

Bilaga 3 till rapport

Långvariga symtom vid covid-19/ Long-term symptoms of Covid-19 Rapport 319 (2020)

Bilaga 3 Inkluderade studier/ Appendix 3 Included studies

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Beskrivning av studier om långvariga symtom (fråga 1)/Studies on long-term symptoms (question 1).

Author Year Ref	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Akter et al. 2020 [1] Bangladesh	Patients (n=734) who had tested negative for covid-19. Mean age: Male: 75.9% Follow-up: 4 weeks after recovery.	A multicenter retrospective cohort study based on self-reported outcome-data. Also stratified as patients with (n=146) or without (n=588) diabetes.	To identify the frequency of diabetic individuals within a cohort of covid-19 diagnosed individuals being provided with medical attention at different health care facilities and to compare the clinical manifestations and long-term complications among the diabetic and non-diabetic COVID-19 patients attending those healthcare facilities.	Mobility (Bedridden, problems walking, no problems). Self-care (Unable, some problems, no problems) Pain/discomfort (Extreme, moderate or no) Anxiety/depression (Extreme, moderate, no) Sleep (Yes/no) Panic attack (Yes/no) Memory loss (Extreme, moderate, no)	Covid-19 patients with diabetes were more likely to be symptomatic and within higher age groups. Cohorts with diabetes exhibited and nested more comorbidities and biochemical aberrations than cases without diabetes. Some post-covid complications were observed significantly among recovered covid-19 patients with diabetes.	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
				Hairfall (Yes/no)		
Boscolo-Rizzo et al 2020 [2] Italy	Mildly symptomatic (n=183) SARS-CoV-2 positive patients. Mean age: Unknown Male: Unknown Follow-up: 4- and 8 weeks.	Prospective single-center case-series without control group.	To assess the prevalence of covid-19 related symptoms among a case series of mildly symptomatic homeisolated subjects with confirmed SARS-CoV-2 infection, with special emphasis to self-reported new onset of altered sense of smell or taste.	Prevalence of symptoms (Yes/No) Prevalence and intensity of altered sense of smell or taste.	Although most patients recovered from loss of smell and taste, this remains the most prevalent long-lasting symptom followed by fatigue and breathing problems. No symptoms at baseline are predictive of persistently altered chemosensory function.	Moderate
Carfi et al. 2020 [3] Italy	Patients (n=143) that had been discharged from hospital after recovery from covid-19. Mean age: 56.5 Male: 47%	Retrospective cross-sectional study without control group and with self-reported data.	To assess persistent symptoms in patients who were discharged from the hospital after recovery from covid-19	Persistent symptoms (None/1 or 2/3 or more). Type of symptoms	This study found that in patients who had recovered from covid-19, 87.4% reported persistence of at least 1	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
	Mean days since symptom onset: 60,3			Days since symptoms onset. Days since discharge Worsened quality of life (Yes/No)	symptom, particularly fatigue and dyspnea.	
Carvalho et al. 2020 [4] France	Patients (n=150) with non-critical covid-19 presentations. Mean age: 49 years Male: 44% Follow-up: 2 months after symptom onset.	Single-center prospective cohort study.	To highlight the initial key symptoms of covid-19 to alert practitioners and patients of the risk of longer symptom duration in individuals with non-critical covid-19.	Persistence of symptoms (yes/no) - Fever (>38 degrees) - Dyspnea - Chest pain - Abnormal auscultation - Digestive disorders - Weight and weight loss - Anosmia - Palpitations - Arthralgia - Cutaneous signs - Sick leave	Up to 2 months after symptom onset, two thirds of adults with noncritical covid-19 had complaints, mainly anosmia/ageusia, dyspnea or asthenia. A prolonged medical follow-up of patients with covid-19 seems essential, whatever the initial clinical presentation.	Low

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Chang et al. 2020 [5] Korea	Patients (n = 107) diagnosed with COVID-19, through RT-PCR who had been hospitalized, treated and discharged from a university hospital in Daegu, Korea, between February and April 2020. Of the 107 patients, 43 had missing contact information, did not answer their phones, or refused to participate. Mean age: PTSD group 58, Non PTSD group 54 Male: 44% Mean follow-up: PTSD group 77 days.	Single-center cohort study.	To determine the prevalence of PTSD among patients with COVID-19 who were treated in a university hospital in Daegu, Korea	Presence of PTSD defined as: a score of ≥33 using The Post- traumatic Stress Disorder Checklist-5 (PCL-5),)	The prevalence rate of PTSD was 20.3% in patients with COVID-19 who had been hospitalized, treated and discharged. Accordingly, clinicians should be aware of the high possibility of PTSD among COVID-19 patients.	Moderate
Chiesa- Estomba et al.	Patients (n=751) with confirmed covid-19. All patients had at least 30 days	A prospective multicenter cohort study	To assess the prevalence of post-viral olfactory	Loss of smell (Yes/No/Partial)	According to our results, at this relatively early point in the pandemic,	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
2020. [6] Spain	of follow-up after their last negative test. Mean age: 41 Male: 36% Mean follow-up: 47 days	without control group	dysfunction for patients with covid-19.	Duration of olfactory dysfunction Treatments used	subjective patterns of recovery of olfactory dysfunction in covid-19 patients are valuable for our patients, for hypothesis generation and for treatment development	
Crameri et al. 2020 [7] Schweiz	Young military recruits (n=199) with available information on SARS-CoV-2 status. Stratified as: SARS-CoV-2 naive (n=54), asymptomatically (n=77) and convalescent (n=68). Mean age: 20.7 Male: 87% Median time between	Cohort study where retrospective baseline data from before covid-19 infection were compared to current data.	To assess if covid-19 correlates with a measurable functional deficit in physical fitness.	Change in predicted maximal aerobic capacity (VO ₂ max) Upper extremity strength Trunk strength	We showed reduced aerobic capacity in young adult recruits 1 to 2 months after symptomatic covid-19 while physical strength was unaffected. Ca 19% of covid-19 convalescent recruits showed a decrease of VO2 max of more than 10% as compared with baseline before infection.	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
	diagnosis and fitness test: 45 days.					
Daher et al. 2020 [8] Germany	Discharged patients (n=33) with severe covid-19 who did not require mechanical ventilation. Mean age: 64 years Male: 77% Follow-up: 6 weeks after discharge	A single center prospective cohort study with control group.	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.	Prevalence of symptoms (yes/no) Examination and vital parameters Pulmonary function (Only at follow-up) Arterial blood gases (Only at follow-up) Depression (PHQ-9) Generalized anxiety disorder (GAD-7) George's respiratory questionnaire (SGRQ) HRQoL (EQ-5D)	Hospitalized patients who suffered from severe covid-19 and did not require mechanical ventilation are unlikely to develop long-term pulmonary and cardiac impairments or thromboembolic complications after discharge from hospital whereas fatigue is a common symptom.	Low

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
				6-min walk test (6MWT)		
Denina et al. 2020 [9] Italy	Discharged patients (n=13) from a pediatric covid-19 department (Children). Mean age: 7.75 years Male: 48% Follow-up: 35 days after discharge	A single center prospective cohort study without control group.	To assess sequelae of covid-19 in hospitalized children.	Laboratory tests (White blood cells, lympocytes, platelets, c-reactive protein, d- dimer, erythrocyte sedimentation rate, fibrinogen, ferritin, alanine aminotransferase, creatine) Pathologic lung ultrasound	The lung ultrasound findings comply with the clinical improvement, showing a complete normalization within 5 weeks from hospital discharge in the majority of patients. Eventually, all our patients showed a clinical and complete laboratory recovery about a month after discharge, without manifestation of any covid-19-related sequelae 4 months later.	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Doyle et al. 2020 [10] United kingdoms	Patients (n=129) with confirmed covid-19 who either has been discharged or are still hospitalized. Follow-up: 90 days	A multicenter prospective cohort study without comparison group.	To asses the risk of venous thromboembolism 90 days following covid-19 pneumonia.	Cumulative incidence of venous thromboembolism	Given the absence of VTE following discharge, our data does not support the use of extended thromboprophylaxis post-hospitalization for patients with covid-19 following critical care admission.	Moderate
Garrigues et al. 2020 [11] France	Discharged patients (n=120) with covid-19. Mean age: 63.2 Male: 75% Mean time from admission to follow-up: 110.9 days. Stratified as ICU- and Ward-patients	A single-center case-series with self-reported follow-up.	To assess post-discharge persistent symptoms and health-related-quality-of-life of patients hospitalized in our COVID-19 ward unit more than 100 days after their admission.	Type of persistent symptom (Type, Yes/No) Quality of life (EQ-5D index and EQ-5D VAS) Disability attributable to breathlessness (mMRC dyspnea scale)	In conclusion, many symptoms persist several months after hospitalization for covid- 19. While there were few differences between HRQoL between ward and ICU patients, our findings must be confirmed in larger cohorts, including more severe ICU patients.	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Halpin et al. 2020 [12] United kingdom	A purposive sample of covid- 19 patients (n=100) discharged from one large university hospital. Median age: 70.5 Male: 51.5% Mean time since discharge: 48 days	A single-center case-series with self-reported follow-up	To inform service development, our multidisciplinary rehabilitation team examined the impact of covid-19 on survivors discharged from hospital.	A self-developed telephone questionnaire, including the domains: - Fatigue - Breathlessness - Neuropsychological - Speech and swallow - Nutrition - Perceived health - Vocation change Quality-of-life (EQ-5D-5L)	New illness-related fatigue, breathlessness, and psychological distress were commonly reported with greater prevalence in those needing ICU care when compared with those managed in wards without needing ICU treatment. There was a clinically significant drop in quality of life in many participants.	Moderate
Huang et al. 2020 [13] China	Patients (n=57) that had recovered from covid-19 and been discharged but are still undergoing rehabilitation. Mean age: 47 years Male: 45.6%	Retrospective cohort study without control group.	To investigate the influence of Coronavirus Disease 2019 (covid-19) on lung function in early convalescence phase.	Pulmonary function (TLC, FEV1, DLCO, Maximum expiatory flow rate, Airway viscosity resistance) Lung imaging examination	Impaired diffusing- capacity, respiratory muscle strength decrease, and lung imaging abnormalities were detected in more than half of the covid-19 patients in early	Moderate

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	Follow-up: 30 days after discharge Stratified as severe and non-severe cases.			Exercise capacity (6 min walk test, 6MWD).	convalescence phase. Compared with non- severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline.	
Huang et al. 2020 [14] China	Recovered patients (n=26) who previously had a confirmed covid-19 diagnosis and now exhibit cardiac symptoms Median age: 38 Male: 38% Median duration between symptom onset and CMR examination: 47 days.	A single-center retrospective observational study with control group of healthy persons (N=20) with similar age and gender distribution.	To evaluate cardiac involvement in patients recovered from covid-19 who reported cardiac symptoms, using cardiac resonance imaging (CMR) as a sensitive imaging tool.	Left and right ventricular cardiac CMR parameters.	There may be sustained cardiac involvement in patients recovered from covid-19. Major CMR manifestation included edema, fibrosis and impaired RV contractile function. The cardiac status of patients with covid-19 and survivors needs to be closely monitored.	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Liu et al 2020 [15] China	Patients (n=51) that had been discharged from hospital after recovery from covid-19. Mean age: 47 Male: 70% Follow-up: 4 weeks after discharge Stratified as recurrence of positive SARS-CoV-2 RNA or not	Retrospective cohort study without control group.	This paper aimed to describe the follow-up of patients with covid-19 in Wenzhou city, Zhejiang, China.	Prevalence of symptoms (Yes/No) CT-imaging features (Focal ground glass opacities, interlobular septal thickening, subpleural lines etc.) Blood tests.	In summary, the lung damage due to covid-19 could be reversible for the common patients. A few cases showed recurring positive results of nucleic acid tests after discharge, probably related to the false negativity of the nucleic acid test at the time of discharge.	Moderate
Lu et al. 2020 [16] China	Patients (n=60) that had been discharged from hospital after recovery from covid-19. Mean age: 44 Male: 34% Follow-up: 3 months	Prospective cohort study with age- and sex matched non-covid-19 volunteers (n=39) as control group.	In the current study, we aimed to apply volumetric and diffusion measurements in recovered covid-19 patients to identify the existence of potential long-term brain	Prevalence of neurological symptoms (Yes/No) Voxel-based morphometry - Grey matter volume - White matter volume - Axial diffusivity - Radial diffusivity	Volumetric and microstructural abnormalities were detected mainly in the central olfactory cortices, partial white matter in the right hemisphere from recovered covid-19 patients, providing new evidence to the	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
			structural changes related to SARS-CoV-2.	- Mean diffusivity - Fractional anisotropy	neurological damage of SARS-CoV-2. The abnormalities in these brain areas might cause long-term burden to covid-19 patients after recovery, which was thus worth public attention.	
Mazza et al. 2020 [17] Italy	Patients (n=402) that had survived covid-19, both those that been treated at hospital (n=300) and at home (n=102). Mean age: 58 years Male: 65.7% Follow-up: 1 month	Data were collected from a prospective cohort study.	Thus, the present study aims to investigate the psychopathological impact of covid-19 in survivors at one month follow-up, also considering the effect of possible risk factors.	Impact of events scale-Revised PTSD Checklist for DSM-5 Zung Self-Rating Depression Scale 13-item Beck's Depression inventory State-Trait Anxiety Inventory Form Y	In conclusion, our study hypotheses were supported by the present results based on a cohort of 402 patients. As predicted, 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	Low

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
				Medical Outcomes Study Sleep Scale Women's health Initiative Insomnia Rating Scale Obsessive-Compulsive inventory	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.	
Patell et al. 2020 [18] USA	Discharged covid-19 patients (n=163) who did not receive anticoagulation after discharge. Mean age: Not known Male: Not known Follow-up: 30 days after discharge	A single center retrospective cohort study without control group	To assess if the prothrombotic state of covid-19 persists after hospital discharge.	Event and timing of thrombosis and hemorrhage.	Based on an observed rate of hemorrhage in the nonanticoagulated cohort, we would be cautious in recommending extended duration thromboprophylaxis without a clear indication outside of a clinical trial.	Moderate
Puntmann, et al. 2020	Recovered COVID-19 (n=100) patients after a minimum of 2 weeks since diagnosis.	Single-center prospective cohort study	To evaluate the presence of myocardial injury in unselected patients	Left and right ventricular ejection fraction.	We demonstrate cardiac involvement in 78 patients (78%) and	Low

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
[19] Germany	Mean age: 49 Male: 53% Median duration between diagnosis and CMR examination: 71 days	with a control group with healthy age-and sex matched controls (n=50) and risk-factor matched controls (n=57).	recently recovered from covid-19 illness.	Left ventricular end- diastolic volume Left ventricular mass index. Native T1 and T2 Late gadolinium enhancement High-sensitivity C-reactive protein High sensitivity troponin N-terminal pro-b-type natriuretic peptide.	ongoing myocardial inflammation in 60 patients (60%) with recent covid-19 illness, independent of preexisting conditions, severity and overall course of the acute illness, and the time from the original diagnosis. These findings indicate the need for ongoing investigation of the long-term cardiovascular consequences of covid-19.	
Roberts et al. 2020 [20] United kingdoms	Discharged patients (n=1877) who recovered from covid- 19. Mean age: Not known Male: Not known	A multicenter (2 hospital sites) retrospective cohort study.	We report the rates of post-discharge venous thromboembolism (VTE) and compare with rates following medical	Events of venomous thromboembolism post-discharge.	Our findings provide reassurance that the rate of post discharge VTE following hospitalization with covid-19 is low, in	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
	Follow-up: 42 days after discharge	Uses a historical cohort (n=18159) as comparison group.	admission in the pre- covid era.		contrast to that seen during critical care admission. Our data suggest that empiric post discharge thromboprophylaxis is not necessary.	
Tomasoni et al. 2020 [21] Italy	Patients (n=105) that has recovered from covid-19 and has documented virus clearance. Median age: 55 Male: 73% Follow-up: 1 to 3 months after virological clearance	A cross-sectional study without control group.	We aimed to investigate prevalence and possible predictors of anxiety and depression after clinical and virological recovery from covid-19 disease.	Prevalence of physical symptom. Hospital Anxiety and Depression Scale. Mini Mental State examination (Only patients over 65).	A considerable proportion of covid-19 patients still experienced psychological distress and ongoing physical symptoms after hospital discharge, underlining the complexity of covid-19 patients management even after clinical and virological recovery, and the need of long-term follow-up within multidisciplinary teams	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
Vaira et al. 2020 [22] Italy	Symptomatic patients (n=150) with a confirmed SARS-CoV-2 infection Mean age: 51.2 Male: 49.3% Follow-up: Every 10 th day for 60 days.	A multicenter prospective cohort study without a control group.	To understand the longer-term recovery rate of chemo sensitive functions, so as to aid the counselling of patients and guide if and when it is appropriate to start a specific therapy	Olfactory score Gustatory score	Olfactory and gustatory disturbances in covid-19 patients are frequent and common in the early stages of the disease. In most cases, they resolve completely within 30 days. Moderate to severe olfactory or gustatory disturbance persisted in 7.2% of patients 60 days after clinical onset of the disease. In order to avoid long-term morbidity, specific therapies should be initiated in patients with moderate to severe olfactory disturbance 20 days after disease onset.	Low
Wang et al. 2020	Discharged covid-19 patients (n= 31). Patients were	A prospective cohort study	To investigate clinical outcomes, distribution of quarantine locations and	Type of symptom (Yes/No)	That the majority of covid-19 patients after discharge were in the	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
[23] China	followed-up every 7 days for 4 weeks after discharge. Mean age: 49 Male: 45.04% Median length of hospital stay: 15 days. Stratified as non-severe and severe cases.	without control group.	the infection status of the contacts of covid-19 patients after discharge	SARS-CoV-2 infection (Positive/Negative) Complete blood count (Normal/Abnormal) Chest CT image (Nondeteriorated/ Deteriorated)	course of recovery, confirmed by the alleviated symptoms, improved laboratory tests and radiological assessment in the 4 weeks of observation period. However, re- hospitalizations were needed in rare patients, due to the recurred fever and positive SARS-CoV-2 tests.	
Xiong et al. 2020 [24] China	Discharged patients (n=538) who recovered from covid-19. Median age: 52 years Male: 45.5% Follow-up: 3 months	A single center prospective cohort study. Uses a comparison group of volunteers without covid-19 (n=184).	To describe the prevalence, nature, and risk factors for the main clinical sequelae in covid-19 survivors who have been discharged from the hospital for more than 3 months.	Prevalence of general symptoms (Yes/No) Prevalence of respiratory symptoms (Yes/No)	The most common early clinical sequelae in covid-19 survivors include physical decline/fatigue post-activity polypnea, resting heart rate increases, somnipathy and alopecia. These sequelae may be related	Moderate

Author Year Ref Country	Population	Study design	Aim	Outcome measures	Authors conclusion	Risk of bias
				Prevalence of cardiovascular-realted symptoms (Yes/No) Prevalence of psychosocial symptoms (Yes/No) Prevalence of alopecia (Yes/No)	to gender, age and clinical characteristics during hospitalization.	
Zhao et al. 2020 [25] China	Patients (n=55) who had recovered from covid-19. Mean age: 47.74 Male: 48% Follow-up: 3 months after discharge.	A retrospective multi-center cohort study.	To report that the long- term effects on changes in both pulmonary function and high- resolution CT (HRCT) imaging.	Presence of HRCT abnormalities Pulmonary function (FVC, FEV1, TLC, DLCO.)	Significant radiographic and physiological abnormalities still existed in a high proportion of covid-19 patients 3 months after discharge.	Moderate

Abbreviations: ICU = Intensive care unit; HRQoL = Health related quality of life; CMR = Cardiac resonance imaging; CT = Computed tomography; FVC = Forced vital capacity; FEV1 = Forced expiratory capacity at the first second of exhalation; TLC = Total lung capacity; DLCO = Diffusion capacity of the lung for carbon monoxide; PTSD = Post-traumatic stress disorder; PROMIS = Patient-Reported Outcomes Measurement Information System.

Beskrivning av studier om behandling- och rehabiliteringsinsatser (fråga 2)/Studies on treatment and rehabilitation (question 2).

Author Year Ref Country	Population	Treatment	Aim	Outcome measures	Conclusion	Risk of bias
Liu et al. 2020 [26] China	Discharged patients above 65 years with a diagnosis of covid-19 Inclusion criteria's: (1) >6 months after the onset of other acute diseases; (2) mini-mental state examination score > 21; (2) no COPD or any other respiratory disease; (4) forced expiratory	Intervention: 6-week respiratory rehabilitation training (n=36). Once a day for 10 min and 2 sessions per week. Including: respiratory muscle training; (2) cough exercise; (3) diaphragmatic training; (4) stretching exercise; and (5) home exercise. Control: No respiratory rehabilitation program (n=36)	Thus, in this study, we conducted a randomised controlled trial to investigate the effects of respiratory rehabilitation on respiratory function, ADL, QoL, and psychological status in elderly with covid-19 who were discharged from the hospital with satisfying results.	Respiratory functions (FEV1, FVC, DLCO) Exercise endurance (6min walk distance) Activities of daily living (ADL) Quality of life (SF-36) Psychological status assessment (SDS and SAS).	Six-week respiratory rehabilitation can improve respiratory function, QoL and anxiety in elderly patients with covid-19, but it has no significant improvement in elderly depressive state and activities of daily living.	Moderate

volume in 1s	
>70%;	

Abbreviations: **FEV1** = Forced expiratory volume in the first second; **FVC** = Forced vital capacity; **DLCO** = Diffusion capacity of the lung for carbon monoxide; **PTSD** = Post traumatic stress syndrome.

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