no correlation to ongoing symptoms	5 4 5
Raman 2021 [63]	Chest MRI	2-3 months	Moderate-severe	60% detected abnormalities	6
Dennis 2021 [71]	Chest MRI	3-4 months	Low risk	11% detected abnormalities	6

* Computed tomography (CT), high-resolution CT (HRCT), chest radiography, and/or magnetic resonance imaging (MRI)

[1] Pooled Prevalence (SD)

[2] Pooled Prevalence (95% confidence interval [CI])

B. Others

	Who (severity of acute COVID-19	**When**	**Findings**	**References**	**NCOS**

Cardiac					
Echocardiogram	Mild-moderate	2-3 months	Evidence is variable. Different rates of abnormal findings (diastolic dysfunction, systolic dysfunction, elevated PAP with or without and 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, ejection fraction was normal in a cohort of 215 patients, but LVGLS was reduced in 29%.	Tudoran 2021 [65]; Lewek 2021 [64]; Hayama 2021[66]	4 5 5
		6 months	A study in healthcare workers found no difference between mild recovering patients and healthy controls.	Joy 2021 [72]	7 (case control)
	Severe	3-4 months	High rates of diastolic dysfunction (55%). Lower rates of pericardial disease, pulmonary arterial hypertension and reduced left ventricular ejection fraction	Sonnweber 2021 [67]	5
	Mixed patient population	Mixed follow up (23-104 days)	A systematic review reporting reduced left ventricular ejection fraction in 0 to 16%; left ventricular hypertrophy in 0% to 0.5%; diastolic dysfunction in 0%-55%; pulmonary hypertension in 0%-10%; and pericardial effusion in 0-6%.	Ramadan 2021 [40]	AMSTAR grade- low
Cardiac MRI	Asymptomatic-mild	Post-acute	It is common to find abnormal MRI myocardial findings in the post acute period. A study in athletes showed abnormalities in 5/26 (20%) in asymptomatic patients following mild disease. In severe cases, abnormalities may be found up to 70% of patients. No correlation was shown to ongoing symptoms.	Malek 2021 [68]; Pan 2021 [69]	3 6

	Severe in a third	2-3 months	Cardiac involvement in 78%, with ongoing myocardial inflammation in 60%	Puntmann 2020 [39]	7
	Moderate-severe	3-4 months	Findings suggestive of myocarditis (late gadolinium enhancement) in recovered patients were common, in 26-29% (13/50, 13/44)	Wang 2021 [70]; Raman 2021 [63]; Dennis 2021 [71]	6 6 6
	Mild	6 months	Study of healthcare workers at 6 months showing complete resolution of cardiac MRI findings in all patients	Joy 2021 [72]	7 (case control)
	Mixed patient population	Mixed follow up (14-180 days)	A systematic review reporting raised T1 in 0% to 73%; raisedT2 in 0% to 60%; late gadolinium enhancement (myocardial or pericardial) in 0% to 46% and up to 100%. In four studies reporting formal diagnoses myocarditis was reported in 0%-37%; myopericarditis 0%-11%; pericarditis 0%-3%; and myocardial infarction 0%-2%	Hassani 2021 [73]; Ramadan 2021 [40]	AMSTAR grade – critically low
Functional					
Functional (6MWT, STS, SPPB)	Hospitalized, mostly severe-critical disease	1-12 months	6MWT and SPPB were moderately-severely impaired in comparison to expected ranges for age and sex. The impairment is mostly dependent on disease severity, and patients post severe disease had lower SPO2 post test.	Truffaut 2021 [42]; Anastasio 2021 [75]; Bellan 2021 [74]; Guler 2021 [50]; Huang 2020 [47]; Shah 2021 [77] van	4 5 5 5 4 4 5

				den Borst 2020 [51]; Jalušić Glunčić 2021 [143]; Cortés-Telles 2021 [144]; Baranauskas 2021 [145]; Betschart 2021 [146]; Jacobson 2021 [147]; Aiello 2021 [148]; Schandl 2021 [149]; Aranda 2021 [150]; Liao 2021 [151]	5 7 7 6 5 6 6 6 6
	Hospitalized	Post-discharge	STS was severely impaired in patients post discharge, correlated to post-effort dyspnea and desaturation	Nunez Cortez 2021 [152]	4
Cardiopulmonary stress testing (CPET)	All degrees	2-4 months	Included individuals had relatively slightly lower than expected peak oxygen consumption [91.2% (19.4%)], a lower probability of achieving the anaerobic threshold and a higher probability of presenting symptoms during the CPET.	Barbagelata 2021 [153]	6 5

			Compared with healthy controls, the 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 dyspnea is suspected to be muscular.	Raman 2021 [63] Szekely 2021 [154] Rinaldo 2021 [155] Kersten 2021[156] Mohr 2021 [157]	6 5 5 5
	Severe	2-4 months	In patients recovering from COVID-19 pneumonia, physical deconditioning is the most common cause of impaired peak oxygen consumption [19/35 (54%) of the sample had peak oxygen consumption <80% of predicted].	Jahn 2021 [158]	5
	All degrees	6 months	Patients with dysautonomia demonstrated objective functional limitations with significantly reduced work rate and peak oxygen consumption.	Ladlow 2021 [159]	5

			Compared with asymptomatic recoverees, those with persistent dyspnea had lower peak oxygen consumption [88% (76-100%) of predicted].	Aparisi 2021 [160]	6
	All degrees	9 months	Physiological abnormalities on CPET were mild [peak oxygen consumption was 86% (69-100%) of predicted] and similar to matched historical controls with dyspnea without antecedent COVID-19. Most (59%) had a 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 2021 [161] Mancini 2021 [162]	6 5
Brain imaging					
PET CT	Any severity	3 months	An increased number of functional complaints was correlated with hypometabolism of the brainstem and cerebellum cluster	Guedj 2021[79]	5
Brain MRI	Moderate-severe	2-3 months	Higher rates vs control group of higher T2* signal on susceptibility-weighted imaging in the left and right thalamus; increased mean diffusivity in the left posterior thalamic radiation and left and right averaged sagittal stratum Compared to controls, volumetric and micro-structural abnormalities were detected mainly in the central olfactory cortices, partial white matter in the right hemisphere	Raman 2021 [63] Lu 2020 [163]	6 7

NCOS - Newcastle-Ottawa score; PFT – pulmonary function tests; DLCO – diffusing capacity for carbon monoxide; TLC – total lung capacity; FEV1 - forced expiratory volume; FVC - forced vital capacity; CXR – chest X-ray; ARDS – acute respiratory distress; MV – mechanical

ventilation; PAP - pulmonary artery pressure; LVGLS - left ventricular global longitudinal strain; 6MWT – 6-minute walk test; STS - sit-to-stand; SPPB – short physical performance battery; SPO2 - peripheral capillary oxygen saturation.

Table 6. Summary of studies addressing management of long-COVID / Post COVID-19 condition

Study	Study design	Participants and setting	Timing	Number included	Intervention	Comparison	Outcome	Results	Quality assessment
Rehabilitation									
Reina-Gutierrez 2021 [89]	SR and MA of RCTs	Patients with interstitial lung diseases including caused by coronaviruses. One trial post COVID discharge (see Liu 2020)	Any time	11 RCTs with 637 patients	Pulmonary rehabilitation	Most non-comparative	Lung function, exercise capacity, HRQoL and dyspnea	Significant improvement in all outcomes (See text for details)	AMSTAR grade - low
De sire 2021 and Ceravolo 2020 [91,92]	SR and MA	COVID-19 patients, both acute and post-acute phases	Any time	24 studies "post acute" phase, 10 studies "chronic" phase, including case reports and series	Rehabilitation	Most non-comparative (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 2020 [93]	RCT	Elderly (age≥65) recovering "with satisfying results" from COVID-19	Hospital discharge	72 (36 vs 36)	Respiratory rehabilitation (once daily 10 min for 6 weeks, including (1) respiratory	No intervention	1. PFT (FEV1, FVC, FEV1/FVC, DLCO%) 2. 6MWT 3. Quality of life score (SF36)	Significant improvement in all PFT; 6MWT; quality of life score (SF36);	Unclear risk of bias for concealment; low risk for generation; open

					muscle training; (2) cough exercise; (3) diaphragmatic training; (4) stretching exercise; and (5) home exercise		4. Anxiety score (SAS) 5. Activity of daily living (FIM) 6. Depression score (SDS)	and anxiety score SAS)	
Sinha 2020 [164]	Prospecti ve cohort	Acute COVID-19 at ICU	ICU admission until 1 month post 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	NCOS - 2
Hermann 2020 [165]	Prospecti ve cohort	post-discharge severe COVID-19 patients (most ICU), at inpatient rehabilitation clinic setting	≥ 10 days of COVID onset, with 2 days asymptoma tic	28	Cardiopulmonar y rehabilitation (2-4 weeks program)	None	Functional assessment by 6MWT) and Feeling Thermometer (FT)	Significant improvement in both 6MWT and FT	NCOS - 4
Udina 2021 [166]	Prospecti ve cohort	Post-acute COVID-19 care facility, most post-ICU	Post-discharge	33	Multi-component therapeutic exercise protocol	None	Physical performance including gait performance, exercise capacity (6MWT), ADL (Barthel index	Significant improvement in all measures	NCOS - 4
Piquet 2021 [167]	Retrospec tive cohort	Inpatients with acute COVID-19 in specialized rehabilitation unit	Mean 20.4+-10.0 days from COVID-19 onset	100	Inpatient specialized rehabilitation unit	None	Barthel Activities of Daily Living Index; sit-to-stand frequency; and grip strength	Significant improvement in all measures	NCOS - 4

Hameed 2021 [168]	Prospecti ve cohort	Discharged COVID-19 patients with persisting symptom	Outpatients following discharge	106	Three groups: 44p virtual rehabilitation program; 25p home physical therapy; 17p independent exercise program	20p - no intervention	Sit-to-stand scores and step test	Significant improvement in both test with virtual rehabilitation and home physical therapy	NCOS - 6
Curci 2021 [169]	Retrospec tive cohort	Post-ICU COVID-19 patients in an inpatient rehabilitation setting	Post-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	NCOS - 5
Al Chikhanie 2021 [170]	Prospecti ve cohort	Post-ICU COVID-19 in a dedicated rehabilitation center	Post-ICU	42	Pulmonary rehabilitation	Non-COVID-19 respiratory failure post-ICU	6MWT	Significant improvement in 6MWT between start and end of intervention in the COVID-19 group and between this group and control	NCOS - 6
Bowles 2021 [171]	Retrospec tive cohort	Discharged patients referred to home health care	Post-discharge	1409	Home health care	None	Symptoms and functional dependencies	Significant improvement in symptoms and function,	NCOS – 4

								as measured by frequency of pain, dyspnea, cognitive function, anxiety and functional status by ADL	
Pulmonary abnormalities									
Myall 2021 [99]	Prospecti ve cohort	Discharged patients with clinical, radiological and functional interstitial lung disease consistent with organising pneumonia	6 weeks post discharge	30	Corticosteroids (max dose 0.5 mg/kg prednisolone) for 3 weeks	None	Symptoms, lung function, radiological findings	Significant improvement in all measures	NCOS - 3
Goel 2021 [100]	Retrospec tive cohort	Abnormal chest CT and desaturation (at rest<90% or decline of>4% during 6MWT(	At least 4 weeks after acute COVID-19	24	Equivalent of prednisolone 0.25-0.5 mg/kg and tapering for 6-8 weeks	None	Symptoms, saturation, radiological findings	Significant improvement in all measures	NCOS - 2
Anosmia/dysgeusia									
Addison 2021 [109]	SR	Postinfectious olfactory dysfunction (non-COVID)	NS	2352	Any intervention (including olfactory training and	Any control	Improvement in olfaction	No meta-analysis performed; authors conclusions	AMSTAR grade – low

					various systemic and topical drugs)			supported olfactory training, and consider steroids (nasal or systemic), theophylline, and sodium citrate	
Abdelalim 2021 [110]	RCT	Recovering COVID-19 patients (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 weeks with olfactory training	Olfactory training alone	Number with recovered smell sense at 3w, change in smell score according to patient reported degree of anosmia/hyposmia (subjectively with a visual analog scale)	Number recovered 31 (62%) intervention 26 (52%) control, p=0.31	Unclear risk of bias for concealment and generation; open
Mohamad 2021 [111]	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 intra-nasal delivery	Placebo (insulin-free fast-dissolving film)	Smell sensation improvement at 4 weeks (using olfactory detection score)	Significantly higher olfactory detection scores with intervention (P=0.0163)	Unclear risk of bias for concealment and generation; double blind

MA – meta-analysis; SR – systematic review; RCT – randomized controlled trial; ICU: intensive care unit; PFT: pulmonary function test; FVC: forced vital capacity; FEV1: forced expiratory volume at 1 s; DLCO: diffusing lung capacity for carbon monoxide; 6MWT: 6-Minute Walk Test; FIM: Functional Independence Measure; POMA: performance-oriented mobility assessment; NCOS – Newcastle-Ottawa score; ADL: activity daily living; HRQoL – health-related quality of life