National Institute for Health and Care Excellence

COVID-19 rapid guideline: managing the long-term effects of COVID-19

[C] Evidence reviews for investigations

NICE guideline NG188

December 2020

Guideline version (Final)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188)

Review question 4: investigations

December 2020

Literature search

NICE's information services team identified relevant evidence through focused evidence searches between 22 and 28 October 2020 (see appendix 3). Additional studies were also considered from NICE surveillance up to 28 October 2020. The studies identified in the searches and through NICE surveillance were subsequently assessed for inclusion (see appendix 3 for further details). Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the protocol (see appendix 2). Four reviewers screened titles and abstracts. Having identified the evidence, four reviewers assessed the full text references of potentially relevant evidence to determine whether they met the inclusion criteria for this evidence review. All uncertainties were discussed amongst the reviewers and referred to an adviser if needed. See appendix 4 for the study flow chart of included studies.

Healthcare Improvement Scotland knowledge management team also conducted a search to identify qualitative evidence to support the questions in this review. See Management of the long-term effects of COVID-19: the views and experience of patients, their families and carers for more information. This review will be referred to in this document as 'patient lived experience'.

Methods and process

This evidence review was developed using the methods and processes described the methods chapter.

Review question 4

What investigations should be carried out to determine appropriate management or treatment of symptoms?

The review protocol is shown in appendix 2.

Included studies

In total 4104 references were identified through the searches. Of these 505 were included and ordered for full text assessment. A total of 58 references were included for the whole guideline, 18 of which were included for this review. Of these 12 were cohort studies and 1 was a cross-sectional study. There was also 1 case study, 1 narrative review and consensus recommendations included for this review due to the indirectness of the cohort studies identified.

See table 1 for more details on the identified studies.

Table 1 Included studies for review question 4: Follow-up after acute COVID-19

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
Aliae 2020	Egypt, Cross sectional, 15th July to 13th August 2020	Patients who have had COVID-19 (positive or indeterminate COVID-19 PCR test or presumed presence of COVID-19 based on clinical & radiological criteria). (n=444)	Post-COVID-19 Functional Status Scale (PCFS) scale	35.31±18.75 days	Most of the COVID-19 recovered cases have diverse degrees of functional restrictions ranging from negligible to severe based on PCFS.
Arnold 2020	UK, Prospective cohort, 30 March to 3 June 2020.	Patients hospitalised with COVID-19 (Positive PCR result for SARS-CoV-2 or a clinico-radiological diagnosis of COVID-19 disease) (n=110); No control group	At 8 to 12 week follow up: Face to face review with a respiratory or infectious disease clinician Chest radiograph Spirometry Exercise testing (sit to stand) Routine bloods Routine observations	28 days after admission (remotely to review hospital/ GP notes)	Patients with COVID-19 remain highly symptomatic at 8 to 12 weeks, however, clinical abnormalities requiring action are infrequent, especially in those without a supplementary oxygen requirement during their acute illness. This has significant implications for physicians assessing patients with persistent symptoms, suggesting that a more holistic approach focussing on rehabilitation and general wellbeing is paramount

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
			HRQoL questionnaires Health status questionnaire		
D'Cruz 2020	UK, Cohort study (prospective), June to July 2020	COVID-19 survivors who had been hospitalised with PCR-confirmed severe COVID-19 pneumonia(n=119); No control group	Chest radiography Symptom questionnaires Mental health screening Physiological testing Computed tomography and pulmonary angiography (CTPA)	Median (IQR) times between hospital admission and discharge to follow-up assessment were 76 (71 to 83) days and 61 (51 to 67) days, respectively (4 to 12 weeks grouping)	Persistent symptoms, adverse mental health outcomes and physiological impairment are common 2 months after severe COVID-19 pneumonia. Follow-up chest radiograph is a poor marker of recovery, therefore holistic face-to-face assessment is recommended to facilitate early recognition and management of post-COVID sequelae
Daher 2020	Germany, Cohort (retrospective), February to May 2020	Patients with COVID-19 who were discharged from the isolation ward and followed up 6 weeks after discharge (n=33) No control group All 33 patients had a severe disease during their hospital stay	Pulmonary function tests (PFTs) Electrocardiography Transthoracic echocardiography Whole-body plethysmography Blood tests	Time from discharge to follow up 56 (48 to 71) days	Hospitalized patients with severe COVID-19, who did not require mechanical ventilation, are unlikely to develop pulmonary long-term impairments, thromboembolic complications or cardiac impairments after discharge but frequently suffer from symptoms of fatigue.

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
			Heath-related quality of life 6-min walk test		
Dennis 2020	UK, Prospective cohort (ongoing), April to August 2020	Patients with previous SARS-CoV-2 infection and low risk for COVID-19 severity and mortality (n=201) No control group	Symptom assessment Multi-organ MRI Blood investigations for inflammatory markers	Around 3 to 5 months	In a young, low-risk population with ongoing symptoms, almost 70% of individuals have impairment in one or more organs four months after initial symptoms of SARS-CoV-2 infection.
Frija- Masson 2020	France, Letter to editor (retrospective cohort), 4 March 2020 and 1 April 2020	Patients under the age of 85 years with confirmed SARS-CoV-2 infection (n=50) No control group	All tests included spirometry, functional residual capacity (FRC), total lung capacity (TLC) and DLCO (single breath real-time CO/NH4) measurements	1 month since symptom onset	1 month after SARS-CoV-2 infection, a majority of patients have mild alterations of lung function
Huang 2020a	China, Retrospective cohort, study date not reported (March 2020?)	Consecutive patients who were initially referred for cardiac CMR examination due to cardiac symptoms (n=26) Healthy controls of a similar age and gender who previously underwent the same CMR examinations were selected from	Cardiac magnetic resonance (CMR)	Duration between cardiac symptoms onset to CMR examination mean 47 days (range 36-58 days)	Cardiac involvement was found in a proportion (58%) of patients recovered from COVID-19. CMR manifestation included myocardial oedema, fibrosis, and impaired right ventricle function.

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
		a database of healthy subjects without cardiovascular disease or systemic inflammation (n=11)			
Huang 2020b	China, Cohort (retrospective), study date not reported	Hospitalised COVID-19 patients that had been released from hospital over a period of 1 month (n=57) No control group	Pulmonary function testing Lung imaging (high resolution spiral CT) 6-min walk test	At least 30 days	Impaired diffusing-capacity, lower respiratory muscle strength, and lung imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline.
Raman 2020	UK, Prospective cohort, 14 March to 25 May 2020	Patients hospitalised with moderate to severe laboratory-confirmed (SARS-CoV-2 polymerase chain reaction positive) COVID-19 (n=58) Uninfected controls group-matched for age, sex, body mass index (BMI) and risk factors (smoking, diabetes, and hypertension) from the community (during the same	Multiorgan magnetic resonance imaging (MRI) of the brain, lungs, heart, liver, kidneys 6-min walk test Cardiopulmonary exercise test (CPET) Spirometry Questionnaires Blood tests	Patients were assessed between 2 and 3 months from disease-onset at median interval of 2 to 3 months (IQR 2·06 to 2·53)	Persistent lung and extra-pulmonary organ MRI findings are common. In COVID-19 survivors, chronic inflammation may underlie multiorgan abnormalities and contribute to impaired quality of life

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
		period) were prospectively enrolled in this study (n=30)			
Savarraj 2020	USA, Prospective cohort, May 2020 to July 2020	Hospitalised COVID-19 patients (n=48) No control group	Telephone questionnaires to assess functional, cognitive, and psychiatric symptoms. Functional outcome was evaluated using the modified Rankin Score (mRS). Cognitive status was evaluated using the brief neurocognitive screening test (BNST). Depression symptoms were evaluated using the Patient Health Questionnaire (PHQ-9). Anxiety symptoms were assessed using the Generalized Anxiety Disorder (GAD-7). Pain, fatigue, and sleepiness were evaluated using the Pain, Enjoyment of life and General activity (PEG), the Fatigue Severity Scale (FSS)	3 months 4 to 12 weeks grouping	71% had continued neurologic symptoms The most common symptom was fatigue (42%) followed by PTSD symptoms (29%)

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
			and Epworth Sleepiness Scale (ESS). Post-traumatic stress disorder was evaluated using the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5).		
Sonnweber 2020	Austria, Cohort (prospective), study date not reported	Patients who previously suffered from mild to critical COVID-19 (n=109) No control group	Medical history assessment Structured COVID-19 symptom questionnaire Performance evaluation (e.g. 6-min walking test) Blood sampling and analysis Computed tomography	Approximately 2 months	COVID19 is associated with prolonged alterations of iron homeostasis which may be linked to severe initial disease but also persisting radiological pathologies in the lung and impaired physical performance.
Podlasin 2020	Poland, Case study, study date not reported	A 27-year-old, otherwise healthy man with no health risks, was admitted to infectious disease ward with a week history of weakness, fever, and sore throat.	X-ray RT-PCR Blood investigations	Follow up hospitalisation on day 35	There were no radiological changes on chest X-ray, negative SASR-CoV-2 RT-PCR from nasopharyngeal swab. However, the level of IL-6 and alanine aminotransferase activity were increased. The patient reported improving tolerance for physical activity, but he was unable to perform his previous activities with the same strength, e.g. singing

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
		The patient was discharged from the hospital on day 21 after confirming significant improvement in his CT scan and two negative SARS-CoV-2 RT-PCR from nasopharyngeal swabs			
Valiente-De Santis 2020	Spain, Prospective cohort, 14 March to 15 April	Patients with previous acute SARS-CoV-2 infection contacted by telephone (n=108) No control group	Blood test Chest radiograph Chest CT Spirometry Serological test	12 weeks after acute phase	The persistence of symptoms in patents with COVID is usually 12 weeks after the 27 acute episode, especially in patients <65 years and health-care workers.
Zhao 2020	China, Cohort (retrospective), Jan 20, 2020 to Feb 24, 2020	Patients previously hospitalised COVID-19 survivors (n=55) No control group	Chest CT scan Pulmonary function test SARS-COV-2 IgG test	Up to 3 months	Radiological and physiological abnormalities were still found in a considerable proportion of COVID-19 survivors without critical cases 3 months after discharge. Higher level of D-dimer on admission could effectively predict impaired carbon monoxide diffusion capacity after 3 months discharge.
Eiros 2020	Spain, Cross sectional observational	Health-care workers with confirmed past SARS-CoV-2	Complete medical history	Approximately 10 weeks after infection onset	Pericarditis and myocarditis with clinical stability are frequent long after SARS-CoV-

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
	cohort, 25 May 2020 to 12 June 2020	infection (103 diagnosed by RT-PCR between March 13 and April 25 and 36 by serology April 10 and May 22) (n=139)	Physical examination Questionnaire ECG Blood investigations CMR		2 infection, even in presently asymptomatic subjects.
Mazza 2020	Italy, Cross sectional, April 6 to June 9, 2020	Patients surviving COVID-19 who had previously been hospitalised (n=402)	Psychiatric assessments Inflammatory biomarkers	4 weeks	COVID-19 survivors presented a high prevalence of emergent psychiatric sequelae, with 55% of the sample presenting a pathological score for at least one disorder. Higher than average incidence of PTSD, major depression, and anxiety, all high-burden non-communicable conditions associated with years of life lived with disability, is expected in survivors.
Greenhalgh 2020a	International/primary care, Narrative review, and expert opinion, 11/8/20	Expert opinion for management of people who have a delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.	Medical and self-management Blood investigations For patients who have had a significant respiratory illness: community follow-up	Post-acute COVID-19 defined as extending beyond three weeks from the onset of first symptoms and chronic COVID-19 as extending beyond 12 weeks.	Recommended clinical assessment should include: • Full history from date of fist symptoms • Nature and severity of current symptoms • Examination Recommended investigations should include:

Study	Country, study design, dates	Population (n)	Investigations	Mean follow-up time since COVID-19	Main results
			with a chest x ray at 12 weeks. For those with evidence of lung damage (such as persistent abnormal chest x ray and oximeter readings), referral to a respiratory service is recommended		• Blood tests for specific clinical indications • Anaemia should be excluded for the breathless patient • Follow up CXR at 12 weeks for patients who were not admitted to ICU but had significant respiratory illness

Key results

Out of the 18 studies identified,17 did not strictly meet all of the PICO criteria. This was because the people included were not specifically enrolled into the studies for persistent and ongoing symptoms. These studies followed up people approximately 1 to 3 months following acute COVID-19. During this follow up, several investigations and assessments were carried out. These fell into the following categories: screening or assessment with questionnaires, physical tests, imaging or laboratory investigations. Only 4 of the 18 studies included only people who had not been hospitalised.

Questionnaires and screening tools

Four of the studies used tools for mental health screening for people who had been hospitalised. These tools included GAD7, PHQ9, PTSD-5 and trauma screening and cognitive impairment assessments. All four studies reported adverse mental health outcomes based on these assessments. One study, Raman 2020, reported a significantly higher PHQ-9 scores 2 to 3 months after COVID-19 compared to controls who had not had COVID-19 ($p=0.009$).

There were also four studies that performed a level of functional assessment during follow up. Only 1 (Aliae 2020) of the 4 studies included people who had not been hospitalised. These included assessments such as the SF-36 questionnaire, Epworth Sleepiness Scale, Fatigue Severity Scale, the Modified Rankin score and the pain, enjoyment of life and general activity scale. Two studies used a new Post-COVID-19 functional status assessment (PCFS). Raman 2020, one of the few studies to include a control group, found that functional status (including physical functioning, role limitations due to physical or emotional health, energy and social functioning) was significantly worse in people 2-3 months after acute COVID-19 compared to those who did not have COVID-19 (all p values <0.05). Aliae 2020 found that most people approximately 35 days since acute COVID-19 had a range of functional restrictions ranging from negligible to severe on PCFS.

D'Cruz 2020 was the only study to report on how to go about conducting assessments. They concluded that assessment should ideally be a face to face, holistic approach with a focus on rehabilitation and general wellbeing.

Physical tests, imaging or laboratory investigations

Respiratory tests were commonly used in the studies. These included pulmonary function tests such as spirometry and assessment using the Medical Research Council (MRC) Breathlessness Scale. Most studies found that people were still experiencing significant breathlessness at follow-up after acute COVID-19. Raman 2020 found that people who had been hospitalised for COVID-19 reported breathlessness (MRC dyspnoea score ≥2) 2-3 months after acute COVID-19 36/53 (64%) compared to 3/29 (10.3%) who had not had COVID-19 ($p<0.0001$).

Exercise tests were performed in many of the studies. The most common investigation was the 6-minute walk test. Other tests included the sit to stand test and the 4-metre gait speed test. Studies reported limitations in exercise such as limited distance walked and desaturation in people followed up after acute COVID-19.

Many studies used imaging when following up people after acute COVID-19. These were mostly chest X-ray, CT and MRI. D'Cruz 2020 reported that only 15/119 (13%) of people had evidence of COVID-related lung disease at 4-6 weeks after hospital discharge. However, they concluded that a chest X-ray is a poor marker of recovery, as people were showing abnormalities in other investigations, regardless of chest X-ray results. Dennis 2020 found that multi-organ MRI showed 70% of a population at low-risk of COVID-19 complications with ongoing symptoms had impairment of 1 or more organs at 4 months after initial symptoms. Huang 2020a found that cardiac MRI in 15/26 (58%) people experiencing cardiac symptoms around 47 days after onset of symptoms had abnormal findings. These manifestations included myocardial oedema, fibrosis and impaired right ventricle function.

Blood investigations carried out in the studies included routine tests, inflammatory markers and markers for iron deficiency and anaemia. Dennis 2020 found that triglycerides ($p=0.002$), cholesterol ($p=0.021$), LDL-cholesterol ($p=0.005$) and transferrin saturation ($p=0.005$) were more likely to be abnormal in hospitalised ($n=164$) versus non-hospitalised individuals ($n=37$). Sonnweber 2020 reported that COVID-19 is associated with prolonged alterations of iron homeostasis, which may be linked to severity initial disease.

Strengths and limitations

This evidence is considered as very low quality for a variety of reasons. The primary aims of the studies were not to investigate ongoing symptoms in people, so can be considered as indirect evidence for this review. Most of the sample sizes were very small and usually recruited people following hospital discharge, which may limit the generalisability of the evidence. The majority of the data in the studies was collected around 4-6 weeks after acute COVID-19 so is limited to short-term follow-up only.

Expert panel discussion

This section describes how the expert panel considered the evidence in relation to the recommendations within the guidance.

Relative value of different outcomes

The expert panel would have expected to see outcomes of investigations carried out to rule out other diagnoses or confirm post-COVID-19 syndrome or dual diagnoses. As the evidence was indirect for this question, the panel were unable to draw conclusions from this evidence. However, they were able to identify the most commonly used tests in the literature during follow-up from acute COVID-19 and determine where abnormalities were often seen in these cohorts of people.

Quality of the evidence

The overall certainty in the evidence was very low. The study designs were limited to mainly cohort studies. Whilst this was expected in terms of SARS-CoV-2 being a novel virus, it means that the data is limited and unlikely to lead to any firm conclusions at this point in time. The aims of the studies did not directly answer the question on which investigations to carry out in people with ongoing symptoms. The panel were also particularly concerned with the generalisability of the evidence. They acknowledged that most of the participants recruited were previously hospitalised with acute COVID-19 and some of the results of the investigations carried out would be reflective of this. The panel also considered that the type of investigations carried out in the literature were more likely to be carried out in secondary care settings.

In addition to this, the panel considered that comorbidities and history of related illness were important in understanding the outcomes of investigations but these

were not consistently reported across the studies. The panel highlighted that the quantitative evidence often excluded children and older people and were unable to extrapolate the evidence for these groups of people.

Trade-off between benefits and harms

The panel were minded that when carrying out investigations for ongoing symptoms following acute COVID-19, it was important that other potential diagnoses are not ignored whilst trying to determine if the symptoms are due to post-COVID-19 syndrome. The panel suggested that it would be useful to carry out blood tests that are commonly carried out to rule out or confirm other conditions. They also considered that people might not associate their symptoms with COVID-19, particularly if another event, for example, a stroke, has happened since. The panel were also aware that people might not always present in a typical way, which may particularly be the case with older adults and children. For these reasons, the panel agreed with the conclusions from D'Cruz 2020 that a holistic and preferably face to face assessment is very important from both a clinical and patient perspective. If a clinician can see the patient, then they may identify concerns that the patient may not be aware of themself and may not have reported in a telephone consultation for example.

Blood tests, chest X-rays and exercise tolerance tests, e.g. sit-to-stand test were the most commonly reported tests in the evidence. The panel considered that these tests would be useful for most people as investigations and to obtain baseline measures. The panel however agreed that clinical judgment would be needed for exercise tolerance tests because it could be harmful to some people (for example, people with chest pain or severe fatigue). The evidence showed that chest X-ray may be a poor marker of improvement so the panel suggested it should only be used to inform a holistic assessment on further care needs.

Implementation and resource considerations

The panel were concerned that some of the investigations reported in the literature were unlikely to be readily available everywhere. For example, spirometry currently has a long waiting list in the UK, due to it being an aerosol-generating procedure and therefore fewer tests are being carried out. Many of the tests in the literature are

generally not carried out in primary care so the panel agreed it is important to consider the setting, availability and resources needed to carry out investigations. The panel had concerns about further over-loading both primary and secondary care clinicians. The evidence suggests that a face-to-face consultation is preferable, but this is currently difficult in the pandemic setting.

Other considerations

The panel agreed that it would be difficult to do a full examination and fully comprehensive history for a patient, especially considering the time constraints. However, they concluded that a full examination, including clinical history was very important. The panel emphasised the need to focus the examination on both what was appropriate to the patient and their symptoms and what matters most to the patient. The panel also highlighted that in their experience there are people who have had mild symptoms of COVID-19 and not realised, then later develop new symptoms. This also supports the need for taking a full history.

The panel did not think a specific battery of tests should be carried out in patients presenting with ongoing symptoms as this might include tests that will not affect how the patient is managed as well as being time and resource intensive. In addition, the evidence reviewed did not provide conclusive information on a battery of tests that should be conducted for this population. Instead, the panel considered that investigations should be focused on what a patient presents with, covering any 'red flags' that require urgent referral, as well as picking up on any 'pink flags' which would be less critical, but cumulatively would be causing significant problems for the patient. These tests should include assessment of cognitive, psychological, and psychiatric symptoms, as well as any physical assessments. As the panel were unable to recommend specific screening tools to be used in these assessments, they suggested research recommendations to determine which tools are the most useful. These research recommendations are outlined in the guideline.

The panel were aware from their experience that postural symptoms are common in people with ongoing symptoms of COVID-19 and therefore should be investigated.

The panel experience was consistent with the patient lived experience evidence. Patient data and consensus asserted that people feel more reassured when

investigations are carried out. However, the panel were also mindful that some investigations could be anxiety-inducing. For example, some panel members reported that some patients are being asked to record pulse-oximetry readings at home. These readings can fluctuate and therefore cause a patient to worry unnecessarily.

The patient lived experience evidence indicated that having someone in a supportive role who could co-ordinate and guide investigations would be beneficial. The panel concluded that whilst such investigations are important, clinicians should ensure that people have clear instructions and know who to contact for support if needed.

Appendix 1 Methods used to develop the guidance

Please refer to methods document for details of the methods used to develop the guidance.

Appendix 2 Review protocols

RQ 4: What investigations should be carried out to determine appropriate management or treatment of symptoms?

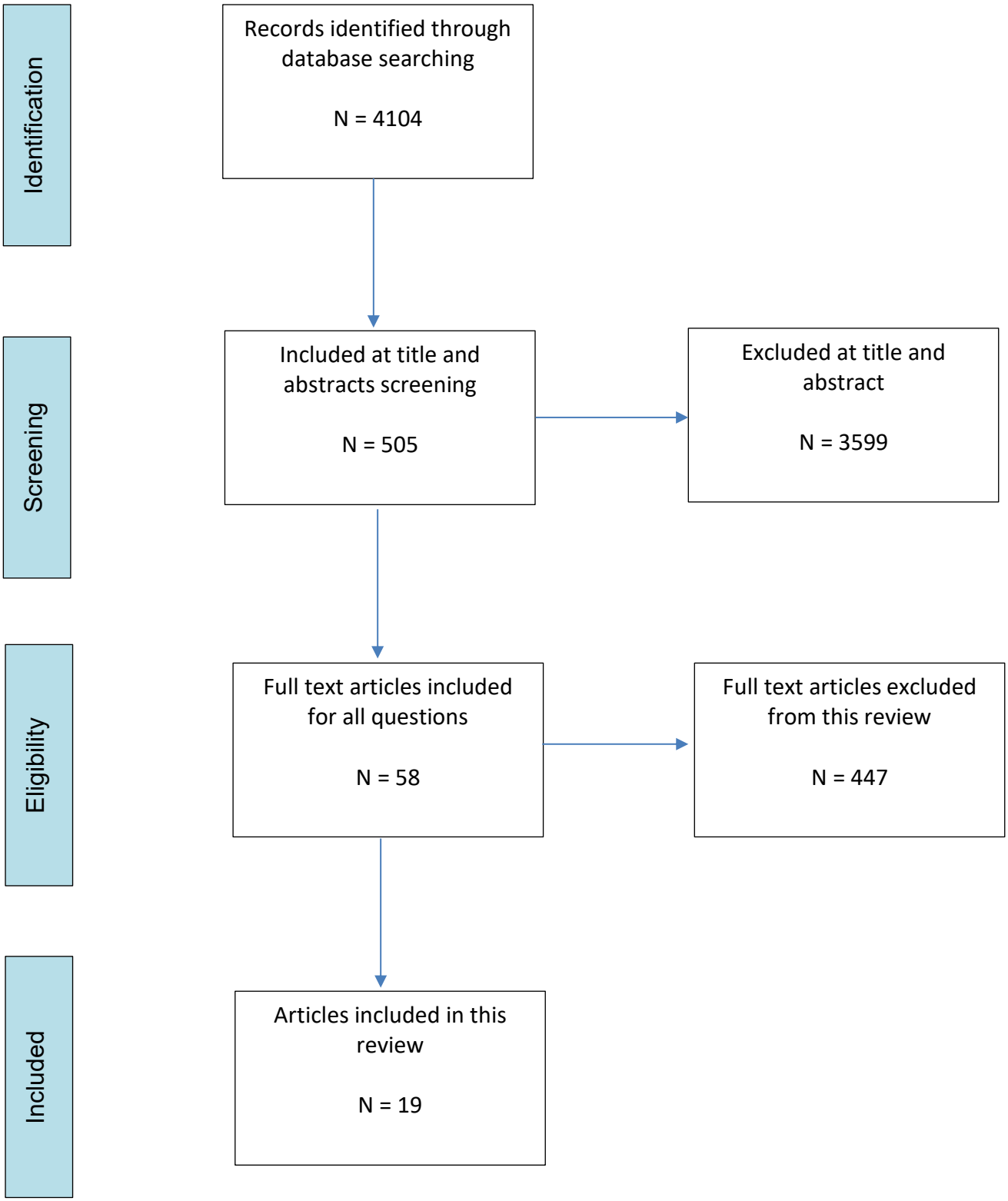
Criteria	Notes
Population	Adults and children who are experiencing new or ongoing symptoms or clusters of symptoms (physical and mental health): • 4 to 12 weeks from onset of acute COVID-19 • 12 weeks from onset of acute COVID-19
Diagnostics tests or assessments	Diagnostic tests or assessments appropriate for the presenting symptoms and the care setting that can be used to: • Rule out or confirm other diagnoses • Understand end organ damage effects
Comparators	Any or no comparator
Outcomes	• Post COVID-19 syndrome (as defined by the study) • Other diagnoses • Dual diagnoses and other multimorbidities (e.g. post-COVID-19 syndrome plus another condition)
Settings	Any
Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity • Diagnosis of COVID-19 (e.g. confirmed or high clinical suspicion) • Duration of symptoms • Care setting
Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. • Cohort studies • Case series • Cross sectional studies
Countries	Any
Timepoints	Any
Other exclusions	None

Appendix 3 Literature search strategy

Database strategies

Please refer to the search history record for full details of the search.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Aliae, Mohamed-Hussein, Islam, Galal, Mahmoud, Saad et al. (2020) Post-COVID-19 Functional Status: Relation to age, smoking, hospitalization and comorbidities. medRxiv

Arnold, David T., Hamilton, Fergus W., Milne, Alice et al. (2020) Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. medRxiv: 2020081220173526

D'Cruz, Rebecca F., Waller, Michael D., Perrin, Felicity et al. (2020) Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Research

Daher, Ayham, Balfanz, Paul, Cornelissen, Christian et al. (2020) Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. Respiratory Medicine: 106197 to 106197

Dennis, Andrea, Wamil, Malgorzata, Kapur, Sandeep et al. (2020) Multi-organ impairment in low-risk individuals with long COVID. medRxiv: 2020101420212555

Eiros, Rocio, Perez Manuel, Barreiro-Perez, Garcia Ana, Martin-Garcia et al. Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers. medrxiv preprint

Frija-Masson, Justine, Debray, Marie-Pierre, Gilbert, Marie et al. (2020) Functional characteristics of patients with SARS-CoV-2 pneumonia at 30â€…days post-infection. Eur. respir. j 56(2)

Greenhalgh, T; Ladds, E; Knight, M ‘Long Covid’: evidence, recommendations and priority research.

Hacettepe, University (2020) Investigation of Validity and Reliability of Post-COVID-19 Functional Status Scale. clinicaltrials.gov

Huang, Lu, Zhao, Peijun, Tang, Dazhong et al. (2020) Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC. Cardiovascular imaging

Huang, Yiying, Tan, Cuiyan, Wu, Jian et al. (2020) Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respiratory research 21(1): 163

Mazza, Mario Gennaro, De Lorenzo, Rebecca, Conte, Caterina et al. (2020) Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain, behavior, and immunity 89: 594 to 600

Podlasin, Regina B, Kowalska, Justyna D, Pihowicz, Andrzej et al. (2020) How to follow-up a patient who received tocilizumab in severe COVID-19: a case report. European journal of medical research 25(1): 37

Raman, Mp, Cassar, Em, Tunnicliffe et al. (2020) Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge.

Savarraj, Jude PJ, Burkett, Angela B., Hinds, Sarah N. et al. (2020) Three-month outcomes in hospitalized COVID-19 patients. medRxiv: 2020101620211029

Savastano, Alfonso, Crincoli, Emanuele, Savastano, Maria Cristina et al. (2020) Peripapillary Retinal Vascular Involvement in Early Post-COVID-19 Patients. Journal of clinical medicine 9(9)

Sonnweber, T., Boehm, A., Sahanic, S. et al. (2020) Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. Respiratory Research 21(1): 276

Zhao, Yu-Miao, Shang, Yao-Min, Song, Wen-Bin et al. (2020) Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 25: 100463

Appendix 6 Evidence tables

Aliae 2020

<table>
<tr><td>Bibliographic reference/s</td><td>Aliae, Mohamed-Hussein, Islam, Galal, Mahmoud, Saad et al. (2020) Post-COVID-19 Functional Status: Relation to age, smoking, hospitalization and comorbidities. medRxiv</td></tr>
<tr><td>Questions relevant to?</td><td>Investigations, risk factors, monitoring</td></tr>
<tr><td>Publication status</td><td>Preprint</td></tr>
<tr><td>Study type</td><td>Prospective cohort</td></tr>
<tr><td>Quality</td><td>Low quality evidence
CASP critical appraisal checklist: High risk of bias</td></tr>
<tr><td>Objective</td><td>Assess the Post COVID-19 functional status in Egypt by the PCFS scale and to evaluate if age, gender, comorbidities have any effect on functional limitations</td></tr>
<tr><td>Study date</td><td>15 July to 13 August 2020</td></tr>
<tr><td>COVID-19 prevalence (high/low) if reported</td><td>Not reported</td></tr>
<tr><td>Country/ Setting</td><td>Egypt</td></tr>
<tr><td>Population (including n)</td><td>444 who have had COVID-19 They were interviewed in our follow-up clinics or by calls</td></tr>
<tr><td>Time since acute COVID-19 illness</td><td>35.31±18.75 days
4 to 12 weeks grouping</td></tr>
<tr><td>Investigations</td><td>Post-COVID-19 Functional Status Scale (PCFS) scale</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>N=444</td></tr>
<tr><td>Mean age</td><td>33.09±12.09 years</td></tr>
<tr><td>Male</td><td>192 (43.2%)</td></tr>
<tr><td>Female</td><td>252 (56.8%)</td></tr>
<tr><td>Reside in urban areas</td><td>316 (71.2%)</td></tr>
<tr><td>Reside in rural areas</td><td>125 (28.2%)</td></tr>
<tr><td>Non-smoker</td><td>346 (77.9%)</td></tr>
<tr><td>Smoker</td><td>58 (13.1%)</td></tr>
<tr><td>Former smoker</td><td>40 (9%)</td></tr>
<tr><td>Admitted to hospital</td><td>336 (75.7%)</td></tr>
<tr><td>Comorbidity</td><td>111 (25.5%)</td></tr>
</table>
</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>• Confirmed COVID-19 in the registry of Ministry of Health and Population in Egypt (positive or indeterminate COVID-19 PCR test or presumed presence of Covid-19 based on clinical & radiological criteria).</td></tr>
<tr><td>Follow up</td><td>Around 5 weeks</td></tr>
</table>

Main results

Post COVID-19 Functional status scale	N=444
No limitation (Grade 0)	89 (20%)
Negligible limitation (grade 1)	280 (63.1%)
Slight limitation (Grade 2)	64 (14.4%)
Moderate limitation (Grade 3)	9 (2%)
Severe (Grade 4)	2 (0.5%)

Association between Demographic and Clinical characteristics and POST COVID19 Functional Status Scale (PCFS)

Variable	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	P value
Age	30.06±10.28	33.11±11.73	36.62±14.12	37.33±18.35	32.50±6.36	**0.003**
Male	50 (26%)	120 (62.5%)	19 (9.9%)	2 (1.0%)	1 (0.5%)	**0.014**
Female	39 (15.5%)	160 (63.5%)	45 (17.9%)	7 (2.8%)	1 (0.4%)	
Residence: Urban	59 (18.7%)	212 (67.1%)	38 (12%)	6 (1.9%)	1 (0.3%)	0.069
Residence: Rural	30 (23.4%)	68 (53.1%)	26 (20.3%)	3 (2.3%)	1 (0.8%)	
Duration since symptoms onset in days	38.87±17.69	34.52±19.01	33.67±17.79	38.89±26.00	25.00±14.14	**<0.001**
Quarantine: Hospital	17 (14.9%)	76 (66.7%)	17 (14.9%)	3 (2.6%)	1 (0.9%)	0.516
Quarantine: Home	72 (21.8%)	204 (61.8%)	47 (14.2%)	6 (1.8%)	1 (0.3%)	
O_2 supplementation: Yes	0 (0%)	70 (76.1%)	19 (20.7%)	2 (2.2%)	1 (1.1%)	**<0.001**
O_2 supplementation: No	89 (25.3%)	210 (59.7%)	45 (12.8%)	7 (2%)	1 (0.3%)	
ICU admission: Yes	2 (3.3%)	42 (70%)	14 (23.3%)	1 (1.7%)	1 (1.7%)	**0.003**
ICU admission: No	87 (22.7%)	238 (62%)	50 (13%)	8 (2.1%)	1 (0.3%)	
Comorbidity: Yes	0 (0%)	36 (32.4%)	64 (57.7%)	9 (8.1%)	2 (1.8%)	**<0.001**
Comorbidity: No	89 (26.7%)	244 (73.3%)	0 (0%)	0 (0%)	0 (0%)	

Most of the COVID-19 recovered cases have diverse degrees of functional restrictions ranging from negligible to severe based on PCFS. These restrictions were affected by age, gender, periodic influenza vaccination, smoking, duration since symptoms onset, need for oxygen or ICU admittance, and lastly the presence of coexisting comorbidity.

	It is recommended that Post COVID-19 monitoring programs should be implemented in specific clinical settings or as an out-patients program to follow the functional status of patients in 1, 3, 6 months visits to support the complete care for cases recovered from COVID-19. Furthermore, extended monitoring using simple scales as PCFS is necessary to determine whether these functional deficits after COVID-19 recovery persist or not.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	Limitations: • Lack of data of functional status before COVID-19 • history of the symptoms both at the onset of COVID-19 and after recovery is not included • pharmacologic therapy given to the patients was not mentioned • random selection bias may be present • inability for personal face-to- face interview in some cases
Additional references	Clinicaltrial.gov: NCT04479293

Arnold 2020

Bibliographic reference/s	**Arnold, David T., Hamilton, Fergus W., Milne, Alice et al. (2020) Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. medRxiv: 2020081220173526**
Questions relevant to?	**Investigations, risk factors, prevalance**
Publication status	Preprint
Study type	Prospective cohort
Quality	Low quality evidence CASP critical appraisal checklist: High risk of bias
Objective	To assess the prevalence of complications from COVID-19 within a UK cohort of hospitalised patients with COVID-19 to inform appropriate follow up in secondary or primary care.
Study date	30 March to 3 June 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	UK
Population (including n)	110 patients hospitalised with COVID-19
	8 to 12 weeks 4 to 12 weeks grouping
Investigations	At 8 to 12 week follow up: Face to face review with a respiratory or infectious disease clinician Chest radiograph Spirometry Exercise testing (sit to stand) Routine bloods

<table>
<tr><td></td><td>Routine observations
HRQoL questionnaires
Health status questionnaire</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Characteristic</td><td colspan="3">Severity of COVID-19 illness</td></tr>
<tr><td></td><td>Mild (n = 27)</td><td>Moderate (n = 65)</td><td>Severe (n =18)</td></tr>
<tr><td>Age (years)</td><td>47 (32,61)</td><td>57 (48, 67)</td><td>62 (54, 71)</td></tr>
<tr><td>BAME</td><td>5 (19%)</td><td>15 (23%)</td><td>3 (19%)</td></tr>
<tr><td>Male</td><td>13 (48%)</td><td>15 (23%)</td><td>3 (19%)</td></tr>
<tr><td>BMI (mean)</td><td>31.2</td><td>32.5</td><td>32.5</td></tr>
<tr><td>T1DM</td><td>1 (3.7%)</td><td>1 (1.5%)</td><td>1 (5.6%)</td></tr>
<tr><td>T2DM</td><td>2 (7.4%)</td><td>12 (18%)</td><td>2 (11%)</td></tr>
<tr><td>Heart Disease</td><td>6 (22%)</td><td>11 (17%)</td><td>3 (17%)</td></tr>
<tr><td>Chronic lung disease</td><td>4 (15%)</td><td>16 (25%)</td><td>8 (44%)</td></tr>
<tr><td>Severe liver disease</td><td>0 (0%)</td><td>1 (1.5%)</td><td>0 (0%)</td></tr>
<tr><td>Severe kidney disease</td><td>1 (3.7%)</td><td>4 (6.2%)</td><td>2 (11%)</td></tr>
<tr><td>Hypertension</td><td>4 (15%)</td><td>16 (25%)</td><td>7 (39%)</td></tr>
<tr><td>HIV</td><td>0 (0%)</td><td>0 (0%)</td><td>1 (5.6%)</td></tr>
<tr><td>SARS CoV-2 PCR +ve (as inpatient)</td><td>21 (78%)</td><td>50 (77%)</td><td>10 (56%)</td></tr>
<tr><td>SARS-CoV-2-IgG +ve (Abbott) (at follow-up)</td><td>18 (67%)</td><td>56 (86%)</td><td>15 (83%)</td></tr>
</table>
</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Inclusion criteria:
Positive PCR result for SARS-CoV-2 or a clinico-radiological diagnosis of COVID-19 disease
Exclusion criteria:
Age <18 years
Inability to give informed consent to study participation</td></tr>
<tr><td>Follow up</td><td>28 days after admission (remotely to review hospital/ GP notes)
8 to 12 weeks (face to face at respiratory outpatient clinic)</td></tr>
<tr><td>Main results</td><td>8 to 12 weeks follow-up:
Ongoing symptoms:
<table>
<tr><td>Total (n=110)</td><td>Mild (n = 27)</td><td>Moderate (n =65)</td><td>Severe (n =18)</td></tr>
<tr><td>81 (74%)</td><td>16 (59%)</td><td>49 (75%)</td><td>16 (89%)</td></tr>
</table>
Symptoms reported:
The most common symptoms at follow-up were breathlessness, excessive fatigue (39% prevalence each) and insomnia (24%), with the incidence of insomnia apparently increased at follow-up compared to baseline.
Patients with more severe disease were more symptomatic especially in terms of breathlessness, fatigue, myalgia, and insomnia.</td></tr>
</table>

Radiology:

	Total (n=110)	Mild (n = 27)	Moderate (n =65)	Severe (n =18)
Normal	95 (86.4%)	NR	NR	NR
Abnormal	15 (13.6%)	0 (0%)	10 (15.4%)	5 (27.8%)

Pulmonary function testing:

	Mild (n = 27)	Moderate (n =65)	Severe (n =18)	P-value
O2 Saturations (%)	98.0 (96.5, 99.0)	97.00 (96.0, 98.00)	97.0 (96.0, 98.0)	0.88
Nadir of O2 saturations on STS test	96.0 (95.0, 97.0)	95.0 (93.0, 96.5)	95.0 (91.8, 96.0)	0.75
Respiratory rate	17.0 (14.0, 18.0)	17.0 (14.2, 19.8)	17.0 (16.0, 18.0)	0.95
FVC (L)	3.58 (3.13, 4.31)	3.52 (2.75, 4.36)	3.65 (2.55, 4.14)	0.70
FVC (% predicted)	97 (90, 105)	91 (78, 100)	89 (76, 98)	0.05
FEV1 (L)	2.97 (2.56, 3.42)	2.71 (2.12, 3.49)	2.54 (1.88, 3.23)	0.5
FEV1 (% predicted)	94 (82, 101)	90 (78, 100)	89 (73, 101)	0.30
Restrictive pattern	0 (0%)	8 (12%)	3 (17%)	0.03
Severe desaturation on STS test	0 (0%)	10 (15%)	5 (28%)	0.02

Health-related quality of life

More severe COVID-19 disease at baseline was associated with greater deficiencies. Physical scores such as physical role and the composite physical score were significantly lower in the severe cohort.

Health status (WEMWBS)

	Mild (n = 27)	Moderate (n =65)	Severe (n =18)	
Median score (IQR)	52 (IQR 44 to 56)	53 (IQR 42 to 59)	50 (39 to 58)	Not significant

Blood results

32/35 patients who had deranged liver or renal function on admission had returned to baseline.

Across the cohort, 4 additional patients had significantly abnormal blood results including ongoing lymphopenia (n=2), CRP greater than 10mg/L (n=2). There was no difference between abnormal results and severity of disease.

Summary

Patients with COVID-19 remain highly symptomatic at 8 to 12 weeks, however, clinical abnormalities requiring action are infrequent, especially in those without

	a supplementary oxygen requirement during their acute illness. This has significant implications for physicians assessing patients with persistent symptoms, suggesting that a more holistic approach focussing on rehabilitation and general wellbeing is paramount.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	• Single-centre study with relatively small patient numbers so rarer complications from COVID-19 may have been missed • Patients were followed up in a manner that might be replicated across may different hospital sites so cross-sectional imaging or full pulmonary function testing was not used routinely • At a time where waiting lists for such investigations are long and departments limited by personal protective equipment requirements, the availability of these tests are limited and should be used only when indicated
Additional references	Part of the DISCOVER study (Diagnostic and Severity markers of COVID-19 to Enable Rapid triage study)

D'Cruz 2020

Bibliographic reference/s	**D'Cruz, Rebecca F., Waller, Michael D., Perrin, Felicity et al. (2020) Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Research**
Questions relevant to?	• **Investigations** • **Monitoring** • **Risk Factors** • **Signs and symptoms/prevalence**
Publication status	Accepted for publication
Study type	Cohort (prospective)
Quality	Low quality evidence CASP critical appraisal checklist: High risk of bias
Objective	To prospectively investigate clinical, radiological, functional, and psychological COVID-19 sequalae of severe COVID-19 pneumonia, and to identify factors associated with symptomatic and functional recovery
Study date	June to July 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Kings College Hospital, UK
Population (including n)	119 COVID-19 survivors who had been hospitalised with PCR-confirmed severe COVID-19 pneumonia
Time since acute COVID-19	Median (IQR) times between hospital admission and discharge to follow-up assessment were 76 (71 to 83) days and 61 (51 to 67) days, respectively (4 to 12 weeks grouping)
Investigations	Chest radiography Symptom questionnaires Mental health screening Physiological testing

	Computed tomography and pulmonary angiography (CTPA)
Baseline characteristics	**Age (years)**: Mean 58.7 SD 14.4 **Sex**: Female 45/119 (37.8%); Male 74/119 (62.2%) **Ethnicity**: White 36/119 (30.3%); Black 52/119 (43.7%); Asian 18/119 (15.1%); Mixed race 5/119 (4.2%); Other 8/119 (6.7%) **BMI (kg/m^2):** 30.0 (25.9-35.2) **Comorbidities:** Any CVD 63/119 (52.9%); Diabetes 41/119 (34.5%); Immunosuppressed 16 (13.4%); Obstructive lung disease 13/119 (10.9%), Malignancy 12/119 (10.1%); End stage renal failure 8/119 (6.7%); Thyroid disease 7/119 (5.9%); Mental health condition 6/119 (5%); Cerebrovascular disease 5/119 (4.2%).
Inclusion and exclusion criteria	• Aged 18 years and above • PCR-confirmed COVID-19 by naso- and oro- pharyngeal swab between 5 March and 28 May 2020 • Severe COVID-19 pneumonia defined as requiring hospitalisation for ≥48 hours and a fraction of inspired oxygen (FiO_2) of ≥40% or intensive care unit (ICU) admission
Follow up	Face to face assessment 4 to 6 weeks post discharge
Main results	**At follow-up:** There was no relationship between age groupings and persistent post-COVID symptoms, self-reported functional disability, or physiological impairment. **Breathlessness**: (Medical Research Council Breathlessness Scale, mMRC): • 55/115 (46.2%) had not returned to pre-COVID mMRC • Of these, 11/55 (20%) had no pre-existing comorbidity • Comorbid obstructive lung disease was associated with failure of mMRC recovery to baseline (OR 5.06 95%CI 1.33 to 19.2) **Post-COVID Functional Status (PCFS)**: • ≥2 in 47/115 (40.9%) • Comorbid obstructive lung disease was associated with PCFS ≥2 (OR 2.84 95%CI 1.01 to 7.98) **Persistent symptoms:** • Median 4 IRQ (2 to 5) • 11% reported no persistent symptoms • Burdensome breathlessness (numerical rating scale, NRS ≥4): 37/115 (32.2%) • Persistent cough (NRS ≥1): 49/115 (42.6%) • Burdensome cough (NRS ≥4): 8/115 (7%) • Fatigue: 78/115 (67.8%) • Sleep disturbance: 65/115 (56.5%) • Pain (commonly reported in shoulder, chest, lower limbs and back): 57/115 (49.6%) • Pre-morbid obstructive lung disease was associated with persistent (NRS ≥1) breathlessness (OR 8.04 95%CI 0.19 to 21.4) and cough (OR 3.43 95% CI 0.98 to 12.0), but not burdensome (NRS ≥4) breathlessness or cough (OR 1.97 95%CI 0.60 to 6.47 and OR 2.27 95% CI 0.38 to 13.7, respectively) • There were no associations between the presence or absence of pre-existing comorbidities and persistent fatigue, sleep disturbance or pain **Mental health outcomes:** • PHQ-9 score ≥9: 20/115 (18%)

	• GAD-7 score ≥9: 25/113 (22.1%) • Trauma screen questionnaire ≥6: 28/113 (24.8%) • 6-item Cognitive impairment test ≥8: 21/97 (21.6%) **Physiological outcomes:** • 4-metre gait speed (4MGS): 44/115 (38.3%) had a 4MGS <0.8m/s; 71/115 (61.7%) • Sit to stand (STS): The number of repetitions performed were below the 2.5 percentile in 56/109 (52%) • There were no adverse events during physiological testing. • There were no associations between pre-morbid obstructive lung disease and physiological functional impairment (OR 0.68 95%CI 0.16 to 2.95) • Cardiovascular disease was associated with a 4MGS <0.8 m/s (OR 3.95 95%CI 0.42 to 2.49). **Chest radiography** • Evidence of COVID-related lung disease (RALE score >4): 15/119 (13%) **CTPA (for patients with abnormal chest radiography, persistent respiratory symptoms, or exercise desaturation)** • Features of COVID-related interstitial lung disease and/or airways disease: 42/56 (37.5%) • No pulmonary emboli were identified on CT pulmonary angiography • Presence of COVID-related CT abnormalities were associated with mental health screening questionnaires (PHQ-9 ≥9, GAD-7 ≥9 and/or Trauma Screening Questionnaire ≥6) (χ^2 =3.98 p=0.046 95%CI -0.56 to -0.02) but not with any measure of patient reported or physiological functional impairment • Only 21% of patients with abnormal CT findings also had an abnormal follow-up chest radiograph • 78% of those with ≥4% desaturation during STS also had abnormal CT findings **Summary:** Persistent symptoms, adverse mental health outcomes and physiological impairment are common 2 months after severe COVID-19 pneumonia. Follow-up chest radiograph is a poor marker of recovery, therefore holistic face-to-face assessment is recommended to facilitate early recognition and management of post-COVID sequelae
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Statistical analysis:** Group comparisons were performed using independent t-tests and Chi square (χ^2) tests. Ordinal logistic regression modelling was used to identify factors associated with measures of COVID-19 recovery. **Limitations:** • Unable to perform lung function testing in serial patients due to decontamination procedures required limiting conclusions on respiratory sequelae • Conventional field walking tests to evaluate exercise capacity (6-minute walk test (6MWT), incremental shuttle walk test (ISWT)) were impractical in the clinic setting. • Authors devised their own definition of “severe” COVID-19 pneumonia which may have missed some patients with persistent symptoms or functional disability.

	• Data collected from a single, urban teaching centre which may limit generalisability **Funding:** This study received no specific funding or grant from any agency in the public, commercial, or not-for-profit sectors. RFD is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (RFD)
Additional references	N/A

Daher 2020

Bibliographic reference/s	**Daher, Ayham, Balfanz, Paul, Cornelissen, Christian et al. (2020) Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. Respiratory Medicine: 106197 to 106197**
Questions relevant to?	**Investigations, prevalence, risk factors**
Publication status	Published
Study type	Cohort (retrospective)
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To investigate pulmonary impairments, as well as the prevalence of other organ dysfunctions and psychological disorders in patients with COVID-19 six weeks after discharge from hospital
Study date	February to May 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Germany
Population (including n)	33 patients with COVID-19 who were discharged from the isolation ward and followed up 6 weeks after discharge All 33 patients had a severe disease during their hospital stay
Time since acute COVID-19 illness	Time from discharge to follow up 56 (48 to 71) days 4 to 12 weeks grouping
Investigations	Pulmonary function tests (PFTs) Electrocardiography Transthoracic echocardiography Whole-body plethysmography Blood tests Heath-related quality of life 6-min walk test
Baseline characteristics	-- / Patients (n=33) Age (years) / 64 ±3 Female / 11 (33%) **Comorbidities** / -- COPD / 3 (9%)

<table>
<tr><td></td><td>
<table>
<tr><td>Bronchial asthma</td><td>4 (13%)</td></tr>
<tr><td>Hypertension</td><td>19 (59%)</td></tr>
<tr><td>Heart failure</td><td>3 (9%)</td></tr>
<tr><td>Atrial fibrillation</td><td>3 (9%)</td></tr>
<tr><td>Chronic kidney disease</td><td>7 (22%)</td></tr>
<tr><td>Coronary artery disease</td><td>6 (19%)</td></tr>
<tr><td>Diabetes mellitus</td><td>8 (25%)</td></tr>
</table>
</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Inclusion criteria
COVID-19 confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR)
Symptomatic patients with severe disease needing hospitalization
Exclusion criteria
Patients with Acute Respiratory Distress Syndrome (ARDS) who needed mechanical ventilation in the intensive care unit (ICU) during their stay</td></tr>
<tr><td>Follow up</td><td>6 weeks from discharge</td></tr>
<tr><td>Main results</td><td>At follow up:
Laboratory findings
Majority had returned to normal
Median D-dimer was not elevated but those patients who did have elevated vales underwent ultrasound duplex scanning and V/Q scan, excluding VTE in all patients.
Symptoms:
<table>
<tr><td></td><td>Admission day (n=33)</td><td>Follow up (n=33)</td></tr>
<tr><td>Fever</td><td>22 (67%)</td><td>1 (3%)</td></tr>
<tr><td>Cough</td><td>23 (70%)</td><td>11 (33%)</td></tr>
<tr><td>Dyspnoea</td><td>16 (48%)</td><td>11 (33%)</td></tr>
<tr><td>Fatigue</td><td>21 (64%)</td><td>15 (45%)</td></tr>
<tr><td>Tiredness</td><td>15 (55%)</td><td>15 (45%)</td></tr>
<tr><td>Haemoptysis</td><td>1 (3%)</td><td>0 (%)</td></tr>
<tr><td>Rhinorrhoea</td><td>2 (6%)</td><td>4 (12%)</td></tr>
<tr><td>Sore throat</td><td>8 (24%)</td><td>3 (9%)</td></tr>
<tr><td>Pharyngalgia</td><td>4 (12%)</td><td>0 (0%)</td></tr>
<tr><td>Angina pectoris</td><td>4 (12%)</td><td>6 (18%)</td></tr>
<tr><td>Myalgia</td><td>12 (42%)</td><td>5 (15%)</td></tr>
<tr><td>Headache</td><td>7 (21%)</td><td>5 (15%)</td></tr>
<tr><td>Cognitive disorders</td><td>--</td><td>6 (18%)</td></tr>
<tr><td>Loss of smell</td><td>8 (24%)</td><td>4 (12%)</td></tr>
<tr><td>Loss of taste</td><td>9 (27%)</td><td>3 (9%)</td></tr>
<tr><td>Diarrhoea</td><td>13 (39%)</td><td>3 (9%)</td></tr>
<tr><td>Nausea</td><td>8 (24%)</td><td>2 (6%)</td></tr>
<tr><td>Emesis</td><td>2 (6%)</td><td>0 (0%)</td></tr>
<tr><td>Stomach pains</td><td>7 (21%)</td><td>1 (3%)</td></tr>
</table>
Pulmonary function parameters and ABGs
<table>
<tr><td>--</td><td>Follow up (n=33)</td></tr>
<tr><td>TLC, % of predicted</td><td>94 (85 to 105)</td></tr>
</table>
</td></tr>
</table>

VC, % of predicted	93 (78 to 101)
RV, % of predicted	112 (98 to 127)
RV/TLC, % of predicted	109 (98 to 126)
FEV1, % of predicted	95 (72 to 103)
FEV1/FVC, %	79 (76 to 85)
R eff, % of predicted	86 (62 to 104)
DLCO, % of predicted	65 (53 to 73)
DLCO/VA, % of predicted	77 (69 to 95)
ABG	--
paO 2, mmHg	72 (67 to 79)
paCO 2, mmHg	38 (35 to 38)
pH	7.4 (7.4 to 7.4)
Base excess, mmol/l	0.8 (-0.6 - +1.2)
COHb, vol%	0.9 (0.71)

6-min walk test

--	Follow up (n=33)
Distance, m	380 (180-470)
Distance < predicted value, n	26 (79%)
Distance < LLN, n	15 (45%)
Walk distance - predicted value, m	138 (-37to -191)
Walk distance - LLN, m	1.5 (-52 to +130)
SpO2 before exercise, %	97 (94 to 98)
SpO2 after exercise, %	96 (94 to 98)
HR before exercise, bpm	76 (61 to 86)
HR after exercise, bpm	91 (74 to 100)
Dyspnoea on Borg scale before exercise	0 (0 to 2)
Dyspnoea on Borg scale after exercise	1 (0 to 4)
Fatigue on Borg scale before exercise	1 (0 to 3)
Fatigue on Borg scale after exercise	1 (0 to 4)

Electrocardiography and echocardiography

Echocardiography did not reveal deterioration of left or right ventricular function and there was no evidence of pulmonary hypertension on electrocardiogram (ECG) or in the echocardiograph [Right Ventricular Systolic Pressure (RVSP): median = 25 mmHg + Central venous pressure (CVP) (IQR: 22 to 31)]. There was no pericardial effusion in any patient.

Health status questionnaires

--	Follow up (n=33)
PHQ-9	7 (4 to 11)
GAD-7	4 (1 to 9)

	SRGQ total score (St. George's respiratory questionnaire)	26 (7 to 42)
	EQ-5D-5L	--
	Mobility (walking)	2 (1 to 3)
	Self-Care	1 (1 to 1)
	Usual Activities	2 (1 to 3)
	Pain/Discomfort	2 (1 to 3)
	Anxiety/Depression	2 (1 to 2)
	EQ VAS	63 (53 to 80)
	Hospitalized patients with severe COVID-19, who did not require mechanical ventilation, are unlikely to develop pulmonary long-term impairments, thromboembolic complications or cardiac impairments after discharge but frequently suffer from symptoms of fatigue.	
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No limitations reported	
Additional references	N/A	

Dennis 2020

Bibliographic reference/s	**Dennis, Andrea, Wamil, Malgorzata, Kapur, Sandeep et al. (2020) Multi-organ impairment in low-risk individuals with long COVID. medRxiv: 2020101420212555**
Questions relevant to?	**Investigations, prevalance, risk factors**
Publication status	Preprint
Study type	Prospective cohort (ongoing)
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	In order to better understand the long-term impact of COVID-19 and ultimately inform preventive measures at health system level, we performed a pragmatic, prospective study in low-risk individuals with symptom assessment, multi-organ magnetic resonance imaging (MRI) and blood investigations for inflammatory markers at three months post-COVID-19 diagnosis.
Study date	April to August 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	UK
Population (including n)	201 patients with previous SARS-CoV-2 infection and low risk for COVID-19 severity and mortality

<table>
<tr><td>Time since acute COVID-19</td><td>Around 3 to 5 months
12+ weeks grouping</td></tr>
<tr><td>Investigations</td><td>• Symptom assessment
• Multi-organ MRI
• Blood investigations for inflammatory markers</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>All (n=201) N (%)</th><th>Not hospitalised (n=164) N (%)</th><th>Hospitalised (n=37) N (%)</th></tr>
<tr><td>Age (years, mean; sd)</td><td>44(11.0)</td><td>43(10.9)</td><td>50(10.0)</td></tr>
<tr><td>Female (No, %)</td><td>140(69.7)</td><td>117(71.3)</td><td>23(62.2)</td></tr>
<tr><td>BMI (kg/m^2, median; IQR)</td><td>25.7(22.7,28.1)</td><td>25.3(22.6,27.7)</td><td>27.2(23.1,31.0)</td></tr>
<tr><td>Ethnicity</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>White</td><td>174(86.6)</td><td>146(89.0)</td><td>28 (75.7)</td></tr>
<tr><td>Mixed</td><td>3 (1.5)</td><td>3 (1.8)</td><td>0 (0)</td></tr>
<tr><td>South Asian</td><td>8 (4.0)</td><td>5 (3.0)</td><td>3 (8.1)</td></tr>
<tr><td>Black</td><td>5 (2.5)</td><td>3 (1.8)</td><td>2 (5.4)</td></tr>
<tr><td>Comorbidities and risks</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>Never smoked</td><td>132 (65.7)</td><td>108 (65.9)</td><td>24 (64.9)</td></tr>
<tr><td>Current smoker</td><td>6 (3.0)</td><td>6 (3.7)</td><td>0 (0)</td></tr>
<tr><td>Ex-smoker</td><td>63 (31.3)</td><td>50 (30.5)</td><td>13 (35.1)</td></tr>
<tr><td>Health care worker</td><td>62 (30.8)</td><td>49 (29.9)</td><td>13 (35.1)</td></tr>
<tr><td>Asthma</td><td>36 (17.9)</td><td>33(20.1)</td><td>3 (8.1)</td></tr>
<tr><td>BMI ≥25 kg/m^2</td><td>112 (56.3)</td><td>87 (53.7)</td><td>25 (67.6)</td></tr>
<tr><td>BMI ≥30 kg/m^2</td><td>40 (20.1)</td><td>28 (17.3)</td><td>12 (32.4)</td></tr>
<tr><td>Hypertension</td><td>12 (6.0)</td><td>10 (6.1)</td><td>2 (5.4)</td></tr>
<tr><td>Diabetes</td><td>4 (2.0)</td><td>4 (2.4)</td><td>0 (0.0)</td></tr>
<tr><td>Previous heart disease</td><td>8 (4.0)</td><td>7 (4.3)</td><td>1 (2.7)</td></tr>
<tr><td>Initial symptoms-to assessment (days: median, [IQR])</td><td>140 (105, 160)
(n=1 missing)</td><td>140 (106, 162)
(n=1 missing)</td><td>138 (97, 150)</td></tr>
<tr><td>COVID-19 positive to-assessment (days: median, [IQR])</td><td>70 (42, 112)
(n=3 missing)</td><td>67 (39, 109)
(n=3 missing)</td><td>105 (59, 126)</td></tr>
</table>
</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Inclusion criteria:
• Tested positive by the oro/nasopharyngeal throat swab forSARS-CoV-2 by reverse-transcriptase-polymerase-chain reaction or
• positive antibody test or
• had typical symptoms and were determined to have COVID-19 by two independent clinicians
Exclusion criteria:</td></tr>
</table>

<table>
<tr><td></td><td>

Symptoms of active respiratory viral infection (temperature >37.8°C or three or more episodes of coughing in 24 hours)
discharged from hospital in the last 7 days
contraindications to MRI, including implanted pacemakers, defibrillators, other metallic implanted devices; claustrophobia

</td></tr>
<tr><td>Follow up</td><td>Around 20 weeks</td></tr>
<tr><td>Main results</td><td>At follow up
<table>
<tr><th>Symptoms</th><th>All (n=201) N (%)</th><th>Not hospitalised (n=164) N (%)</th><th>Hospitalised (n=37) N (%)</th></tr>
<tr><td>Fatigue</td><td>197 (98.0)</td><td>160 (97.6)</td><td>37 (100.0)</td></tr>
<tr><td>Muscle ache</td><td>176 (87.6)</td><td>145 (88.4)</td><td>31 (83.8)</td></tr>
<tr><td>Shortness of breath</td><td>175 (87.1)</td><td>140 (85.4)</td><td>35 (94.6)</td></tr>
<tr><td>Headache</td><td>175 (87.1)</td><td>139 (84.8)</td><td>27 (73.0)</td></tr>
<tr><td>Joint pain</td><td>157 (78.1)</td><td>128 (78.0)</td><td>29 (78.4)</td></tr>
<tr><td>Fever</td><td>151 (75.1)</td><td>127 (77.4)</td><td>24 (64.9)</td></tr>
<tr><td>Chest pain</td><td>147 (73.1)</td><td>116 (70.7)</td><td>31 (83.8)</td></tr>
<tr><td>Cough</td><td>148 (73.6)</td><td>119 (72.6)</td><td>29 (78.4)</td></tr>
<tr><td>Sore throat</td><td>143 (71.1)</td><td>120 (73.2)</td><td>23 (62.2)</td></tr>
<tr><td>Diarrhoea</td><td>119 (59.2)</td><td>92 (56.1)</td><td>27 (73.0)</td></tr>
<tr><td>Abnormal pain</td><td>108 (53.7)</td><td>91 (55.5)</td><td>17 (45.9)</td></tr>
<tr><td>Wheezing</td><td>97 (48.3)</td><td>74 (45.1)</td><td>23 (62.2)</td></tr>
<tr><td>Inability to walk</td><td>81 (40.3)</td><td>59 (36.0)</td><td>22 (59.5)</td></tr>
<tr><td>Runny nose</td><td>68 (33.8)</td><td>55 (33.5)</td><td>13 (35.1)</td></tr>
</table>
Blood investigations

Triglycerides (p=0.002), cholesterol (p=0.021), LDL-cholesterol (p=0.005) and transferrin saturation (p=0.005) were more likely to be abnormal in hospitalised versus non-hospitalised individuals.
Mean corpuscular haemoglobin concentration (26%), alanine transferase (14%), lactate dehydrogenase (16%), triglycerides (12%) and cholesterol (42%) were all abnormally high in ≥10% of all individuals (without separation by hospitalisation status).
ESR (13%), bicarbonate (13%), uric acid (16%) and high-sensitivity CRP (13%) were abnormally high in ≥10% of individuals in the hospitalisation group
Bicarbonate (10%), phosphate (13%), uric acid (11%), and transferrin saturation (19%) were abnormally low in ≥10% of individuals (without separation by hospitalisation status)

Single and multi- organ impairment
<table>
<tr><th>Heart</th><th>All (n=201) N (%)</th><th>Not hospitalised (n=164) N (%)</th><th>Hospitalised (n=37) N (%)</th><th>P value</th></tr>
<tr><td>LVEF (%)</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>Normal</td><td>155 (77.1)</td><td>129 (78.7)</td><td>26 (70.3)</td><td rowspan="2">0.079</td></tr>
<tr><td>Borderline impairment (50 to 55%)</td><td>38 (18.9)</td><td>31 (18.9)</td><td>7 (18.9)</td></tr>
</table>
</td></tr>
</table>

Definite impairment (<50%)	8 (4.0)	4 (2.4)	4 (10.8)	
Evidence of myocarditis	--	--	--	--
≥ 3 segments with high T1 (≥1264ms at 3T; ≥1015ms at 1.5T)	22 (10.9)	18 (11.0)	4 (10.8)	1

Lungs	All (n=201) N (%)	Not hospitalised (n=164) N (%)	Hospitalised (n=37) N (%)	P value
Deep Breathing Fractional area change <39%	63 (33.2) (n= 11 missing)	47 (30.1) (n= 8 missing)	16 (47.1) (n= 3 missing)	0.071

Pancreas	All (n=201) N (%)	Not hospitalised (n=164) N (%)	Hospitalised (n=37) N (%)	P value
Pancreatic inflammation (T1 in ms)	--	--	--	--
Normal (800ms)	157 (83.1)	136 (87.2)	21 (63.6)	0.003
Borderline (800-865ms)	20 (10.6)	11 (7.1)	9 (27.3)	
Significant (>865ms)	12 (6.3)	9 (5.8)	3 (9.1)	
Pancreatic fat	(n= 6 missing)	(n= 4 missing)	(n= 2 missing)	
Normal (<5%)	126 (64.6)	111 (69.4)	15 (42.9)	0.005
Borderline (5-10%)	44 (22.6)	33 (20.6)	11 (31.4)	
Significant (>10%)	25 (12.8)	16 (10.0)	9 (25.7)	

Liver	All (n=201) N (%)	Not hospitalised (n=164) N (%)	Hospitalised (n=37) N (%)	P value
Liver Inflammation (cT1 in ms)	(n= 1 missing)	(n= 1 missing)	--	--
Normal (800ms)	181 (90.5)	150 (92.0)	31 (83.8)	0.040
Borderline (800-865ms)	5 (2.5)	5 (3.1)	0 (0.0)	

	Significant (>865ms)	14 (7.0)	8 (4.9)	6 (16.2)	
	Liver fat	--	--	--	--
	Normal (<5%)	162 (80.6)	138 (84.1)	24 (64.9)	0.025
	Borderline (5 to 10%)	18 (9.0)	12 (7.3)	6 (16.2)	
	Definite (>10%)	21 (10.4)	14 (8.5)	7 (18.9)	

Spleen	All (n=201) N (%)	Not hospitalised (n=164) N (%)	Hospitalised (n=37) N (%)	P value
Splenic length (mm)	(n= 10 missing)	(n= 10 missing)	--	--
Normal	179 (9.4)	144 (9.5)	35 (9.5)	1
Borderline	12 (6.3)	10 (6.5)	2 (5.4)	

In a young, low-risk population with ongoing symptoms, almost 70% of individuals have impairment in one or more organs four months after initial symptoms of SARS-CoV-2 infection. There are implications not only for burden of long COVID but also public health approaches which have assumed low risk in young people with no comorbidities.

Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding**: This work was supported by the UK's National Consortium of Intelligent Medical Imaging through the Industry Strategy Challenge Fund, Innovate UK Grant, and also through the European Union's Horizon 2020 research and innovation programme **Limitations:** • Partly limited by access to laboratory testing during the pandemic • Causality of the relationship between organ impairment and infection cannot be deduced but may be addressed by longitudinal follow-up of individuals with organ impairment. • Study population was limited by ethnicity despite disproportionate impact of COVID-19 in non-white individuals • Pulse oximetry and spirometry were added later to the protocol and follow up; they were not included from the outset to limit interaction and exposure between trial team and patients • Did not include healthy controls or MRI assessment of brain or muscle function
Additional references	Ongoing study (https://clinicaltrials.gov/ct2/show/NCT04369807

Frija-Masson 2020

Bibliographic reference/s	**Frija Masson 2020**
Questions relevant to?	**Investigations, monitoring**

<table>
<tr><td>Publication status</td><td>Published</td></tr>
<tr><td>Study type</td><td>Letter to editor (short report)</td></tr>
<tr><td>Quality</td><td>Very low quality</td></tr>
<tr><td>Objective</td><td>to assess the pulmonary functional status 1 month after symptom onset and correlate lung function alteration with the severity of pneumonia.</td></tr>
<tr><td>Study date/</td><td>Patients in hospital between 4 March 2020 and 1 April, 2020</td></tr>
<tr><td>COVID-19 prevalence (high/low) if reported</td><td>NR</td></tr>
<tr><td>Country/ Setting</td><td>France</td></tr>
<tr><td>Population (including n)</td><td>Patients under the age of 85 years with confirmed SARS-CoV-2 infection
N=50</td></tr>
<tr><td>Time since acute COVID-19 illness</td><td>1 month since symptom onset
4 to 12-week group</td></tr>
<tr><td>Interventions/ Prognostic factors</td><td>All tests included spirometry, functional residual capacity (FRC), total lung capacity (TLC) and DLCO (single breath real-time CO/NH4) measurements</td></tr>
<tr><td>Baseline characteristics</td><td>There was no difference between groups regarding BMI, age, or comorbidities. Prevalence of hypertension and diabetes mellitus were 48% and 16%, respectively
<table>
<tr><td></td><td>All</td><td>No CT</td><td>None/ mild</td><td>moderate</td><td>severe</td></tr>
<tr><td>n</td><td>50</td><td>5</td><td>12</td><td>17</td><td>16</td></tr>
<tr><td>Age (yrs)</td><td>54 (46 to 62)</td><td>30 (30 to 46)</td><td>55 (46 to 63)</td><td>53 (47 to 56)</td><td>58 (49 to 67)</td></tr>
<tr><td>Male</td><td>28 (56)</td><td>2 (40)</td><td>4 (33)</td><td>9 (53)</td><td>13 (81)</td></tr>
<tr><td>Care setting-outpatient</td><td>9 (18)</td><td>4 (80)</td><td>4 (33)</td><td>1 (6)</td><td>0</td></tr>
<tr><td>ID ward</td><td>33 (66)</td><td>1 (20)</td><td>8 (66)</td><td>15 (88)</td><td>9 (56)</td></tr>
<tr><td>ICU</td><td>8 (16)</td><td>0</td><td>0</td><td>1 (6)</td><td>7 (44)</td></tr>
</table></td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Patients under the age of 85 years with confirmed SARS-CoV-2 infection (positive RT-PCR on nasopharyngeal swab) and respiratory symptoms, discharged from Bichat Hospital, Paris, France</td></tr>
<tr><td>Follow up</td><td>30 days after symptom onset</td></tr>
<tr><td>Main results</td><td>A senior radiologist reviewed all chest CT and evaluated the extent of pneumonia as absent, mild (<10% of parenchyma involved), moderate (10 to 24%), wide (25 to 49%), or severe (⩾50%), according to European guidelines [7].
For the analysis, we classified patients into three groups according to the extent of pneumonia: none or mild, moderate, and wide-to-severe.
More than half of patients (27/50) had impaired lung function, with a mix of restrictive and low diffusion patterns
We found no difference in FVC, TLC or DLCO (% predicted values) between groups according to CT extent, but a significant difference in the proportion of abnormal values (i.e. restriction and/or altered DLCO) (p=0.0277). Lower DLCO was significantly associated with older age (>50 years) (p=0.0351), but TLC and FVC were not. Finally, FVC, TLC and DLCO were not significantly different between groups of clinical severity (i.e. oxygen requirement)</td></tr>
</table>

<table>
<tr><td></td><td>Overall, our study shows that 1 month after SARS-CoV-2 infection, a majority of patients have mild alterations of lung function
<table>
<tr><th>PFT interpretation</th><th>All</th><th>No CT</th><th>None/ mild</th><th>moderate</th><th>severe</th></tr>
<tr><td>normal</td><td>23 (46)</td><td>3 (60)</td><td>8 (66)</td><td>9 (53)</td><td>3 (19)</td></tr>
<tr><td>Restrictive pattern</td><td>6 (12)</td><td>1 (20)</td><td>0</td><td>3 (18)</td><td>2 (13)</td></tr>
<tr><td>Restriction with altered diffusion capacity</td><td>8 (16)</td><td>0</td><td>0</td><td>2 (12)</td><td>6 (38)</td></tr>
<tr><td>Altered diffusion capacity only</td><td>13 (26)</td><td>1 (20)</td><td>4 (33)</td><td>3 (18)</td><td>5 (31)</td></tr>
</table>
PFT= pulmonary function tests</td></tr>
<tr><td>Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)</td><td>we included neither patients with acute respiratory distress syndrome, since most were still hospitalised at the time of our study, nor patients over 85 years, because of the lack of valuable predicted values. This could lead to underestimation of the percentage of patients with functional impairment.
No systematic CT of participants</td></tr>
<tr><td>Additional references</td><td>N/A</td></tr>
</table>

Eiros 2020

Bibliographic reference/s	**Eiros, Rocio, Perez Manuel, Barreiro-Perez, Garcia Ana, Martin-Garcia et al. Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in healthcare workers. medrxiv preprint**
Questions relevant to?	**Prevalence, Investigations**
Publication status	Preprint
Study type	Cross sectional observational cohort
Quality	Low quality evidence JBI critical appraisal checklist rating: Moderate risk of bias
Objective	A cross-sectional study in health-care workers to report evidence of pericarditis and myocarditis after SARS-CoV-2 infection.
Study date	25 May 2020 to 12 June 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Spain
Population (including n)	139 health-care workers with confirmed past SARS-CoV-2 infection (103 diagnosed by RT-PCR between March 13 and April 25 and 36 by serology April 10 and May 22)

<table>
<tr><td>Time since acute COVID-19 illness</td><td>Approximately 10 weeks after infection onset
4 to 12 weeks grouping</td></tr>
<tr><td>Investigations</td><td>• Complete medical history
• Physical examination
• Questionnaire
• ECG
• Blood investigations
• CMR</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>--</td><td>--</td><td colspan="4">Presence of pericardial and myocardial manifestations</td><td>--</td></tr>
<tr><td>--</td><td>All participants (n=139)</td><td>No (n=84)</td><td>Pericarditis (n=4)</td><td>Myopericarditis (n=15)</td><td>Myocarditis (n=36)</td><td>P value</td></tr>
<tr><td>Age, median (range)</td><td>52 (41 to 57)</td><td>52 (38 to 57)</td><td>45 (34 to 52)</td><td>54 (44 to 60)</td><td>52 (48 to 57)</td><td>0.503</td></tr>
<tr><td>Female sex</td><td>100 (72)</td><td>56 (67)</td><td>3 (75)</td><td>12 (80)</td><td>29 (81)</td><td>0.4</td></tr>
<tr><td>Healthcare worker category</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>0.669</td></tr>
<tr><td>- Medical Staff</td><td>35 (25)</td><td>22 (26)</td><td>1 (25)</td><td>6 (40)</td><td>6 (17)</td><td>--</td></tr>
<tr><td>- Nurse</td><td>49 (35)</td><td>28 (33)</td><td>1 (25)</td><td>4 (27)</td><td>16 (44)</td><td>--</td></tr>
<tr><td>- Other</td><td>55 (40)</td><td>34 (40)</td><td>2 (50)</td><td>5 (33)</td><td>14 (39)</td><td>--</td></tr>
<tr><td>Coexisting conditions</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>Obesity</td><td>17 (12)</td><td>14 (17)</td><td>1 (25)</td><td>0</td><td>2 (6)</td><td>0.108</td></tr>
<tr><td>Hypertension</td><td>17 (12)</td><td>11 (13)</td><td>1 (25)</td><td>1 (7)</td><td>4 (11)</td><td>0.679</td></tr>
<tr><td>Diabetes</td><td>2 (1)</td><td>2 (2)</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Dyslipidaemia</td><td>27 (19)</td><td>17 (20)</td><td>1 (25)</td><td>2 (13)</td><td>7 (19)</td><td>0.936</td></tr>
<tr><td>Current smoking</td><td>6 (4)</td><td>4 (5)</td><td>0</td><td>1 (7)</td><td>1 (3)</td><td>0.741</td></tr>
<tr><td>Past smoking</td><td>70 (50)</td><td>43 (51)</td><td>0</td><td>6 (40)</td><td>21 (58)</td><td>0.140</td></tr>
<tr><td>Alcohol (≥1 drink per day)</td><td>23 (16)</td><td>10 (12)</td><td>1 (25)</td><td>3 (20)</td><td>9 (25)</td><td>0.217</td></tr>
<tr><td>CVD</td><td>8 (6)</td><td>5 (6)</td><td>0</td><td>2 (13)</td><td>1 (3)</td><td>0.472</td></tr>
<tr><td>Pulmonary disease</td><td>8 (6)</td><td>5 (6)</td><td>0</td><td>0</td><td>3 (8)</td><td>0.805</td></tr>
</table>
</td></tr>
</table>

	Sleep apnoea-hypopnea	8 (6)	5 (6)	0	2 (13)	1 (3)	0.472
	CKD	5 (4)	2 (2)	0	0	3 (8)	0.319
	Cancer	4 (3)	3 (4)	0	0	1 (3)	1

Inclusion and exclusion criteria	Inclusion criteria: • tested positive for SARSCoV-2 by RT-PCR between March 13 and April 25; and 36 health-care workers were diagnosed after testing positive for anti-SARS-CoV-2-IgG antibodies between April 10 and May 22
Follow up	

Main results

--	All participants	Presence of pericardial and myocardial manifestations				P value
--	All participants (n=139)	No (N=84)	Pericarditis (n=4)	Myopericarditis (N=15)	Myocarditis (N=36)	--
Time from onset to exam (weeks)	10.4 (9.3 to 11.0)	10.4 (9.0 to 11.1)	9.0 (6.9 to 13.3)	10.4 (9.9 to 10.9)	10.3 (9.3 to 11.1)	0.841
Symptoms on examination						
No symptoms	48 (34%)	33 (39%)	0	3 (20%)	12 (33%)	0.274
General						
Fatigue	37 (27%)	23 (27%)	1 (25%)	4 (27%)	9 (25%)	0.982
Anosmia	12 (9%)	5 (6%)	1 (25%)	1 (7%)	5 (14%)	0.188
Ageusia	7 (5%)	4 (5%)	1 (25%)	0	2 (6%)	0.307
Headache	7 (5%)	4 (5%)	0	2 (13%)	1 (3%)	0.455
Sore throat	7 (5%)	3 (4%)	0	1 (7%)	3 (8%)	0.515
Abdominal pain	6 (4%)	3 (4%)	0	1 (7%)	2 (6%)	0.625
Memory loss	4 (3%)	2 (2%)	0	0	2 (6%)	0.770
Joint pain	3 (2%)	1 (1%)	0	2 (13%)	0	0.071
Piloerection	2 (1%)	1 (1%)	1 (25%)	0	0	0.068
Cardiac	--	--	--	--	--	--

Dyspnoea	36 (26%)	20 (24%)	2 (50%)	7 (47%)	7 (19%)	0.115
Chest pain	27 (19%)	8 (9%)	3 (75%)	11 (73%)	5 (14%)	**<0.001**
Chest pain (pericarditis like)	18 (13%)	3 (4%)	3 (75%)	11 (73%)	1 (3%)	**<0.001**
Palpitations	20 (14%)	10 (12%)	2 (50%)	3 (20%)	5 (14%)	0.163
Dizziness	8 (6%)	2 (2%)	1 (25%)	2 (13%)	0	0.071
At least one cardiac symptom	58 (42%)	28 (33%)	4 (100%)	11 (73%)	15 (42%)	**0.002**
Electrocardiographic measures						
Widespread ST elevation	13 (9%)	7 (8%)	0	5 (33%)	1 (3%)	**0.017**
PR depression	33 (24%)	17 (20%)	2 (50%)	8 (53%)	6 (17%)	**0.016**
Laboratory measures						
GFR <60ml/min x 1.73[3]	2 (1%)	0	1 (25%)	0	1 (3%)	**0.033**
CMR imaging measures						
T2-weighted hyperintensity	6 (4%)	0	0	1 (7%)	5 (14%)	**0.006**
Increase of native myocardial T1-relaxation time	58 (42%)	24 (29%)	0	7 (47%)	27 (75%)	**<0.001**
Increase of T1-extracellular volume	52 (37%)	17 (20%)	0	9 (60%)	26 (72%)	**<0.001**
T1-late gadolinium enhancement	10 (7%)	2 (2%)	0	4 (27%)	4 (11%)	**0.008**
Pericardial effusion	42 (30%)	4 (5%)	3 (75%)	15 (100%)	20 (57%)	**<0.001**

- CMR abnormalities were observed in 104 (75%)

Pericarditis and myocarditis with clinical stability are frequent long after SARS-CoV-2 infection, even in presently asymptomatic subjects. These observations will probably apply to the general population infected and may indicate that cardiac

	sequelae might occur late in association with an altered (delayed) innate and adaptative immune response
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	Funding: This study was supported by CIBERCV (CB16/11/00374), CIBERONC (CB16/12/00400) and the COV20/00386 grant from the Instituto de Salud Carlos III and FEDER, Ministerio de Ciencia e Innovación, Madrid, Spain. Limitations: • Focused only on HCWs so may have limited generalisability to non-healthcare settings
Additional references	The study is registered with ClinicalTrials.gov NCT04413071

Huang 2020a

Bibliographic reference/s	**Huang, Lu, Zhao, Peijun, Tang, Dazhong et al. (2020) Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC. Cardiovascular imaging**
Questions relevant to?	**Investigations**
Publication status	Published
Study type	Retrospective cohort
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	This study evaluated cardiac involvement in patients recovered from coronavirus disease-2019 (COVID19) using cardiac magnetic resonance (CMR)
Study date	Not reported
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Tongji Hospital, Tongji Medical College, Wuhan, China
Population (including n)	• 26 consecutive patients since March 2020 who were initially referred for cardiac CMR examination due to cardiac symptoms • 11 healthy controls of a similar age and gender who previously underwent the same CMR examinations were selected from a database of healthy subjects without cardiovascular disease or systemic inflammation
Time since acute COVID-19	Duration between cardiac symptoms onset to CMR examination mean 47 days (range 36 to 58 days) 4 to 12 weeks grouping
Investigations	Cardiac magnetic resonance (CMR)
Baseline characteristics	**Age (years):** 38 (IQR 32-45) **Male:** 10/26 (38%) **BMI (kg/m^2):** 23.2 SD 3.6 **Comorbidities:** Hypertension 2/26 (8%). No other comorbidities reported.

Bibliographic reference/s	**Huang, Lu, Zhao, Peijun, Tang, Dazhong et al. (2020) Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC. Cardiovascular imaging**
Questions relevant to?	**Investigations**
Publication status	Published
	Cardiac symptoms: Precordial chest pain 3/26 (12%), palpitation 23/26 (88%), chest distress 6/26 (23%)
Inclusion and exclusion criteria	**Inclusion criteria** • Patients were previously confirmed with SARS-CoV-2 infection using reverse transcription polymerase chain reaction (RT-PCR) swab test • Patients were considered recovered by the discharging criteria (normal temperature lasting longer than 3 days, resolved respiratory symptoms, and substantially improved exudative lesions on chest CT images, and 2 consecutive negative RT-PCR test results separated by at least 24h) and were isolated for 14 days • Patients reported cardiac symptoms after being discharged, including chest pain, palpitation, and chest distress. **Exclusion criteria** • A history of coronary artery disease or myocarditis • Contradictions to gadolinium contrast • CMR image quality that was not sufficient for analysis
Follow up	Not reported
Main results	• 15/26 (58%) had abnormal CMR findings • 14/26 (54%) had myocardial oedema • Decreased right ventricle functional parameters including ejection fraction, cardiac index, and stroke volume/body surface area were found in patients with positive conventional CMR findings • Global native T1, T2, and ECV were all found to be significantly elevated in patients with positive conventional CMR findings, compared with patients without positive findings and controls. **Summary** Cardiac involvement was found in a proportion of patients recovered from COVID-19. CMR manifestation included myocardial oedema, fibrosis, and impaired right ventricle function. Attention should be paid to the possible myocardial involvement in patients recovered from COVID-19 with cardiac symptoms.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding:** This work was supported in part by the National Natural Science Foundation of China, the National Mega Project on Major Infectious Disease Prevention and the National Key Research and Development Program of China **Limitations:** • Small sample size Most patients had moderate COVID-19 so cannot be generalised to all levels of severity
Additional references	N/A

Huang 2020b

Bibliographic reference/s	**Huang, Yiying, Tan, Cuiyan, Wu, Jian et al. (2020) Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respiratory research 21(1): 163**
Questions relevant to?	**Investigations, risk factors**
Publication status	Published
Study type	Cohort (retrospective)
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	This study investigated the influence of Coronavirus Disease 2019 (COVID-19) on lung function in early convalescence phase
Study date	Not reported
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Fifth Affiliated Hospital of Sun Yat-sen University, China
Population (including n)	57 hospitalised COVID-19 patients that had been released from hospital over a period of 1 month
Time since acute COVID-19 illness	At least 30 days 4 to 12 weeks grouping
Investigations	• Pulmonary function testing • Lung imaging (high resolution spiral CT) • 6-min walk test
Baseline characteristics	**Age (years):** 46.72 (SD 13.7) **Male:** 26/57 (45.6%) **BMI (kg/m^2):** 23.99 (SD 3.55) **Pre-existing medical illness:** 21//57 (36.8%) (most common were hypertension, diabetes, malignant tumour and CVD) **COVID-19 severity:** • Severe cases 17/57 (29.8%) • Non-severe cases 40/57 (70.2%)
Inclusion and exclusion criteria	**Inclusion criteria:** • Over age 18 • All patients had laboratory-confirmed SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) or next-generation sequencing **Exclusion criteria:** • Patients with a previous history of pulmonary resection, neurological disease, or mental illness
Follow up	Around 30 days from discharge
Main results	At follow up: **Lung function tests and respiratory muscle strength** • 30/57 (52.6%) had abnormal diffusion capacity • Of these, 26/30 (86.7%) had mild impairment of DLCO and 4/30 (13.3%) had moderate impairment.

	• Impaired diffusing capacity was significantly higher in severe COVID-19 cases compared to non-severe cases (75.6% vs 42.5%, p<0.02) • 5/57 (8.7%) had mild impairment of FVC 1/57 (1.8%) had moderate impairment of FVC • 5/57 (8.7%) had mild impairment of FEV1 • 25/57 (43.9%) had mild impairment of FEV1/FVC. • 8/57 (14.0%) and 10/57 (17.5%) had increased R5 and R20 more than 150% of the predicted value, respectively • 7/57 (12.2%) had a reduction in parameters of lung volume (TLC) (6 with mild impairment and 1 with moderate impairment) • There was no difference in FVC, FEV1, and FEV1/FVC between the two groups (severe vs non-severe) • More than half of the subjects had impairment in respiratory muscle strength. • 28/57 (49.1%) and 13/57 (22.8%) had Pimax and Pemax values less than 80% of the predicted value respectively • 13/57 (22.8%) had moderate impairment of respiratory muscle strength, of whom 11 were non-severe cases **Chest radiographs and correlations with lung function** • Slight cough 6/57 (10.5%) • Shortness of breath 4/57 (7%) • Occasional wheezing 3/57 (5.3%) • Residual abnormality on CT scan 31/57 (54.4%) of which 16/31 (94.1%) were severe COVID-19 cases • 4/31 (12.9%) had pulmonary fibrosis (all severe COVID-19 cases) • Compared with non-severe cases, severe patients had a significantly higher CT score (3.94[SD, 2.23]; 0.83 [SD, 1.39]; p < 0.01). **6-min walk test** • Mean 6 min walking distance (6MWD): 561.97m (±45.29m) • 6MWD of severe cases reached only 88.4% of the predicted values, which was significantly lower than non-severe cases (p = 0.011) **Summary** Impaired diffusing-capacity, lower respiratory muscle strength, and lung imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding**: None reported **Limitations:** • Small sample size with a short follow up • Only 57/102 COVID-19 patients completed the serial assessments so might not be generalisable to the whole group • Cardiopulmonary exercise testing was not performed because many patients complained of generalised muscle weakness on follow up.
Additional references	N/A

Mazza 2020

<table>
<tr><td>Bibliographic reference/s</td><td>Mazza, Mario Gennaro, De Lorenzo, Rebecca, Conte, Caterina et al. (2020) Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain, behavior, and immunity 89: 594 to 600</td></tr>
<tr><td>Questions relevant to?</td><td>Investigations, prevalence</td></tr>
<tr><td>Publication status</td><td>Published</td></tr>
<tr><td>Study type</td><td>Cross sectional</td></tr>
<tr><td>Quality</td><td>Low quality evidence
JBI critical appraisal checklist rating: High risk of bias</td></tr>
<tr><td>Objective</td><td>To investigate the psychopathological impact of COVID-19 in survivors at one month follow up, also considering the effect of possible risk factors</td></tr>
<tr><td>Study date</td><td>April 6 to June 9 2020</td></tr>
<tr><td>COVID-19 prevalence (high/low) if reported</td><td>Not reported</td></tr>
<tr><td>Country/ Setting</td><td>Italy</td></tr>
<tr><td>Population (including n)</td><td>402 patients surviving COVID-19 who had previously been hospitalised</td></tr>
<tr><td>Time since acute COVID-19 illness</td><td>4 weeks
4 to 12 weeks grouping</td></tr>
<tr><td>Investigations</td><td>Psychiatric assessments
Inflammatory biomarkers</td></tr>
<tr><td>Baseline characteristics</td><td>Male 265/402 (65.9%)
Mean age 57.8 years, range (18 to 87 years)</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Exclusion criteria:
Patients under 18 years</td></tr>
<tr><td>Follow up</td><td>Psychiatric assessment was performed 31.29 ± 15.7 days after discharge, or 28.56 ± 11.73 days after ED</td></tr>
<tr><td>Main results</td><td>Psychiatric symptoms by gender
<table>
<tr><td>--</td><td>Females (n=137)</td><td>Males (n=265)</td><td>P value</td></tr>
<tr><td>Age</td><td>55.90 ± 14.69</td><td>58.79 ± 12.49</td><td>--</td></tr>
<tr><td>Follow-up oxygen saturation level</td><td>97.87 ± 1.27</td><td>97.84 ± 1.38</td><td>0.868</td></tr>
<tr><td>IES-R (n = 368, 91.5%)</td><td>34.24 ± 16.58</td><td>18.30 ± 16.58</td><td><0.001</td></tr>
<tr><td>PCL-5 (n = 341, 84.8%)</td><td>22.63 ± 12.39</td><td>10.29 ± 12.39</td><td><0.001</td></tr>
<tr><td>ZSDS (n = 368, 91.5%)</td><td>51.20 ± 9.26</td><td>40.61 ± 9.26</td><td><0.001</td></tr>
<tr><td>BDI-13 (n = 372, 91.5%)</td><td>5.08 ± 3.48</td><td>2.32 ± 3.48</td><td><0.001</td></tr>
</table></td></tr>
</table>

STAI-state (n = 341, 84.8%)	44.51 ± 9.55	34.84 ± 9.55	<0.001
STAI-trait (n = 352, 87.6%)	41.23 ± 9.52	33.21 ± 9.52	<0.001
MOS (n = 328, 87.6%)	23.46 ± 5.00	19.08 ± 5.00	<0.001
WHIIRS (n = 367, 91.3%)	9.25 ± 4.62	6.18 ± 4.62	<0.001
OCI (n = 360, 89.5%)	14.44 ± 9.40	10.41 ± 9.40	<0.001

Psychiatric symptoms by psychiatric history

--	Positive psychiatric history (n=106)	Negative psychiatric history (n=296)	P value
Males	52 (19.7%)	212 (80.3%)	< 0.001
Age	55.45 ± 12.47	58.61 ± 13.56	0.036
Follow-up oxygen saturation level	97.98 ± 1.16	97.80 ± 1.40	0.313
IES-R (n = 368, 91.5%)	35.76 ± 22.15	19.34 ± 17.16	< 0.001
PCL-5 (n = 341, 84.8%)	23.30 ± 18.89	10.99 ± 12.93	< 0.001
ZSDS (n = 368, 91.5%)	50.24 ± 13.09	42.00 ± 9.83	< 0.001
BDI-13 (n = 372, 91.5%)	5.58 ± 5.87	2.41 ± 3.29	< 0.001
STAI-state (n = 341, 84.8%)	44.61 ± 12.44	35.74 ± 9.48	< 0.001
STAI-trait (n = 352, 87.6%)	41.88 ± 12.07	33.78 ± 9.23	< 0.001
MOS (n = 328, 87.6%)	22.53 ± 6.68	19.78 ± 5.23	< 0.001
WHIIRS (n = 367, 91.3%)	9.07 ± 5.29	6.57 ± 4.76	< 0.001
OCI (n = 360, 89.5%)	15.94 ± 11.55	10.28 ± 9.17	< 0.001

Psychiatric symptoms by COVID-19 management setting

--	Managed at home (n=102)	Admitted (n=300)	P value
Males	45 (17%)	220 (83%)	< 0.001
Age	50.82 ± 14.43	60.18 ± 12.07	< 0.001
Follow-up oxygen saturation level	98.24 ± 1.40	97.73 ± 1.31	0.005

IES-R (n = 368, 91.5%)	26.81 ± 20.35	22.83 ± 19.85	0.098
PCL-5 (n = 341, 84.8%)	16.90 ± 15.91	13.74 ± 15.78	0.117
ZSDS (n = 368, 91.5%)	45.78 ± 11.04	43.71 ± 11.50	0.128
BDI-13 (n = 372, 91.5%)	4.04 ± 4.62	3.03 ± 4.30	0.055
STAI-state (n = 341, 84.8%)	40.37 ± 11.69	37.44 ± 10.80	0.033
STAI-trait (n = 352, 87.6%)	37.99 ± 10.48	35.25 ± 10.70	0.032
MOS (n = 328, 87.6%)	22.18 ± 6.16	20.03 ± 5.60	0.003
WHIIRS (n = 367, 91.3%)	7.81 ± 5.44	7.05 ± 4.87	0.210
OCI (n = 360, 89.5%)	12.55 ± 10.34	11.56 ± 10.12	0.417

A significant proportion of patients self-rated symptoms in the pathological range: overall, 55.7% scored in the clinical range in at least one psychopathological dimension, 36.8% in two, 20.6% in three, and 10% in four.

Severity of depression also included suicide ideation and planning, with 2.9% scoring 1 (suicidal ideation) at the BDI suicide item, 0.8% scoring 2 and 0.8% scoring 3 (suicidal planning)

Females, patients with a positive previous psychiatric diagnosis, and patients who were managed at home showed an increased score on most measures.

Considering the previous need for psychiatric interventions, prior of COVID-19, 36 patients had been diagnosed with major depressive disorder, 28 with generalized anxiety disorder, 20 with panic attack disorder, 5 with bipolar disorder, 5 with social phobia, 3 with eating disorders, and 4 with other disorders. These patients suffered a more significant impact on mental health, as rated on most measures.

Summary

COVID-19 survivors presented a high prevalence of emergent psychiatric sequelae, with 55% of the sample presenting a pathological score for at least one disorder.

Higher than average incidence of PTSD, major depression, and anxiety, all high-burden non-communicable conditions associated with years of life lived with disability, is expected in survivors.

Considering the alarming impact of COVID-19 infection on mental health, we now suggest assessing psychopathology of COVID-19 survivors, to diagnose and treat emergent psychiatric conditions, monitoring their changes over time, with the aim of reducing the disease burden, which is expected to be very high in patients with psychiatric conditions.

Comments (e.g. source of funding, statistical analysis, any major limitations,	Limitations: The main limitation of the present study is its cross-sectional nature that does not allow interpretation for causality

or issues with studies)	
Additional references	N/A

Podlasin 2020

Bibliographic reference/s	**Podlasin, Regina B, Kowalska, Justyna D, Pihowicz, Andrzej et al. (2020) How to follow-up a patient who received tocilizumab in severe COVID-19: a case report. European journal of medical research 25(1): 37**
Questions relevant to?	**Investigations**
Publication status	Published
Study type	Case study
Quality	Very low-quality evidence
Objective	Case presentation
Study date	Not reported
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Poland
Population (including n)	A 27-year-old, otherwise healthy man with no health risks, was admitted to infectious disease ward with a week history of weakness, fever and sore throat. The patient was discharged from the hospital on day 21 after confirming significant improvement in his CT scan and two negative SARS-CoV-2 RT-PCR from nasopharyngeal swabs
Time since acute COVID-19 illness	35 days 4 to 12 weeks grouping
Investigations	• X-ray • RT-PCR • Blood investigations
Baseline characteristics	**Age (years): 27** **Concomitant chronic conditions:** None **BMI (kg.m^2):** 27.8
Inclusion and exclusion criteria	Not applicable
Follow up	Follow up hospitalisation on day 35
Main results	There were no radiological changes on chest X-ray, negative SASR-CoV-2 RT-PCR from nasopharyngeal swab. However, the level of IL-6 and alanine aminotransferase activity were increased. The patient reported improving tolerance for physical activity, but he was unable to perform his previous activities with the same strength, e.g., singing In terms of kidney and hepatic injury in the presented patient, it is uncertain whether this was an effect of prescribed treatment (chloroquine, antibiotics and TCZ), hyperinflammation or post hypoxic organ injury

Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding:** No funding was received **Limitations**: None reported
Additional references	N/A

Raman 2020

Bibliographic reference/s	**B, Raman, Mp, Cassar, Em, Tunnicliffe et al. (2020) Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge.**
Questions relevant to?	**Investigations**
Publication status	Preprint
Study type	Prospective cohort
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To investigate the prevalence of persistent multiorgan injury/inflammation and assess the effects of COVID-19 on physical, psychological, and cognitive health and well-being.
Study date	14 March to 25 May 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	UK
Population (including n)	58 patients hospitalised with moderate to severe laboratory-confirmed (SARS-CoV-2 polymerase chain reaction positive) COVID-19 30 uninfected controls group-matched for age, sex, body mass index (BMI) and risk factors (smoking, diabetes, and hypertension) from the community (during the same period) were prospectively enrolled in this study
Time since acute COVID-19 illness	2 to 3 months 4 to 12 weeks grouping
Investigations	• Multiorgan magnetic resonance imaging (MRI) of the brain, lungs, heart, liver, kidneys • 6 min walk test • Cardiopulmonary exercise test (CPET) • Spirometry • Questionnaires • Blood tests
Baseline characteristics	

--	COVID (n=58)	Control (n=30)	P value
Age (years)	55.34 (13.2)	53.9 (12.3)	0.62
Sex	--	--	1.00

<table>
<tr><td></td><td>
<table>
<tr><td>Female</td><td>24/58 (41·4%)</td><td>12/30 (40·0%)</td><td>--</td></tr>
<tr><td>Male</td><td>34/58 (58·6%)</td><td>18/30 (60·0%)</td><td>--</td></tr>
<tr><td>BMI, kg/m^2</td><td>30·8 (26·2 - 36·4)</td><td>27·3 (23·1 - 35·1)</td><td>0·17</td></tr>
<tr><td>Black/Asian and minority ethnic groups</td><td>13/58 (22·4%)</td><td>1/30 (3·3 %)</td><td>0.03</td></tr>
<tr><td>Current/Ex-smoker</td><td>20/58 (34·5%)</td><td>7/30 (23·3%)</td><td>0·34</td></tr>
<tr><td>Type 1 Diabetes</td><td>1/58 (1·7%)</td><td>0/30 (0·0%)</td><td>1</td></tr>
<tr><td>Type 2 Diabetes</td><td>8/58 (13·8%)</td><td>3/30 (10·0%)</td><td>0.74</td></tr>
<tr><td>Hypertension</td><td>22/58 (37·9%)</td><td>9/30 (30·0%)</td><td>0.49</td></tr>
<tr><td>Coronary artery disease</td><td>2/58 (3·4%)</td><td>0/30 (0·0%)</td><td>0.55</td></tr>
<tr><td>Cerebrovascular Disease</td><td>1/58 (1·7%)</td><td>0/30 (0·0%)</td><td>1</td></tr>
<tr><td>Asthma</td><td>20/58 (34·5%)</td><td>6/30 (20·0%)</td><td>0.22</td></tr>
<tr><td>COPD</td><td>3/58 (5·2%)</td><td>0/30 (0·0%)</td><td>0.55</td></tr>
<tr><td>Previous cancer</td><td>2/58 (3·4%)</td><td>3/30 (10·0%)</td><td>0.33</td></tr>
<tr><td>Depression</td><td>3/58 (5·2%)</td><td>1/30 (3·3%)</td><td>1</td></tr>
</table>
</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>No additional criteria reported</td></tr>
<tr><td>Follow up</td><td>Patients were assessed between 2-3 months from disease-onset at median interval of 2·3 months (IQR 2·06 - 2·53)</td></tr>
<tr><td>Main results</td><td>Lung health and exercise tolerance
<table>
<tr><th></th><th>COVID</th><th>Control</th><th>P value</th></tr>
<tr><td>Lung parenchymal abnormalities, %</td><td>32/53 (60·4%)</td><td>3/30 (10·7%)</td><td><0·0001</td></tr>
<tr><td>Significant breathlessness (MRC dyspnoea score ≥2)</td><td>36/53 (64%)</td><td>3/29 (10·3%)</td><td><0·0001</td></tr>
<tr><td>Fatigue (FSS ≥4)</td><td>30/55 (55%)</td><td>5/29 (17·2%)</td><td>0·010</td></tr>
<tr><td>FVC % predicted <80%</td><td>7/56 (12·5%)</td><td>0/28</td><td>0.09</td></tr>
<tr><td>FEV1 % predicted <80%</td><td>6/56 (10·7%)</td><td>1/28 (3·6%)</td><td>0.42</td></tr>
<tr><td>FEV1/FVC</td><td>0·77 (0·73 to 0·80)</td><td>0·75 (0·70 to 0·78)</td><td>0.027</td></tr>
<tr><td>VO2 peak, % of predicted VO2 max < 80%</td><td>28/51 (54·9%)</td><td>2/27(7·4%)</td><td><0·0001</td></tr>
<tr><td>Anaerobic threshold (% of predicted VO2 max)</td><td>40·7 (36.2 to 47.5)</td><td>46.8 (43.3 to 51.3)</td><td>0·0005</td></tr>
<tr><td>VE/VCO2 Slope</td><td>33·4 (29·2 to 40·3)</td><td>28·2 (26·7 to 30·0)</td><td><0·0001</td></tr>
</table>
Brain health and cognition</td></tr>
</table>

- Blinded qualitative assessment (by expert neuroradiologist) of brain MRI at 2 to 3 months did not reveal group differences in burden of small vessel disease, white matter hyperintensities, haemorrhage or ischaemic changes between patients and controls
- Quantitative measurements of grey matter volumes (globally and regionally), white matter volumes and cerebral perfusion were not different between groups
- Compared to controls, COVID-19 patients had a higher T2* signal on susceptibility-weighted imaging in the left and right thalamus and increased mean diffusivity in the left posterior thalamic radiation and sagittal stratum (left and right averaged).

	COVID	Control	P value
(MoCA visuospatial score ≤4	40% (n=NR)	16% (n=NR)	P=0.01
Total MoCA score <26	16/58 (28%)	5/30 (17%)	NR

Cardiac health

- At follow-up, troponin was normal in all patients
- eft ventricular function was normal and comparable between groups
- Right ventricular ejection fraction in patients ranged from 43 to 79%, and on average was normal and not different from controls
- Slice-averaged basal and mid-ventricular native T1, a marker of fibrosis or inflammation on cardiac MRI, was significantly elevated in patients
- Basal myocardial T1 was elevated (> 2 SD from average control T1) in 26% (13/50) of patients.
- Mid myocardial T1 was elevated in 8% (4/51) and average of base and mid myocardial T1 in 24% (12/50) of patients.
- Native T2, a
- Focal fibrosis burden was mildly increased in patients.
- Both basal and mid-ventricular myocardial T1 correlated moderately with CRP and pro-calcitonin in patients, but not in controls (p>0·1). marker of oedema, was not different between patients and controls (p>0.1)

Liver health

- 11% had persistent liver injury (non-specific pattern) on blood tests (n = NR)
- 5/52 (10%) had signs of liver injury evidenced by increased iron-corrected liver T1
- Liver fat, iron and extracellular volume fraction (a marker of diffuse fibrosis) did not differ between group

Haematological system and spleen

- At follow-up, all abnormalities in lymphocyte and platelet count returned to normal
- Patients tended to have higher a CRP (p=0·058)
- Splenic volume and tissue characteristics on MRI did not differ significantly between patients and controls

Kidney health

- 2/58 (3%) of patients had residual renal impairment which was not present prior to COVID-19.
- Creatinine and estimated glomerular filtration rate were not significantly different between patients and controls
- Both average (left and right) renal cortical T1 and corticomedullary differentiation, markers of renal injury/fibro-inflammation, were abnormal in patients
- A significantly higher renal cortical T1 (> 2 SD than control mean) was seen in 29% (15/51) of patients
- Patients with acute kidney injury during admission had a higher average renal cortical T1 (1711±90ms versus 1582±81ms, p=0·001) and lower corticomedullary differentiation (318±59 versus 405±83, p=0·016;) compared to those without.

Mental health and quality of life

--	COVID	Control	P value
GAD-7	2·0 (0·0 - 7·5)	0·5 (0·0 - 4·3)	0·066
Moderate or worse anxiety	--	--	0·012
<6 (None - Mild)	37/57 (64·9%)	27/30 (90·0%)	--
≥6 (Moderate or more)	20/57 (35·1%)	3/30 (10·0%)	--
PHQ-9	3·0 (1·0 - 7·5)	1·5 (0·0 - 5·0)	0·009
Moderate or worse mood symptoms	--	--	0·036
<6 (None - Mild)	35/57 (61·4%)	25/30 (83·3%)	--
≥6 (Moderate or more)	22/57 (38·6%)	5/30 (16·7%)	--
SF-36 Domains	--	--	--
Physical Functioning	65·0 (45·0 to 90·0)	92·5 (83·8 to 100·0)	<0·0001
Role Limitations Due to Physical Health	25·0 (0·0 to 75·0)	100·0 (100·0 to 100·0)	<0·0001
Role Limitations Due to Emotional Health	33·3 (0·0 to 100·0)	100·0 (100·0 to 100·0)	<0·0001
Energy	45·0 (25·0 to 70·0)	65·0 (55·0 to 80·0)	<0·0001
Emotional wellbeing	76·0 (62·0 to 88·0)	84·0 (72·0 to 92·0)	0·044
Social functioning	50·0 (37·5 to 87·5)	100·0 (62·5 to 100·0)	0·0002
Pain	67·5 (35·0 to 90·0)	85·0 (67·5 to 100·0)	0·003
General health	68·8 (43·8 to 81·3)	75·0 (60·9 to 87·5)	0·022

Summary

	A significant proportion of COVID-19 patients discharged from hospital experience ongoing symptoms of breathlessness, fatigue, anxiety, depression, and exercise limitation at 2-3 months from disease-onset. Persistent lung and extra-pulmonary organ MRI findings are common. In COVID-19 survivors, chronic inflammation may underlie multiorgan abnormalities and contribute to impaired quality of life
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding:** NIHR Oxford and Oxford Health Biomedical Research Centres, British Heart Foundation Centre for Research Excellence, UKRI, Wellcome Trust, British Heart Foundation. **Limitations:** • Small sample size of this single-centre study, its cross-sectional design and lack of correction for multiple comparisons are important limitations which curtail the generalisability of our findings and accuracy of prevalence estimates • The lack of pre-COVID imaging also limits our ability to make causal inferences about the mechanism of multiorgan abnormalities in patients recovering from COVID-19 infection • Controls in our study were not hospitalised, thus group differences in symptomatology, mental health, exercise capacity and quality of life may not be specific to COVID-19
Additional references	ClinicalTrials.gov (NCT04510025)

Savastano 2020

Bibliographic reference/s	**Savastano, Alfonso, Crincoli, Emanuele, Savastano, Maria Cristina et al. (2020) Peripapillary Retinal Vascular Involvement in Early Post-COVID-19 Patients. Journal of clinical medicine 9(9)**
Questions relevant to?	**Signs and symptoms, investigation**
Publication status	Published
Study type	Case control
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To investigate peripapillary vascular impairment in post SARS-CoV-2 patients compared to controls, analysing OCTA imaging of the RPCP and structural OCT parameters
Study date	1 March 2020 to 1 June 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Italy
Population (including n)	The post-COVID-19 group included patients who contracted and successively recovered from SARS-CoV-2 infection (n=80). The CONTROL group consisted of 30 patients without previous or current SARS-CoV-2 infection.

Time since acute COVID-19 illness	Average 60.3 days
Investigation	Structural OCT (optical coherence tomography) and OCTA (optical coherence tomography angiography)

Baseline characteristics

Variable	Post-COVID-19	Controls	*p*
Age (years)	52.9 ± 13.5	48.5 ± 13.4	0.71
Sex	M = 46/80 (57.5%) F = 34/80 (42.5%)	M = 13/30 (43.3%) F = 17/30 (56.6%)	0.26
Systemic arterial hypertension	19/80 (23.8%)	3/30 (10%)	0.03
Diabetes	34/80 (42.5%)	0/30 (0%)	<0.001
Autoimmune or inflammatory diseases	19/80 (23.8%)	0/30 (0%)	<0.001
Myopia > 1D	11/80 (13.8%)	(13.3%)	0.87
IOP	16.2 ± 1.5 mmHg	14.4 ± 2.1 mmHg	0.34
Red/dry eye during infection	36/80 (45%)	--	--
Days since symptoms onset	60.3 ± 13.6	--	--
Days since hospital discharge	36.1 ± 12.9	--	--
ICU admission	5/80 (6.25%)	--	--
Oxygen therapy	33/80 (41.25%)	--	--
Non-invasive ventilation	7/80 (8.8%)	--	--
Pulmonary embolism	2/80 (2.5%)	--	--
Venous thrombosis	2/80 (2.5%)	--	--
Hydroxychloroquine	55/80 (68.8%)	--	--
Lopinavir + ritonavir	27/80 (33.8%)	--	--
Darunavir + ritonavir	35/80 (43.8%)	--	--
Azithromycin	28/80 (35%)	--	--
Heparin	33/80 (41.3%)	--	--
Antiplatelet therapy	6/80 (7.5%)		
Corticosteroids	4/80 (5%)		

Inclusion and exclusion criteria	Inclusion criteria were: two successive oropharyngeal swabs resulted negative for the SARS-CoV-2 genome, absence of symptoms suggestive of SARS-CoV-2 infection during the previous months, and blood detection of anti-SARS-CoV-2 IgGs resulted negative. Exclusion criteria for both groups were: choroidal atrophy, high myopia, exudativeAMD, previous episode of central serous chorioretinopathy, glaucoma, acquired and hereditary optic neuropathy, hereditary retinal diseases, demyelinating disorders, neurodegenerative disorders, and keratoconus. Furthermore, image quality was mandatory and was defined acceptable if > 7/10.
Follow up	One month after infection
Main results	lower RPCP-PD value in post-COVID-19 group compared to the control group ($p < 0.04$) was observed. This difference was further confirmed by the binary logistic regression analysis including all potential confounders ($p < 0.039$). None of the other outcome measures showed statistically significant differences between the two groups. Within the post-COVID-19 group, patients affected by systemic arterial hypertension were characterized by a statistically relevant reduction of the RPCP-FI ($p < 0.001$). Moreover, age distribution showed an inverse linear correlation with both RPCP-FI ($p < 0.001$) and RPCP-PD ($p < 0.01$). Furthermore, patients treated with lopinavir + ritonavir during SARS-CoV-2 infection showed both a lower RPCP-FI ($p < 0.01$) and a lower RPCP-PD ($p < 0.01$) compared to the other patients in the POST-COVID-19 group. A similar result was demonstrated in patients treated with antiplatelet therapy during hospital recovery. Indeed, in these patients, RPCP-FI and RPCP-PD were statistically lower than those not treated (respectively $p = 0.004$ and $p = 0.003$).
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	Limitations The selected sample of post-COVID-19 patients is not fully representative of the average post-COVID-19 population of patients. A larger cohort of healthy controls would be needed to increase the power of the study.
Additional references	N/A

Savarraj 2020

Bibliographic reference/s	**Savarraj, Jude PJ, Burkett, Angela B., Hinds, Sarah N. et al. (2020) Three-month outcomes in hospitalized COVID-19 patients. medRxiv: 2020101620211029**
Questions relevant to?	**Investigations**
Publication status	Preprint (not full publication)
Study type	Prospective cohort
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To characterize long-term neurologic outcomes after COVID-19

<table>
<tr><td>Study date</td><td>May 2020 to July 2020</td></tr>
<tr><td>COVID-19 prevalence (high/low) if reported</td><td>Not reported</td></tr>
<tr><td>Country/ Setting</td><td>Houston, Texas, USA</td></tr>
<tr><td>Population (including n)</td><td>48 patients</td></tr>
<tr><td>Time since acute COVID-19</td><td>3 months
4 to 12 weeks grouping</td></tr>
<tr><td>Investigations</td><td>Telephone questionnaires to assess functional, cognitive, and psychiatric symptoms.
Functional outcome was evaluated using the modified Rankin Score (mRS).
Cognitive status was evaluated using the brief neurocognitive screening test (BNST).
Depression symptoms were evaluated using the Patient Health Questionnaire (PHQ-9).
Anxiety symptoms were assessed using the Generalized Anxiety Disorder (GAD-7).
Pain, fatigue and sleepiness were evaluated using the Pain, Enjoyment of life and General activity (PEG), the Fatigue Severity Scale (FSS) and Epworth Sleepiness Scale (ESS).
Post-traumatic stress disorder was evaluated using the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5).</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><td>--</td><td>N=48</td></tr>
<tr><td>Age (mean, SD)</td><td>50(17)</td></tr>
<tr><td>Sex (Female,%)</td><td>23(48)</td></tr>
<tr><td>Ethnicity (Hispanic, %)</td><td>32(67)</td></tr>
<tr><td>Obesity (n,%)</td><td>25(52)</td></tr>
<tr><td>Diabetes (n,%)</td><td>18(38)</td></tr>
<tr><td>Hypertension (n,%)</td><td>24(50)</td></tr>
<tr><td>Smoking (n,%)</td><td>5(11)</td></tr>
<tr><td>COPD (n,%)</td><td>2(4)</td></tr>
<tr><td>CCI (median, IQR)</td><td>2[1-3]</td></tr>
<tr><td>WHO Classification (Severe, %)</td><td>21(44)</td></tr>
</table></td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Inclusion criteria:
Laboratory-confirmed SARS-CoV-2 infection by real-time PCR and admission to the hospital for COVID-19
All hospitalized patients were either hospitalized mild (WHO scale 4, requiring oxygen by mask or nasal cannula) or severe (WHO scale ≥ 5, requiring at least high–flow oxygen)
Exclusion criteria:
Subjects with diagnosis of pre-morbid conditions interfering with outcome domains being assessed</td></tr>
<tr><td>Follow up</td><td>3 months</td></tr>
<tr><td>Main results</td><td>At follow up:<table>
<tr><td>Outcomes</td><td>N, (%)</td><td>Responses</td></tr>
<tr><td>Any neurologic symptom</td><td>34(71%)</td><td>48</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Fatigue symptoms (FSS)</td><td>19(42%)</td><td>45</td></tr><tr><td>Post-traumatic stress disorder (PC-PTSD-5)</td><td>12(29%)</td><td>44</td></tr><tr><td>Functional outcome (mRS)</td><td>10(21%)</td><td>48</td></tr><tr><td>Sleepiness (ESS)</td><td>7(17%)</td><td>42</td></tr><tr><td>Cognitive Deficit (BNST)</td><td>5(12%)</td><td>43</td></tr><tr><td>Depression Symptoms (PHQ-9)</td><td>5(11%)</td><td>45</td></tr><tr><td>Anxiety (GAD-7)</td><td>4(9%)</td><td>45</td></tr><tr><td>Pain (PEG)</td><td>29(64%)</td><td>45</td></tr></table> Neither the maximum C-reactive protein levels [(137 (73) v 153 (92); p=0.59] nor the clinical severity [WHO≤4 v WHO>5, p=0.58] were associated with 3-month symptoms. Our preliminary findings suggest the importance of investigating long-term and rationalizes the need for further studies investigating the neurologic outcomes after COVID-19.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	No targeted funding reported
Additional references	N/A

Sonnweber 2020

Bibliographic reference/s	**Sonnweber, T., Boehm, A., Sahanic, S. et al. (2020) Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. Respiratory Research 21(1): 276**
Questions relevant to?	**Risk factors, investigations**
Publication status	Published
Study type	Cohort (prospective)
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To analyse persisting alterations of iron metabolism in survivors of COVID-19 aiming to evaluate their prevalence and their association with persisting pathologic processes linked to COVID-19
Study date	Not reported
COVID-19 prevalence	Not reported

(high/low) if reported	
Country/ Setting	Austria
Population (including n)	109 patients who previously suffered from mild to critical COVID-19
Time since acute COVID-19	Approximately 2 months 4 to 12 weeks grouping
Investigations	• Medical history assessment • Structured COVID-19 symptom questionnaire • Performance evaluation (e.g. 6-min walking test) • Blood sampling and analysis • Computed tomography
Baseline characteristics	**Age (years):** 58 (SD 14) **Female:** 44/109 (44%) **Median BMI**: 26.7 (SD 4.8) **Comorbidities**: None 21/109 (19%); CVD 44/109 (40%); Hypertension 32/109 (29%); Pulmonary disease 21/109 (19%), Endocrine disease 49/109 (45%); CKD 7/109 (6%); Chronic liver disease 6/109 (6%); Malignancy 16/109 (15%); Immunodeficiency 9/109 (8%) **COVID-19 disease severity:** Mild (outpatient treatment) 22/109 (20%); moderate (inward treatment without respiratory support, 34/109 (31%)]; severe (inward treatment with additional oxygen therapy, 35/109 (32%); 18/109 (17%) had critical disease with the need for mechanical ventilation at an intensive care unit (ICU)
Inclusion and exclusion criteria	• 18 years and older • Diagnosis of COVID-19 was based on typical clinical symptoms and a positive RT-PCR SARS-CoV-2 result obtained from a nasopharyngeal or oropharyngeal swab.
Follow up	60 days (SD 12) days after the onset of first COVID-19 symptoms
Main results	At follow up: **Iron deficiency (ID) and anaemia** • ID: Still present in 30% (n not reported; approx 33 patients) • Of these 13% had absolute ID and 17% had functional ID • Anaemia: 10/109 (9.2%) • Anaemia was more frequent in males (12%) than females (5%) • Disease severity strongly correlated with the prevalence of anaemia, as 90% of anaemic patients previously had severe to critical COVID-19 **Post-acute signs of hyperinflammation, coagulopathy and hyperferritinaemia** • Hyperferritinaemia: Still present in 38% (n not reported; approx 35 patients) • Hyperferritinaemia was far more frequent in males (48%) compared to females (23%) (p=0.009) • Serum ferritin strongly correlated with serum hepcidin concentrations, but not with markers of cellular iron demand (e.g. soluble transferrin receptor) or markers of inflammation such as CRP or IL6 • Serum hepcidin was positively correlated with TSAT (ρ=0.328, p<0.01), and negatively correlated with sTFRF index (ρ=−0.439, p<0.01), whereas markers of inflammation such as IL6 or CRP were not related to hepcidin levels

	CT Evaluation • In patients with persisting hyperferritinaemia pathological CT findings were more frequent and more severe as compared to those with normal ferritin levels **6-min walking test** • In a subgroup of 23 study participants, who were evaluated with a six-minute walking test (SMWT), hyperferritinaemia was associated with a decreased walking distance • In comparison to individuals with normal ferritin levels, patients with hyperferritinaemia did not significantly differ in age, gender, frequency of co-morbidities or signs of inflammation, which would otherwise explain the difference in walking performance **Summary** COVID19 is associated with prolonged alterations of iron homeostasis which may be linked to severe initial disease but also persisting radiological pathologies in the lung and impaired physical performance.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding:** Austrian National bank fund an**d** "Verein zur Förderung von Forschung und Weiterbildung in Infektiologie und Immunologie, Innsbruck (G.W.)" **Limitations:** None reported currently but this is an ongoing study
Additional references	Study ongoing (ClinicalTrials.gov number, NCT04416100) CovILD cohort study

Valiente De-Santis 2020

Bibliographic reference/s	**Lucia Valiente-De, Santis, Ines, Perez-Camacho, Beatriz, Sobrino et al. (2020) Clinical and immunoserological status 12 weeks after infection with COVID-19: prospective observational study. medRxiv**
Questions relevant to?	**Risk factors, prevelance, investigations**
Publication status	Preprint
Study type	Prospective cohort
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	A multidisciplinary follow-up of all COVID-19 patients seen at a hospital to determine their functional and immunoserological status, assess the presence of possible sequelae and evaluate their course.
Study date	14 March to 15 April
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	Spain
Population (including n)	108 patients with previous acute SARS-CoV-2 infection contacted by telephone

<table>
<tr><td>Time since acute COVID-19</td><td>12 weeks after acute phase
(4 to 12 weeks grouping)</td></tr>
<tr><td>Investigations</td><td>• Blood test
• Chest radiograph
• Chest CT
• Spirometry
• Serological test</td></tr>
<tr><td>Baseline characteristics</td><td>During acute episode
<table>
<tr><th>Characteristic</th><th>Total (N=108)</th><th>Symptomatic (n=82)</th><th>Asymptomatic (n=26)</th><th>P value</th></tr>
<tr><td>Age > 65 years</td><td>29 (26.9%)</td><td>17 (20.7%)</td><td>12 (46.2%)</td><td>0.011</td></tr>
<tr><td>Female</td><td>60 (55.6%)</td><td>47 (57.3%)</td><td>13 (50%)</td><td rowspan="2">NS</td></tr>
<tr><td>Male</td><td>48 (44.4%)</td><td>35 (42.7%)</td><td>12 (50%)</td></tr>
<tr><td>Health care worker</td><td>30 (27.8)</td><td>28 (34.1)</td><td>2 (7.7)</td><td>0.009</td></tr>
<tr><td>Mild acute symptoms</td><td>64 (59.3)</td><td>48 (58.5)</td><td>16 (61.5)</td><td rowspan="2">NS</td></tr>
<tr><td>Severe acute symptoms</td><td>44 (40.7)</td><td>34 (41.5)</td><td>10 (38.5)</td></tr>
<tr><td>ICU during acute episode,</td><td>4 (3.7)</td><td>3 (3.7)</td><td>1 (3.8)</td><td>NS</td></tr>
</table></td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Confirmed case (symptoms compatible with COVID-19 and positive result for the SARS-CoV-2 polymerase chain reaction (PCR) in respiratory samples, or a suspected case (symptoms compatible with COVID-19 and negative PCR)</td></tr>
<tr><td>Follow up</td><td>12 weeks</td></tr>
<tr><td>Main results</td><td>Symptoms 12 weeks after the acute episode
<table>
<tr><th>Symptom</th><th>N= 82 (75.9%)</th></tr>
<tr><td>Dyspnoea</td><td>60 (55.6)</td></tr>
<tr><td>Asthenia</td><td>48 (44.9)</td></tr>
<tr><td>Cough</td><td>28 (25.9)</td></tr>
<tr><td>Chest pain</td><td>28 (25.9)</td></tr>
<tr><td>Palpitations</td><td>24 (22.2)</td></tr>
<tr><td>Headache</td><td>10 (9.3)</td></tr>
<tr><td>Anosmia</td><td>10 (9.3)</td></tr>
<tr><td>Dysgeusia</td><td>5 (5.6)</td></tr>
<tr><td>Fever</td><td>4 (3.7)</td></tr>
<tr><td>Chills</td><td>4 (3.7)</td></tr>
<tr><td>Arthomyalgia</td><td>3 (2.8)</td></tr>
<tr><td>Hair loss</td><td>3 (2.8)</td></tr>
<tr><td>Diarrhoea</td><td>2 (1.9)</td></tr>
<tr><td>Anxiety</td><td>7 (6.4)</td></tr>
<tr><td>Sadness</td><td>7 (6.4)</td></tr>
<tr><td>Insomnia</td><td>2 (1.9)</td></tr>
<tr><td>Loss of memory</td><td>2 (1.9)</td></tr>
<tr><td>Difficulty concentrating</td><td>2 (1.9)</td></tr>
</table></td></tr>
</table>

Main results of the laboratory studies

Parameters	--
Leukopenia (leukocytes <4000)	6 (5.8)
Lymphopenia (lymphocytes <900)	7 (6.8)
CD4/CD8 ratio <1	6 (5.8)
D-dimer >500 ng/mL	32 (31.3)
LDH > 246 U/L	7 (6.8)
CRP >2.9 mg/dL	25 (24.5)
Ferritin >252 ng/mL	9 (8.8)
IL-6 >40 pg/mL	4 (3.9)
IgM <40 mg/dL	6 (5.8)
IgG <600 mg/dL	11 (10.7)

Chest radiograph at 12 weeks

--	N = 89 (82.4%)
Normal	56 (62.9%)
Favourable evolution	24 (26.0%)
Persistent or worsened	9 (10.1%)

Chest CT scan

--	N = 37 (41.5%)
Normal	7 (18.9%)
Pathological	24 (64.9%)

Spirometry

--	N = 32 (29.6%)
Normal	23 (71.9%)
Obstructive pattern	4 (12.5%)
Mixed pattern	2 (6.3%)

None of the baseline characteristics was associated with radiological or respiratory function changes.

Serological response

Antibodies, N (%)	Total	Symptomatic	Asymptomatic	P value
IgM positive	60 (57.1)	45 (56.3)	15 (60)	NS
IgM negative	35 (33.3)	28 (35.5)	7 (28)	NS
IgM indeterminate	10 (9.5)	7 (8.8)	3 (12)	NS
IgG positive	103 (98.1)	79 (98.8)	24 (96)	NS
IgG negative	2 (9.1)	1 (1.3)	1 (4)	NS
IgM and IgG positive	58 (55.5)	44 (55)	14 (56)	NS

Risk factors for persistence of symptoms

	<table><tr><td>Variable</td><td>OR multivariate analysis (95% CI)</td><td>P value</td></tr><tr><td>Age >65 years</td><td>0.33 (0.12-0.87)</td><td>0.026</td></tr><tr><td>Health-care worker</td><td>4.79 (1.02-22.38)</td><td>0.046</td></tr><tr><td>Mild or severe acute episode</td><td>--</td><td>0.087</td></tr><tr><td>Charlson > 3</td><td>--</td><td>0.130</td></tr><tr><td>D-dimer >500 ng/mL</td><td>--</td><td>0.317</td></tr><tr><td>Specific treatment for COVID-19</td><td>--</td><td>0.435</td></tr></table>The persistence of symptoms in patents with COVID is usual 12 weeks after the 27 acute episode, especially in patients <65 years and health-care workers. All our patients had 28 developed antibodies by 12 weeks.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	No limitations reported by author
Additional references	N/A

Zhao 2020

Bibliographic reference/s	**Zhao, Yu-Miao, Shang, Yao-Min, Song, Wen-Bin et al. (2020) Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 25: 100463**
Questions relevant to?	**Investigations, risk factors**
Publication status	Published
Study type	Cohort (retrospective)
Quality	Low quality evidence CASP critical appraisal rating: High risk of bias
Objective	To investigate the relationship between the clinical characteristics and pulmonary function or CT scores 3 months after recovery
Study date	Jan 20 2020 to Feb 24 2020
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	China
Population (including n)	55 previously hospitalised COVID-19 survivors
Time since acute COVID-19	Up to 3 months 4 to 12 weeks grouping
Investigations	• Chest CT scan

<table>
<tr><td></td><td>

Pulmonary function test
SARS-COV-2 IgG test

</td></tr>
<tr><td>Baseline characteristics</td><td>See results</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Follow up</td><td>The final follow-up evaluation was carried out at the time ranged from 64 to 93 days after discharge from hospital</td></tr>
<tr><td>Main results</td><td>
At follow up:

The presenting symptoms included gastrointestinal (GI) symptoms (30.91%), headache (18.18%), fatigue (16.36%), exertional dyspnoea (14.55%), as well as cough and sputum (1.81%) (n not reported).
Although there was a significant improvement in self-rating of severity of olfactory and gustatory loss, 2 female patients still experienced a decrease sense of taste during follow-up period.
All 55 patients had returned to their original work

CT scan

Radiological abnormalities were detected in 39 patients (70.91%)

<table>
<tr><td></td><td>Normal CT (n=16)</td><td>Abnormal CT (n = 39)</td><td>P value</td></tr>
<tr><td>Age, (years)</td><td>37.13 ± 11.73</td><td>52.05 ± 15.05</td><td>0.001</td></tr>
<tr><td>Sex, (% female)</td><td>37.50%</td><td>43.59%</td><td>0.643</td></tr>
<tr><td>Incubation period, d</td><td>4.50 (2.50 to 6.00)</td><td>6.00 (4.00 to 9.00)</td><td>0.046</td></tr>
<tr><td>Hypertension</td><td>0</td><td>6</td><td>0.236</td></tr>
<tr><td>CHD</td><td>0</td><td>2</td><td>0.897</td></tr>
<tr><td>Diabetes mellitus</td><td>0</td><td>2</td><td>0.897</td></tr>
</table>
Compared with survivors with normal CT, on admission, survivors with abnormal CT had lower albumin level (41.76 ±3.31 vs. 44.64 ±3.83, P = 0.007), lower serum sodium concentration (140.60 [137.10-142.00] vs. 141.80 [137.10-142.00], P = 0.038), higher urea nitrogen level (4.73 [3.96-5.32] vs. 3.86 [3.03-4.23], P = 0.000).
Admission values of glucose, hsCRP, and Ddimer concentration were also significantly higher in the COVID-19 survivors with abnormal CT.
Based on these variables, further multivariate analysis using the forward method was performed, and it was found that the increase of urea nitrogen was the independent risk factor associated with the presence of CT abnormalities (P = 0.046, OR 7.149, 95% CI 1.038 to 49.216)

Pulmonary function

Lung function abnormalities were detected in 14 patients (25.45%).
Anomalies were noted in TLC of 4 patients (7.27%), FEV1 of 6 patients (10.91%), FVC of 6 patients (10.91%), DLCO of 9 patients (16.36%), and small airway function in 7 patients (12.73%).

</td></tr>
</table>

	<table><tr><td>--</td><td>DLCO normal group (n = 46)</td><td>DLCO impaired group (n = 9)</td><td>P value</td></tr><tr><td>Age, (years)</td><td>44.99 ± 14.70</td><td>52.57 ± 18.91</td><td>0.095</td></tr><tr><td>Sex, (% female)</td><td>19 (41.30%)</td><td>4 (44.44%)</td><td>0.861</td></tr><tr><td>Incubation period, d</td><td>6.00 (4.00-7.25)</td><td>6.00 (4.50-7.50)</td><td>0.503</td></tr></table> The median TBIL concentration in the abnormal DLCO group (13.20 [9.65-16.35]) was obviously higher than the normal DLCO group (8.90 [7.28-13.38]) (P = 0.048). Levels of urea nitrogen (abnormal DLCO group: 5.14 [4.68-6.91] vs. normal DLCO group: 4.25 [3.73-4.97]), D-dimer (abnormal DLC group: (0.42 ± 0.21) vs. normal DLCO group (0.23 ± 0.17) were higher in the DLCO-impaired group than in the DLCO-normal group (P < 0.05). In DLCO-impaired group, blood level of prothrombin time (15.20 [11.40-16.35]) was higher compared with that in DLCO-normal group (12.25 [10.75-14.55]). Levels of ALB were significantly decreased in abnormal DLCO group (40.38 ± 3.12) g/L compared with normal DLCO group (43.03 ± 3.66) g/L. No other significant differences were found between patients with normal and abnormal lung function. Higher level of D-dimer at admission were associated with DLCO% predicted < 80% (P = 0.031, OR 1.066, 95% CI 1.006 to 1.129) **Summary** Radiological and physiological abnormalities were still found in a considerable proportion of COVID-19 survivors without critical cases 3 months after discharge. Higher level of D-dimer on admission could effectively predict impaired DLCO after 3 months discharge. It is necessary to follow up the COVID-19 patients to appropriately manage any persistent or emerging long-term sequelae.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	**Funding**: Key Scientific Research Projects of Henan Higher Education Institutions **Limitations:** • Small sample size • Patients were non-critical COVID-19 patients so may not be generalisable to critical patients
Additional references	N/A

Greenhalgh 2020a

Bibliographic reference/s	**Greenhalgh, T; Ladds, E; Knight, M 'Long Covid': evidence, recommendations and priority research. Written evidence (COV0050)**
Questions relevant to?	Risk factors, signs and symptoms, investigations, interventions, referral, service models.
Publication status	Published
Study type	Report

Objective	Not stated
Study date/	23/9/20
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	UK
Population (including n)	Patients with long COVID falling into three groups: A. People who were very ill (perhaps on ITU) with acute COVID-19 and now have significant long-term organ damage (e.g. lungs, heart, brain, kidneys) along with weakness and debility. B. People who were not so ill in the acute stage but who also now have some evidence of long-term organ damage; and C. People who have persistent symptoms after COVID-19 but who do not have persisting organ damage.
Time since acute COVID-19 illness	3 weeks or more
Interventions/ Prognostic factors	See main recommendations
Baseline characteristics	Not applicable
Inclusion and exclusion criteria	Not applicable
Follow up	3 weeks or more
Main recommendations and research priorities	A 4-tier clinical service should be developed: a) Tier 1: resources and support for self-care. • Accurate information about the disease and its likely course • Resources to support self-care (including online programmes) • Careful pacing and self-monitoring towards recovery b) Tier 2: generalist care including a therapeutic relationship in general practice and a community-based interdisciplinary rehabilitation service led by allied health professionals. • Therapeutic relationship with a generalist clinician Full history, clinical examination, and functional assessment • Confirm that long COVID is the likely or possible diagnosis (even in the absence of a positive test), and document on medical record • Basic tests (e.g. bloods, ECG, X-rays, pulse oximetry) if appropriate to exclude alternative diagnoses (e.g. sepsis) and rule out serious complications. Note: not all patients will need such tests • Generalist rehabilitation support (remote or face to face) • Ongoing monitoring and support (e.g. by telephone, video, or in-person check-ups) as needed • Management of other long-term conditions c) Tier 3: specialist care including system-based investigation, management and rehabilitation. • Dedicated Covid-19 rehabilitation clinic (usually respiratory but sometimes neuro- or cardiac) • Personalised rehabilitation plan with (e.g.) breathing exercises, supervised pacing, and psychological support • Referral to other specialties as appropriate e.g. cardiology, neurology, haematology, psychiatry • Testing according to specialist guidelines (e.g. CT, MRI)

	• Dialogue and agreed division of responsibility between secondary (and tertiary care) d) Tier 4: specialist management of specific complications. • Inpatient admission Priority areas for research: a) Basic science studies on upstream causes, including genetics and metabolomics. b) Observational studies of long-term outcome, especially in non-hospitalised patients. c) Trials of interventions, including different rehabilitation protocols. d) Studies to optimise and evaluate the service model, including virtual wards and remote care. e) Interdisciplinary studies of how socio-economic and racial disadvantage affects the development, course and outcome of long COVID.
Comments (e.g. source of funding, statistical analysis, any major limitations, or issues with studies)	This report was submitted as written evidence to the parliamentary select committee.
Additional references	N/A

Appendix 7 Excluded studies

Please refer to the full list of excluded studies for this guideline.

Appendix 8 Supporting evidence

Spruit 2020

Bibliographic reference/s	**Spruit, M.A., Holland, A.E., Singh, S.J. et al. (2020) COVID-19: Interim Guidance on Rehabilitation in the Hospital and Post-Hospital Phase from a European Respiratory Society and American Thoracic Society-coordinated International Task Force. The European respiratory journal**
Questions relevant to?	**Investigations, Interventions**
Publication status	Published
Study type	Guideline
Objective	To make interim recommendation for the rehabilitation in the hospital and post-hospital phase in COVID-19 and post-COVID-19 patients
Study date/	Survey administered 27/4/20-11/5/20
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	International
Population (including n)	Patients with COVID-19 or post-COVID-19 (no empirical data)
Time since acute COVID-19	6-8 weeks following discharge
Interventions/ Prognostic factors	Comprehensive assessment of rehabilitation needs including physical as well as mental aspects 6-8 weeks after discharge. Multidisciplinary rehabilitation with attention for skeletal muscle and functional as well as mental restoration.
Baseline characteristics	Not applicable
Inclusion and exclusion criteria	Not applicable
Follow up	6-8 weeks after discharge
Main results	Relevant Recommendations: 5. Patients with COVID-19 should have a formal assessment of physical and emotional functioning at 6-8 weeks following discharge, to identify unmet rehabilitation needs. 6. Follow up of a hospitalised patient with COVID-19 should include the core outcomes set for survivors of acute respiratory failure at 6-8 weeks following hospital discharge. 7. Follow up of a hospitalised patient with COVID-19 should include measures of respiratory function at 6-8 weeks following hospital discharge

	8. Follow up of a hospitalised patient with COVID-19 should include measures of exercise capacity at 6-8 weeks following hospital discharge 9. COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge (e.g., multiple treatable traits) should receive a comprehensive rehabilitation program, compared to no rehabilitation program. 10. COVID-19 survivors with pre-existing/ongoing lung function impairment at 6-8 weeks following hospital discharge should receive a comprehensive pulmonary rehabilitation program consistent with established international standards, compared to no pulmonary rehabilitation program 11. COVID-19 survivors with loss of lower limb muscle mass and/or function at 6-8 weeks following hospital discharge should receive a muscle strengthening program, rather than no strengthening program 12. COVID-19 survivors with loss of lower-limb muscle mass at 6-8 weeks following hospital discharge should receive nutritional support rather than no nutritional support. 13. COVID-19 survivors with symptoms of psychological distress (using questionnaires) at 6-8 weeks after discharge from the hospital should receive a formal psychological assessment.
Comments (e.g. source of funding, statistical analysis, any major limitations or issues with studies)	Consensus based recommendations from survey of experts. Some recommendations relate to acute phase.
Additional references	None relevant – mainly relate to acute phase or non_COVID studies