Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Guidelines

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 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 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 the assessment and management of individuals with persistent symptoms of COVID-19. **Dana Yelin, Clin Microbiol Infect 2022;▪:1**

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,

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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.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, 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 ($\geq$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,

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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 sequelae 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, autoimmunity, 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, 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, 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 $<0.8 \times 10^9$ 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

Table 1
Summary of definitions for long COVID/post-acute COVID according to level of certainty of COVID-19 diagnosis

Acute COVID-19 diagnosis[a]/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

[a] For asymptomatic patients: Confirmed acute COVID-19 diagnosis is considered a positive PCR test in a relevant epidemiological setting.

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

Meta-analysis	Included studies	Maximum follow-up duration (d)	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 d 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 wk 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 (0.08v0.24)	0.44 (0.13–0.78)	0.12 (0.03–0.23)	0.19 (0.07–0.34)
Iqbal et al. [23]	24	90	Symptoms <12 wk after COVID-19	Risk of Bias Tool [169]	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 (0.15v0.35)	0.20 (0.09–0.33)	
Iqbal et al. [23]	15	180	Symptoms >12 wk after COVID-19	Risk of Bias Tool [169]	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. [121]	35	210	Adults with symptoms >1 mo 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 patients hospitalized with COVID-19	NA	Random-effect model, I^2				0.18 (0.12–0.24)						
Sanchez-Ramirez et al. [26])	24	>3 months	Follow up > 3 mo 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 wk after COVID -19 diagnosis	Risk of Bias Tool [169]	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 after admission	Hospitalized >1 mo after discharge or >2 mo after admission	Newcastle–Ottawa scale	Fixed- 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% CI). NA, Not available; NHLBI, National Heart, Lung, and Blood Institute.

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, CPK-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

Table 3
Prevalence of symptoms by time from acute diseases

	Symptom	4–12 wk (%), range [27]	3–6 mo (meta-analysis), % (95% CI) [25]	6–12 mo (%), range [28,29,122–124]
General	Fever/feverish	1–51	1.1 (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/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	Dyspnoea	2–64	25 (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)	1.5–43.3
	Posttraumatic stress disorder	—	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

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]. This correlates with the finding that, on serial testing of patients with a restrictive pattern, tested individuals demonstrated an overall improvement at 6 months compared with 10 weeks, but not complete resolution [48,49]. 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

Table 4
Prevalence of long COVID symptoms in studies investigating patients regardless of disease severity and in studies in hospitalized patients [23,25,28,47,55,74,122–140]

	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	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	—	5.8–10.4	7
Cardiovascular	Palpitations	3.9–40	—	7.3
Skin	Rash	3–35.7	—	1.6

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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	FEV[a] <80% predicted	FVC <80% predicted	FEV[b]/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; FEV; forced expiratory volume; FVC, forced vital capacity; TLC, total lung capacity.
[a] Pooled prevalence (standard deviation).
[b] Pooled prevalence (95% CI).

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[a]	>12 wk	Variable	28% ± 17%	24% ± 26%	7% ± 9%	11% ± 12%	—	3% ± 3%	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%)	6% (2%–11%) 89<	Critically low
Other studies										**Newcastle–Ottawa score**
Huang et al., 2021 (Late follow up) [29]	CT	12 mo	Hospitalized	65/118 (55%)	54/118 (46%)	—	4/118 (4%)	—	1/118 (0.8%)	7
D'Cruz et al., 2021 [53]	Chest x-ray	6–8 wk	Severe and critical patients	Most patients (up to 87%) showed improvement to complete resolution of follow-up chest x-ray related to disease severity, but no correlation to ongoing symptoms						5
Mallia et al., 2021 [52]										4
van den Borst et al., 2020 [51]										5
Raman et al., 2021 [63]	Chest MRI	2–3 mo	Moderate to severe	60% detected abnormalities						6
Dennis et al., 2021 [71]	Chest MRI	3–4 mo	Low risk	11% detected abnormalities						6

AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CT, computed tomography; MRI, magnetic resonance imaging.
[a] CT, high-resolution CT, chest radiography, and/or MRI.

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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] Lewek et al., 2021 [64] Hayama et al., 2021 [66]	4 5 5
		6 mo	A study in health care workers found no difference between mild recovering patients and healthy controls.	Joy et al., 2021 [72]	7 (case control)
	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	Mixed follow-up (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] Pan et al., 2021 [69]	3 6
	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] Raman et al., 2021 [63] Dennis et al., 2021 [71]	6 6 6
	Mild	6 mo	Study of health care workers at 6 mo showing complete resolution of cardiac MRI findings in all patients	Joy et al., 2021 [72]	7 (case control)
	Mixed patient population	Mixed follow up (14–180 d)	Systematic review reporting increased T1 in 0%–73%; increased T2 in 0%–60%; late gadolinium enhancement (myocardial or pericardial) 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%.	Hassani et al., 2021 [73] Ramadan et al., 2021 [40]	AMSTAR grade: Critically low
Functional					
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] Anastasio et al., 2021 [75] Bellan et al., 2021 [74] Guler et al., 2021 [50] Huang et al., 2020 [47] Shah et al., 2021 [77] van den Borst et al., 2020 [51] Jalušić Glunčić et al., 2021 [142] Cortés-Telles et al., 2021 [143] Baranauskas et al., 2021 [144] Betschart et al., 2021 [145] Jacobson et al., 2021 [146] Aiello et al., 2021 [147] Schandl et al., 2021 [148] Aranda et al., 2021 [149] Liao et al., 2021 [150]	4 5 5 5 4 4 5 5 7 7 6 5 6 6 6 6
	Hospitalized	After discharge	STS was severely impaired in patients after discharge, correlated with post-effort dyspnoea and desaturation	Nunez Cortez et al., 2021 [151]	4

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Table 7 (*continued*)

	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
	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	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

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.

Table 8
Summary of studies addressing management of long-COVID/postCOVID-19 condition

Study	Study design	Participants and setting	Timing	Number included	Intervention	Comparison	Outcome	Results	Quality assessment
Rehabilitation									
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	NCOS: 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	NCOS: 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	NCOS: 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	NCOS; 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	NCOS: 6
Curci 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	NCOS: 5
Al Chikhanie et al., 2021 [93]	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	NCOS: 6

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Table 8 (*continued*)

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
Pulmonary abnormalities									
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
Anosmia/dysgeusia									
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/ hyposmia (subjectively with visual analogue scale)	Number recovered: 31 (62%) intervention, 26 (52%) 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 reticular opacities/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 *at el.*, and demonstrated resolution of findings 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-

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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 interventional/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 hyperintensities 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, health care 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

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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.

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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 penetrance 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 evolvement 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.

References

[1] Peghin M, Palese A, Venturini M, De Martino M, Gerussi V, Graziano E, et al. Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. Clin Microbiol Infect 2021;27:1507–13.

[2] Office for National Statistics. Updated estimates of the prevalence of long COVID symptoms. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/

healthandsocialcare/healthandlifeexpectancies/adhocs/12788updatedestimatesoftheprevalenceoflongcovidsymptoms. [Accessed 9 February 2022].
[3] Worldometers. Coronavirus cases. Available at: https://www.worldometers.info/coronavirus/.
[4] Burke MJ, del Rio C. Long COVID has exposed medicine's blind-spot. Lancet Infect Dis 2021;21:1062–4.
[5] Sivan M, Taylor S. NICE guideline on long COVID. BMJ 2020;371:m4938.
[6] Sisó-Almirall A, Brito-Zerón P, Conangla Ferrín L, Kostov B, Moragas Moreno A, Mestres J, et al. Long COVID-19: proposed primary care clinical guidelines for diagnosis and disease management. Int J Environ Res Public Health 2021;18:4350.
[7] Autorité de Santé Haute. Fiches réponses rapides dans le cadre du COVID-19 de la HAS–Symptômes prolongés suite à une COVID-19 de l'adulte–Diagnostic et prise en charge. Available at: https://www.has-sante.fr/jcms/p_3237041/fr/symptomes-prolonges-suite-a-une-covid-19-de-l-adulte-diagnostic-et-prise-en-charge.
[8] WHO. Living guidance for clinical management of COVID-19. Geneva, Switzerland: WHO; 2021.
[9] Guidelines International Network. Resources. Available at: https://g-i-n.net/get-involved/resources/.
[10] McMaster University. COVID-END: COVID-19 evidence network to support decision-making. Available at: https://globalhealthoffice.mcmaster.ca/covid-end-evidence-network-to-support-decision-making/.
[11] Coronavirus Cochrane. (COVID-19): special collections. Available at: https://www.cochrane.org/coronavirus-covid-19-resources/special-collections.
[12] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[13] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[14] Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.
[15] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 18 July 2020].
[16] Kavanagh BP. The GRADE system for rating clinical guidelines. PLoS Med 2009;6:e1000094.
[17] Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. WHO clinical case definition working group on post-COVID-19 condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2021;S1473–3099. 00703–9.
[18] Centers for Disease Control and Prevention. COVID-19 and your health. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. [Accessed 4 February 2022].
[19] National Institutes of Health. NIH launches new initiative to study "Long COVID". Available at: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid. [Accessed 4 February 2022].
[20] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep 2021;11:16144.
[21] Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Chron Respir Dis 2021;18. 14799731211002240.
[22] Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med 2021;9:533–44.
[23] Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: a systematic review and meta-analysis. EClinicalMedicine 2021;36:100899.
[24] Long Q, Li J, Hu X, Bai Y, Zheng Y, Gao Z. Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: a systematic review and meta-analysis. Front Med (Lausanne) 2021;8:702635.
[25] Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. BMJ Glob Health 2021;6:e005427.
[26] Sanchez-Ramirez DC, Normand K, Zhaoyun Y, Torres-Castro R. Long-term impact of COVID-19: a systematic review of the literature and meta-analysis. Biomedicines 2021;9:900.
[27] Jennings G, Monaghan A, Xue F, Mockler D, Romero-Ortuño R. A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: ongoing symptomatic phase vs. post-COVID-19 syndrome. J Clin Med 2021;10:5913.
[28] Boscolo-Rizzo P, Guida F, Polesel J, Marcuzzo AV, Capriotti V, D'Alessandro A, et al. Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). Int Forum Allergy Rhinol 2021;11:1685–8.
[29] Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021;398:747–58.
[30] Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond) 2021:1–18.
[31] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27:601–15.
[32] Xie Y, Bowe B, Al-Aly Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. Nat Commun 2021;12:6571.
[33] Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long COVID in adults discharged from UK hospitals after Covid-19: a prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Eur 2021;8:100186.
[34] Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect 2021;S1198–743X. 00629–7.
[35] Akter F, Mannan A, Mehedi HMH, Rob MA, Ahmed S, Salauddin A, et al. Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with and without diabetes in Bangladesh. Diabetes Metab Syndr 2020;14:2031–8.
[36] Estiri H, Strasser ZH, Brat GA, Semenov YR. Consortium for Characterization of COVID-19 by EHR (4CE), Patel CJ et al. Evolving phenotypes of non-hospitalized patients that indicate long COVID. BMC Med 2021;19:249.
[37] Mohiuddin Chowdhury ATM, Karim MR, Ali MA, Islam J, Li Y, He S. Clinical characteristics and the long-term post-recovery manifestations of the COVID-19 patients–A prospective multicenter cross-sectional study. Front Med (Lausanne) 2021;8:663670.
[38] Townsend L, Fogarty H, Dyer A, Martin-Loeches I, Bannan C, Nadarajan P, et al. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. J Thromb Haemost 2021;19:1064–70.
[39] Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1265–73.
[40] Ramadan MS, Bertolino L, Zampino R. Durante-mangoni E, monaldi hospital cardiovascular infection study group. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect 2021;27:1250–61.
[41] Trimboli P, Cappelli C, Croce L, Scappaticcio L, Chiovato L, Rotondi M. COVID-19-associated subacute thyroiditis: evidence-based data from a systematic review. Front Endocrinol (Lausanne) 2021;12:707726.
[42] Truffaut L, Demey L, Bruyneel AV, Roman A, Alard S, De Vos N, et al. Post-discharge critical COVID-19 lung function related to severity of radiologic lung involvement at admission. Respir Res 2021;22:29.
[43] Wu Q, Zhong L, Li H, Guo J, Li Y, Hou X, et al. A follow-up study of lung function and chest computed tomography at 6 months after discharge in patients with coronavirus disease 2019. Can Respir J 2021;2021:6692409.
[44] Qin W, Chen S, Zhang Y, Dong F, Zhang Z, Hu B, et al. Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up. Eur Respir J 2021;58:2003677.
[45] So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. BMC Pulm Med 2021;21:97.
[46] George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 2020;8:807–15.
[47] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:220–32.
[48] Smet J, Stylemans D, Hanon S, Ilsen B, Verbanck S, Vanderhelst E. Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection. Respir Med 2021;176:106276.
[49] Stylemans D, Smet J, Hanon S, Schuermans D, Ilsen B, Vandemeulebroucke J, et al. Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: real-life data from a Belgian University Hospital. Respir Med 2021;182:106421.
[50] Guler SA, Ebner L, Aubry-Beigelman C, Bridevaux P-O, Brutsche M, Clarenbach C, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J 2021;57:2003690.
[51] van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, et al. Comprehensive health assessment three months after recovery from acute COVID-19. Clin Infect Dis 2020. ciaa1750.
[52] Mallia P, Meghji J, Wong B, Kumar K, Pilkington V, Chhabra S, et al. Symptomatic, biochemical and radiographic recovery in patients with COVID-19. BMJ Open Respir Res 2021:8.
[53] D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, et al. Chest radiography is a poor predictor of respiratory symptoms and functional

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impairment in survivors of severe COVID-19 pneumonia. ERJ Open Res 2021;7.
[54] Alarcón-Rodríguez J, Fernández-Velilla M, Ureña-Vacas A, Martín-Pinacho JJ, Rigual-Bobillo JA, Jaureguízar-Oriol A, et al. Radiological management and follow-up of post-COVID-19 patients. Radiologia (Engl Ed) 2021;63:258–69.
[55] Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax 2021;76:399–401.
[56] Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging 2017;27:342–9.
[57] Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005;60:401–9.
[58] Froidure A, Mahsouli A, Liistro G, De Greef J, Belkhir L, Gérard L, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med 2021;181:106383.
[59] Balbi M, Conti C, Imeri G, Caroli A, Surace A, Corsi A, et al. Post-discharge chest CT findings and pulmonary function tests in severe COVID-19 patients. Eur J Radiol 2021;138:109676.
[60] González J, Benítez ID, Carmona P, Santisteve S, Monge A, Moncusí-Moix A, et al. Pulmonary function and radiologic features in survivors of critical COVID-19: a 3-month prospective cohort. Chest 2021;160:187–98.
[61] Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res 2020;21:163.
[62] Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month follow-up chest CT findings after severe COVID-19 pneumonia. Radiology 2021;299:E177–86.
[63] Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 2021;31:100683.
[64] Lewek J, Jatczak-Pawlik I, Maciejewski M, Jankowski P, Banach M. COVID-19 and cardiovascular complications–Preliminary results of the LATE-COVID study. Arch Med Sci 2021;17:818–22.
[65] Tudoran C, Tudoran M, Pop GN, Giurgi-Oncu C, Cut TG, Lazureanu VE, et al. Associations between the severity of the post-acute COVID-19 syndrome and echocardiographic abnormalities in previously healthy outpatients following infection with SARS-CoV-2. Biology (Basel) 2021;10.
[66] Hayama H, Ide S, Moroi M, Kitami Y, Bekki N, Kubota S, et al. Elevated high-sensitivity troponin is associated with subclinical cardiac dysfunction in patients recovered from coronavirus disease 2019. Glob Health Med 2021;3:95–101.
[67] Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J 2021;57.
[68] Małek ŁA, Marczak M, Miłosz-Wieczorek B, Konopka M, Braksator W, Drygas W, et al. Cardiac involvement in consecutive elite athletes recovered from Covid-19: a magnetic resonance study. J Magn Reson Imaging 2021;53:1723–9.
[69] Pan C, Zhang Z, Luo L, Wu W, Jia T, Lu L, et al. Cardiac T1 and T2 mapping showed myocardial involvement in recovered COVID-19 patients initially considered devoid of cardiac damage. J Magn Reson Imaging 2021;54:421–8.
[70] Wang H, Li R, Zhou Z, Jiang H, Yan Z, Tao X, et al. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2021;23:14.
[71] Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open 2021;11:e048391.
[72] Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, et al. Prospective case-control study of cardiovascular abnormalities 6 months following mild COVID-19 in healthcare workers. JACC Cardiovasc Imaging 2021;14:2155–66.
[73] Hassani NS, Talakoob H, Karim H, Bazargany MHM, Rastad H. Cardiac magnetic resonance imaging findings in 2954 COVID-19 adult survivors: a comprehensive systematic review. J Magn Reson Imaging 2022;55:866–80.
[74] Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, et al. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. JAMA Netw Open 2021;4:e2036142.
[75] Anastasio F, Barbuto S, Scarnecchia E, Cosma P, Fugagnoli A, Rossi G, et al. Medium-term impact of COVID-19 on pulmonary function, functional capacity and quality of life. Eur Respir J 2021;58:2004015.
[76] Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J 2021;57:2003448.
[77] Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax 2021;76:402–4.
[78] Dun Y, Liu C, Ripley-Gonzalez JW, Liu P, Zhou N, Gong X, et al. Six-month outcomes and effect of pulmonary rehabilitation among patients hospitalized with COVID-19: a retrospective cohort study. Ann Med 2021;53:2099–109.
[79] Guedj E, Campion JY, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, et al. 18F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging 2021;48. 2823–3.
[80] Rudroff T, Workman CD, Ponto LLB. 18F-FDG-PET imaging for post-COVID-19 brain and skeletal muscle alterations. Viruses 2021;13:2283.
[81] Bonazza F, Borghi L, di San Marco EC, Piscopo K, Bai F, d'Arminio MA, et al. Psychological outcomes after hospitalization for COVID-19: data from a multidisciplinary follow-up screening program for recovered patients. Res Psychother 2020;23:491.
[82] Dong F, Liu H, Dai N, Yang M, Liu J. A living systematic review of the psychological problems in people suffering from COVID-19. J Affect Disord 2021;292:172–88.
[83] Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021;8:416–27.
[84] British Thoracic Society. BTS guidance on venous thromboembolic disease in patients with COVID-19. Available at: https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-guidance-on-venous-thromboembolic-disease-in-patients-with-covid-19/.
[85] National Institutes of Health. Antithrombotic therapy in patients with COVID-19. Available at: https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_10.pdf.
[86] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2950–73.
[87] American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions. Available at: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation.
[88] Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet 2022;399:50–9.
[89] Reina-Gutiérrez S, Torres-Costoso A, Martínez-Vizcaíno V, de Arenas-Arroyo SN, Fernández-Rodríguez R, Pozuelo-Carrascosa DP. Effectiveness of pulmonary rehabilitation in interstitial lung disease including coronavirus diseases: a systematic review and meta-analysis. Arch Phys Med Rehabil 2021;102. 1989–97.e3.
[90] Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. Complement Ther Clin Pract 2020;39:101166.
[91] Ceravolo MG, Arienti C, de Sire A, Andrenelli E, Negrini F, Lazzarini SG, et al. Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Eur J Phys Rehabil Med 2020;56:642–51.
[92] de Sire A, Andrenelli E, Negrini F, Patrini M, Lazzarini SG, Ceravolo MG, et al. Rehabilitation and COVID-19: a rapid living systematic review by Cochrane Rehabilitation Field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020. Eur J Phys Rehabil Med 2021;57:181–8.
[93] Al Chikhanie Y, Veale D, Schoeffler M, Pépin JL, Verges S, Hérengt F. Effectiveness of pulmonary rehabilitation in COVID-19 respiratory failure patients post-ICU. Respir Physiol Neurobiol 2021;287:103639.
[94] Hameed F, Palatulan E, Jaywant A, Said R, Lau C, Sood V, et al. Outcomes of a COVID-19 recovery program for patients hospitalized with SARS-CoV-2 infection in New York City: a prospective cohort study. PM R 2021;13:609–17.
[95] British Society of Rehabilitation Medicine. Rehabilitation in the wake of COVID-19–A phoenix from the ashes. Available at: https://www.bsrm.org.uk/downloads/covid-19bsrmissue1-published-27-4-2020.pdf.
[96] National Institute for Health and Care Excellence. Overview: rehabilitation after critical illness in adults. Available at: https://www.nice.org.uk/guidance/cg83. [Accessed 1 June 2021].
[97] Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 2020;54:949–59.
[98] Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Ann Am Thorac Soc 2021;18:799–806.
[99] Goel N, Goyal N, Nagaraja R, Kumar R. Systemic corticosteroids for management of "long-COVID": an evaluation after 3 months of treatment. Monaldi Arch Chest Dis 2021 [Epub ahead of print].
[100] Denneny EK, Garthwaite HS, Heightman MJ, Porter JC. A role for steroids in COVID-19-associated pneumonitis at six-week follow-up? Ann Am Thorac Soc 2021;18:1082–3.
[101] LaFond E, Weidman K, Lief L. Care of the postcoronavirus disease 2019 patient. Curr Opin Pulm Med 2021;27:199–204.
[102] Udwadia ZF, Koul PA, Richeldi L. Post-COVID lung fibrosis: the tsunami that will follow the earthquake. Lung India 2021;38:S41–7.
[103] Momen ABI, Khan F, Saber S, Sultana A, Alam RF, Raihan SG, et al. Usefulness of pirfenidone in COVID lung: a case series. Eur J Med Health Sci 2021;3:24–6.
[104] Dhooria S. A study of the efficacy and safety of pirfenidone vs. nintedanib in the treatment of fibrotic lung disease after coronavirus disease-19 pneumonia. Available at: https://clinicaltrials.gov/ct2/show/NCT04856111.

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[105] Molina M. Phase-II randomized clinical trial to evaluate the effect of pirfenidone compared to placebo in post-COVID-19 pulmonary fibrosis. Available at: https://clinicaltrials.gov/ct2/show/NCT04607928.
[106] Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung fibrosis after COVID-19: treatment prospects. Pharmaceuticals (Basel) 2021;14:807.
[107] O'Byrne L, Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ. Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. Cochrane Database Syst Rev 2021;7:CD013876.
[108] Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. J Allergy Clin Immunol 2021;147:1704–19.
[109] Abdelalim AA, Mohamady AA, Elsayed RA, Elawady MA, Ghallab AF. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: a randomized controlled trial. Am J Otolaryngol 2021;42:102884.
[110] Mohamad SA, Badawi AM, Mansour HF. Insulin fast-dissolving film for intranasal delivery via olfactory region, a promising approach for the treatment of anosmia in COVID-19 patients: design, in-vitro characterization and clinical evaluation. Int J Pharm 2021;601:120600.
[111] Wong TL, Weitzer DJ. Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)–A systemic review and comparison of clinical presentation and symptomatology. Medicina (Kaunas) 2021;57.
[112] Smith MEB, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162:841–50.
[113] Fowler-Davis S, Platts K, Thelwell M, Woodward A, Harrop D. A mixed-methods systematic review of post-viral fatigue interventions: are there lessons for long COVID? PLoS One 2021;16:e0259533.
[114] National Institute of Health and Care Excellence. NICE draft guidance addresses the continuing debate about the best approach to the diagnosis and management of ME/CFS. Available at: https://www.nice.org.uk/news/article/nice-draft-guidance-addresses-the-continuing-debate-about-the-best-approach-to-the-diagnosis-and-management-of-me-cfs. [Accessed 10 July 2021].
[115] Theoharides TC, Cholevas C, Polyzoidis K, Politis A. Long-COVID syndrome-associated brain fog and chemofog: luteolin to the rescue. Biofactors 2021;47:232–41.
[116] Sarkar I, Sen G, Bhattacharya M, Bhattacharyya S, Sen A. Insilico inquest reveals the efficacy of cannabis in the treatment of post-COVID-19 related neurodegeneration. J Biomol Struct Dyn 2021:1–10.
[117] Magoon R, Bansal N, Singh A, Kashav R. Methylene blue: subduing the post-COVID-19 blues. Med Hypotheses 2021;150:110574.
[118] Nobile B, Durand M, Olié E, Guillaume S, Molès JP, Haffen E, et al. The anti-inflammatory effect of the tricyclic antidepressant clomipramine and its high penetration in the brain might be useful to prevent the psychiatric consequences of SARS-CoV-2 infection. Front Pharmacol 2021;12:615695.
[119] Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. Nat Med 2021;27:1129–30.
[120] Amin-Chowdhury Z, Harris RJ, Aiano F, Zavala M, Bertran M, Borrow R, et al. Characterising long COVID more than 6 months after acute infection in adults; prospective longitudinal cohort study. England 2021. 2021.03.18.21253633.
[121] Hoshijima H, Mihara T, Seki H, Hyuga S, Kuratani N, Shiga T. Incidence of long-term post-acute sequelae of SARS-CoV-2 infection related to pain and other symptoms: a living systematic review and meta-analysis. MedRxiv 2021. 2021.04.08.21255109.
[122] Einvik G, Dammen T, Ghanima W, Heir T, Stavem K. Prevalence and risk factors for post-traumatic stress in hospitalized and non-hospitalized COVID-19 patients. Int J Environ Res Public Health 2021;18:2079.
[123] Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. JAMA 2021;325:2015–6.
[124] Zhou F, Tao M, Shang L, Liu Y, Pan G, Jin Y, et al. Assessment of sequelae of COVID-19 nearly 1 year after diagnosis. Front Med (Lausanne) 2021;8:717194.
[125] Carfì A, Bernabei R, Landi F. Gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324:603–5.
[126] Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: a longitudinal prospective study nested to a population cohort. Eur J Neurol 2021;28:3245–53.
[127] Gaber TAZK, Ashish A, Unsworth A. Persistent post-covid symptoms in healthcare workers. Occup Med (Lond) 2021;71:144–6.
[128] Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J, et al. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. Eur Neuropsychopharmacol 2021;46:39–48.
[129] Nersesjan V, Amiri M, Lebech AM, Roed C, Mens H, Russell L, et al. Central and peripheral nervous system complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up. J Neurol 2021;268:3086–104.
[130] Petersen MS, Kristiansen MF, Hanusson KD, Danielsen ME, Á Steig B, Gaini S, et al. Long COVID in the Faroe Islands–A longitudinal study among non-hospitalized patients. Clin Infect Dis 2020:ciaa1792.
[131] Rass V, Beer R, Schiefecker AJ, Kofler M, Lindner A, Mahlknecht P, et al. Neurological outcome and quality of life 3 months after COVID-19: a prospective observational cohort study. Eur J Neurol 2021;28:3348–59.
[132] Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. J Neurovirol 2021;27:154–9.
[133] Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. Int J Environ Res Public Health 2021;18:2030.
[134] Suárez-Robles M, Iguaran-Bermúdez MDR, García-Klepizg JL, Lorenzo-Villalba N, Méndez-Bailón M. Ninety days post-hospitalization evaluation of residual COVID-19 symptoms through a phone call check list. Pan Afr Med J 2020;37:289.
[135] Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: what is long COVID and how should we manage it? Lung 2021;199:113–9.
[136] Taboada M, Moreno E, Cariñena A, Rey T, Pita-Romero R, Leal S, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. Br J Anaesth 2021;126:e110–3.
[137] Tarsitani L, Vassalini P, Koukopoulos A, Borrazzo C, Alessi F, Di Nicolantonio C, et al. Post-traumatic stress disorder among COVID-19 survivors at 3-month follow-up after hospital discharge. J Gen Intern Med 2021;36:1702–7.
[138] Venturelli S, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. Epidemiol Infect 2021;149:e32.
[139] Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 2020;25:100463.
[140] Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics of long COVID: findings from a social media survey. MedRxiv 2021. 2021.03.21.21253968.
[141] Guo T, Jiang F, Liu Y, Zhao Y, Li Y, Wang Y. Respiratory outcomes in patients following COVID-19-related hospitalization: a meta-analysis. Front Mol Biosci 2021;8:750558.
[142] Jalušić Glunčić T, Muršić D, Basara L, Vranić L, Moćan A, Janković Makek M, et al. Overview of symptoms of ongoing symptomatic and post-COVID-19 patients who were referred to pulmonary rehabilitation–First single-centre experience in Croatia. Psychiatr Danub 2021;33:565–71.
[143] Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, Pou-Aguilar YN, Wong AW, Milne KM, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. Respir Physiol Neurobiol 2021;288:103644.
[144] Baranauskas MN, Carter SJ. Evidence for impaired chronotropic responses to and recovery from 6-minute walk test in women with post-acute COVID-19 syndrome. Exp Physiol 2021. https://doi.org/10.1113/EP089965.
[145] Betschart M, Rezek S, Unger I, Ott N, Beyer S, Böni A, et al. One year follow-up of physical performance and quality of life in patients surviving COVID-19: a prospective cohort study. Swiss Med Wkly 2021;151:w30072.
[146] Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients with uncomplicated coronavirus disease 2019 (COVID-19) have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic. Clin Infect Dis 2021;73:e826–9.
[147] Aiello M, Marchi L, Calzetta L, Speroni S, Frizzelli A, Ghirardini M, et al. Coronavirus disease 2019: COSeSco–A risk assessment score to predict the risk of pulmonary sequelae in COVID-19 patients. Respiration 2021:1–9.
[148] Schandl A, Hedman A, Lyngå P, Fathi Tachinabad S, Svefors J, Roël M, et al. Long-term consequences in critically ill COVID-19 patients: a prospective cohort study. Acta Anaesthesiol Scand 2021;65:1285–92.
[149] Aranda J, Oriol I, Martín M, Feria L, Vázquez N, Rhyman N, et al. Long-term impact of COVID-19 associated acute respiratory distress syndrome. J Infect 2021;83:581–8.
[150] Liao T, Meng D, Xiong L, Wu S, Yang L, Wang S, et al. Long-term effects of COVID-19 on health care workers 1-year post-discharge in Wuhan. Infect Dis Ther 2022;11:145–63.
[151] Núñez-Cortés R, Rivera-Lillo G, Arias-Campoverde M, Soto-García D, García-Palomera R, Torres-Castro R. Use of sit-to-stand test to assess the physical capacity and exertional desaturation in patients post COVID-19. Chron Respir Dis 2021;18. 1479973121999205.
[152] Barbagelata L, Masson W, Iglesias D, Lillo E, Migone JF, Orazi ML, et al. Cardiopulmonary exercise testing in patients with post-COVID-19 syndrome. Med Clin (Barc) 2021;S0025–7753. 00462–0.
[153] Szekely Y, Lichter Y, Sadon S, Lupu L, Taieb P, Banai A, et al. Cardiorespiratory abnormalities in patients recovering from coronavirus disease 2019. J Am Soc Echocardiogr 2021;34:1273–84. e9.
[154] Rinaldo RF, Mondoni M, Parazzini EM, Baccelli A, Pitari F, Brambilla E, et al. Severity does not impact on exercise capacity in COVID-19 survivors. Respir Med 2021;187:106577.

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[155] Kersten J, Baumhardt M, Hartveg P, Hoyo L, Hüll E, Imhof A, et al. Long COVID: distinction between organ damage and deconditioning. J Clin Med 2021;10:3782.
[156] Mohr A, Dannerbeck L, Lange TJ, Pfeifer M, Blaas S, Salzberger B, et al. Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. Multidiscip Respir Med 2021;16:732.
[157] Jahn K, Sava M, Sommer G, Schumann DM, Bassetti S, Siegemund M, et al. Exercise capacity impairment after COVID-19 pneumonia is mainly caused by deconditioning. Eur Respir J 2022;59:2101136.
[158] Ladlow P, O'Sullivan O, Houston A, Barker-Davies R, May S, Mills D, et al. Dysautonomia following COVID-19 is not associated with subjective limitations or symptoms but is associated with objective functional limitations. Heart Rhythm 2021;S1547−5271. 02430−9.
[159] Á Aparisi, Ybarra-Falcón C, García-Gómez M, Tobar J, Iglesias-Echeverría C, Jaurrieta-Largo S, et al. Exercise ventilatory inefficiency in post-COVID-19 syndrome: insights from a prospective evaluation. J Clin Med 2021;10:2591.
[160] Alba GA, Ziehr DR, Rouvina JN, Hariri LP, Knipe RS, Medoff BD, et al. Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea. EClinicalMedicine 2021;39:101066.
[161] Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of cardiopulmonary stress testing for patients with unexplained dyspnea post-coronavirus disease. JACC Heart Fail 2021;9:927−37.
[162] Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, et al. Cerebral micro-structural changes in COVID-19 patients−An MRI-based 3-month follow-up study. EClinicalMedicine 2020;25:100484.
[163] Sinha RK, Sinha S, Varadharajulu G. Effectiveness of structured exercise protocol on functional performance in subjects with COVID-19. Int J Res Pharmaceut Sci 2020. 1244−9.
[164] Hermann M, Pekacka-Egli AM, Witassek F, Baumgaertner R, Schoendorf S, Spielmanns M. Feasibility and efficacy of cardiopulmonary rehabilitation after COVID-19. Am J Phys Med Rehabil 2020;99:865−9.
[165] Udina C, Ars J, Morandi A, Vilaró J, Cáceres C, Inzitari M. Rehabilitation in adult post-COVID-19 patients in post-acute care with therapeutic exercise. J Frailty Aging 2021;10:297−300.
[166] Piquet V, Luczak C, Seiler F, Monaury J, Martini A, Ward AB, et al. Do patients with COVID-19 benefit from rehabilitation? Functional outcomes of the first 100 patients in a COVID-19 rehabilitation unit. Arch Phys Med Rehabil 2021;102:1067−74.
[167] Curci C, Negrini F, Ferrillo M, Bergonzi R, Bonacci E, Camozzi DM, et al. Functional outcome after inpatient rehabilitation in post-intensive care unit COVID-19 patients: findings and clinical implications from a real-practice retrospective study. Eur J Phys Rehabil Med 2021;57:443−50.
[168] Bowles KH, McDonald M, Barrón Y, Kennedy E, O'Connor M, Mikkelsen M. Surviving COVID-19 after hospital discharge: symptom, functional, and adverse outcomes of home health recipients. Ann Intern Med 2021;174:316−25.
[169] Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934−9.

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