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COVID-19-EPIDEMIC :

COVID-19: Long-Term Effects of COVID-19
– a rapid review

Key messages

This rapid review is a first look at possible long-term effects of COVID-19 (>28 days), including long COVID. We performed a systematic literature search on January 26th for studies with more than 100 participants. One researcher screened the search results. Two researchers selected studies for inclusion and summarised study findings. Experts in the field assisted with study inclusion and provided input during the review process. In the current situation, there remains an urgent need for identifying the most important evidence quickly. Hence, we opted for this semi rapid approach despite an inherent risk of overlooking key evidence or making misguided judgements.

We included 43 studies stratified by length of follow-up, 1-3 months, 3-6 months, and longer than six months follow-up. For six months of follow-up, we have included studies without peer-review. Our approach reflects the early stage of research and emphasises that current findings need to be considered critically. Meta-analysis was not feasible, and the main results of this rapid review are therefore presented tabular and narratively.

Studies with 6 months of follow-up
We identified 11 studies with six months follow-up, of which only four studies are peer reviewed. We identified seven European, two Chinese, one Israeli study and one international survey. Only four studies performed clinical follow-ups, and seven studies used a PCR test to diagnose COVID-19. Included participants were mostly middle-aged. Loss to follow up was generally high. The majority of the studies focused on prevalence of symptoms. These studies showed that at least any one symptom remained at six months of follow-up for many patients. Most commonly reported symptoms were dyspnoea, fatigue and smell and taste abnormalities. Fewer studies included analysis for correlating factors between initially registered clinical information and measured outcomes, findings remain heterogeneous, whilst indicating that severity of initial COVID-19 illness is associated with prolonged symptoms. Echoing this, one study assessing healthcare utilisation found that patients with severe COVID-19 probably consumed more healthcare due to their initial illness, not seen in patients with initial mild COVID-19. Similarly, one study found that among non-hospitalised COVID patients quality of life scores were similar to the population norms, at 1.5-6 months post infection.

Studies with 3-6 months of follow-up
We identified six peer-reviewed studies with 3-6 months follow up of COVID-19 patients. Five studies came from Europe, and one from China. All but one study included PCR confirmed hospitalised COVID-19 patients. There is high heterogeneity across the studies. Four studies conducted clinical follow-ups, in addition to self-reported symptoms. One study only looked at the pulmonary function. Two studies compared COVID-19 intensive care unit vs. non-intensive care unit patients concluding that there were few differences in the symptoms at follow-up. All

studies reported lasting symptoms in some of the included patients on follow-up. Most commonly reported symptoms were dyspnoea, fatigue, anosmia and sleeping problems. Most consistent predicting factors for symptom duration were age and severity of COVID-19 illness.

The included studies were heterogeneous in terms of statistical methods and procedures. Most studies suffered from large loss to follow up, and were prone to recall bias. The majority of studies did not include matched controls, which is a strong limitation in evaluating COVID-19 specific effects. Due to lack of controls, it remains uncertain how far prevailing symptoms are specific to COVID-19 or more generally attributable to a period of illness. Equally, pandemic related infringements on personal liberty, lockdowns and changes to pre-pandemic lifestyle might also be factors underlying reporting of some symptoms. These factors are not limited to patients who have had COVID-19, but apply to the whole population. The long-termed effects of COVID-19 and long-termed effect of the pandemic situation are difficult to single out in un-controlled studies.

Patients who have been admitted to intensive care unit with COVID-19 seem to be at greatest risk for developing long COVID, but without controlled studies it remains unclear to what extent their symptoms are COVID-19 specific or reflects more general consequences of intensive care. It is well-known that many patients who are admitted to intensive care units after invasive medical treatment experience post-intensive care syndrome (PICS). PICS shares many similarities with long COVID-19. In line with some studies on long COVID, typical risk factor for PICS are older age, female sex and disease severity. Furthermore, the majority of studies focused on the prevalence of symptoms, but it remains unclear to what extent these symptoms affect activities of daily living and quality of life.

Only one study assessed changes in healthcare utilisation for patients before and after COVID-19. The large prevalence of symptoms in mild COVID-19 patients over time is not reflected in respective changes of healthcare utilisation. Interestingly, for more severe COVID-19 patients this inconsistency is not apparent. This might indicate that patients with mild COVID-19 continue to experience symptoms, but not to the extent that they consider medical help as necessary. It could also be that there is an over-reporting of symptoms, possibly due to loss to follow up and recall bias. With the currently available data, still too much uncertainty remains to reach a clear conclusion.

Conclusion
Based on 43 studies of mixed quality and limited representativeness we have found that; Hospitalised COVID-19 patients report prevailing symptoms long after infection, with a large proportion continuing to experience one or more symptoms at six months of follow-up. Severe COVID-19 illness, requiring intensive treatment, correlates with longer and more functional limitations on follow up. It appears that patients with more severe COVID-19 require more healthcare services and are more affected by adverse effects over time. Due to an over representation of hospitalised patients with severe COVID-19 in the reviewed studies, the findings are not considered representative for those with milder symptoms. The long-term impact of COVID-19 on the quality of life in the general population remains unclear.

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Hovedbudskap

Denne hurtigoppsummeringen er en første oversikt om langtidseffekter av covid-19 (> 28 dager). Den 26. januar utførte vi et systematisk litteratursøk etter studier med mer enn 100 deltakere. Én forsker screenet søkeresultatene. To forskere leste artiklene i fulltekst og avgjorde hvilke studier som skulle inkluderes og oppsummeres. Fageksperter ble konsultert og ga tilbakemelding om hvordan oversikten skulle utformes. Det er fortsatt pressende behov for å identifisere de mest relevante studiene raskt. Derfor valgte vi en hurtigoppsummerings-tilnærming for denne rapporten på tross av den potensielle risikoen for å overse viktig informasjon eller å foreta forhastede vurderinger.

Vi inkluderte 43 studier som vi grupperte etter lengde på oppfølging: 1-3 måneder, 3-6 måneder og mer enn seks måneders oppfølging. For seks måneders oppfølging har vi inkludert både fagfellevurderte studier og studier som enda ikke har gjennomgått fagfellevurdering. Denne tilnærming var nødvendig da det fortsatt finnes få studier, men innebærer at funnene må leses med et kritisk blikk. Sammenstilling av resultater i metaanalyser var ikke mulig, så hovedresultatene i denne hurtigoppsummeringen blir presentert narrativt og i tabeller.

Studier med 6 måneders oppfølging
Vi identifiserte 11 studier med seks måneders oppfølging, hvorav bare fire studier er fagfellevurdert. Vi identifiserte sju europeiske, to kinesiske, en israelsk studie og en internasjonal spørreundersøkelse. Bare fire studier utførte klinisk oppfølging, og syv studier brukte en PCR-test for å diagnostisere covid-19. Deltakerne i studiene var for det meste middelaldrende. Frafallet av deltakere under oppfølging var generelt høyt. Flertallet av studiene fokuserte på forekomst av symptomer og viste at mange pasienter hadde minst ett symptom som vedvarte frem til seks måneders oppfølging. De vanligste symptomene var dyspné, tretthet og nedsatt lukte- og smakssans. Funnene er heterogene, men indikerer at alvorlighetsgraden av covid-19 er forbundet med økt risiko for langvarige symptomer. Samsvarende med dette fant en studie om bruk av helsetjenester at pasienter med alvorlig covid-19 (sykehusinnlagte) sannsynligvis hadde økt forbruk av helsetjenester etter covid-19 infeksjon. Tilsvarende økning ble ikke sett blant pasienter med mild covid-19. En studie fant at blant ikke-innlagte covid-positive individer var livskvaliteten lik populasjonsnormene 1,5-6 måneder etter infeksjon.

Studier med 3-6 måneders oppfølging
Vi identifiserte seks fagfellevurderte studier med 3-6 måneders oppfølging. Fem studier kom fra Europa, og en fra Kina. Alle unntatt en studie inkluderte pasienter med PCR-bekreftet covid-19 innlagt på sykehus. Det var høy heterogenitet på tvers av studiene. Fire studier gjennomførte klinisk oppfølgning i tillegg til selvrapporterte symptomer via spørreskjema. Én studie undersøkte kun lungefunksjon. To studier sammenlignet covid-19 intensivpasienter med ikke-intensivpasienter, og konkluderte med at det var få forskjeller i symptomene ved oppfølgning.

Alle studiene rapporterte vedvarende symptomer hos noen av de inkluderte pasientene. De vanligste symptomene var dyspné, tretthet, anosmi (manglende luktesans) og søvnproblemer. Assosierte faktorer for symptomlengde var alder og alvorlighetsgrad av covid-19.

De inkluderte studiene var heterogene når det gjaldt hvilke statistiske metoder og prosedyrer som var benyttet. De fleste studiene var preget av stort frafall og var utsatt for recall bias. Få studier inkluderte kontrollgrupper, noe som er en sterk begrensning for å kunne evaluere covid-19 spesifikke effekter. Uten kontrollgrupper er det vanskelig å avgjøre om de vedvarende symptomer er spesifikke for covid-19 eller mer generelt kan tilskrives en sykdomsperiode. På samme måte kan pandemirelaterte begrensninger i personlig frihet, nedstenging og livsstilsendringer påvirke rapportering av noen symptomer uavhengig av om respondentene har hatt covid-19. De langvarige effektene av covid-19 og den langvarige effekten av pandemisituasjonen kan være vanskelig å skille ut i ukontrollerte studier.

Pasienter som er innlagt på intensivavdeling med covid-19 ser ut til å ha størst risiko for å utvikle langvarig covid-19, men uten kontrollerte studier er det fortsatt uklart om symptomene er spesifikke for covid-19 eller gjenspeiler mer generelle konsekvenser av intensivbehandling. Mange pasienter som legges inn på intensivavdelinger etter invasiv medisinsk behandling opplever postintensivsyndrom (PICS), og PICS deler mange likheter med langvarig covid-19. Både for langvarig covid-19 og PICS kan det se ut til at typiske risikofaktorer er eldre alder, kvinnelig kjønn og sykdomsalvorlighet. Videre fokuserte de fleste studiene på forekomsten av symptomer, men det er fortsatt uklart i hvilken grad disse symptomene påvirker dagliglivets aktiviteter og livskvalitet.

Én studie undersøkte endringer i bruk av helsetjenester for pasienter før og etter covid-19. De langvarige symptomene hos pasienter med mild covid-19 reflekteres ikke i økt bruk av helsevesenet, men pasienter med alvorlige covid-19 forløp bruker mer helsetjenester etter gjennomgått infeksjon. Dette kan indikere at pasienter med mild covid-19 fortsetter å oppleve symptomer, men ikke i den grad at de anser medisinsk hjelp som nødvendig. Det kan også være at det er en overrapportering av symptomer, muligens på grunn av frafall under oppfølging og recall bias.

Konklusjon
Basert på 43 studier av varierende kvalitet og begrenset representativitet har vi funnet at; Pasienter som har vært innlagt på sykehus med covid-19 rapporterer vedvarende symptomer lenge etter infeksjon. En stor andel opplever fortsatt symptomer ved seks måneders oppfølging. Sykdomsforløp som krever innleggelse på intensivavdeling er assosiert med mer langvarige senfølger, mer funksjonelle begrensninger og økt bruk av helsetjenester. På grunn av en overrepresentasjon av innlagte pasienter med alvorlig covid-19 i studiene er ikke funnene representative for de med mildere symptomer. Den langsiktige effekten av covid-19 på livskvaliteten i befolkningen er fortsatt uklar.

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Problem statement

In relation to the ongoing COVID-19 outbreak, it is important to gather information about which patient groups are most at risk of long-term effects of COVID-19, and what characterises them. The outbreak team at the Norwegian Institute of Public Health has asked us to provide a rapid review of existing research.

Methods

Literature search

We applied an open search strategy to identify all relevant studies on prevalence of lasting COVID-19 symptoms, demographic and medical risk factors associated with long presenting COVID-19 symptoms, and studies analysing the impact of long presenting COVID-19 on the healthcare system. We searched for studies with more than 100 participants that had suspected/confirmed COVID-19 and reported on symptoms, radiological findings and predicting factors for prolonged illness. One researcher (JH) conducted a search on January 26th, 2021 in the MEDLINE database for studies published in the period 01.01.2020 -26.01.2021. This search was expanded with a search in the WHO COVID-19 Global literature on coronavirus disease database on January 29th, 2021. After title and abstract screening on February 4th, 2021 a neural network search was conducted on identified articles to capture further relevant articles using EPPI reviewer's neural network search function using Microsoft Academic Graph's database.

Inclusion criteria:

Population:	More than 100 suspected/confirmed COVID-19 participants
Outcome:	Any symptoms, consequences associated with COVID-19 illness
Study types:	Cohort studies, prospective studies, retrospective studies, surveys
Exclusion criteria:	Non-peer-reviewed studies, with less than 6 months follow-up

Study selection

We included publications reporting on lasting symptoms of COVID-19, assessing various demographic and medical risk factors for the risk of long COVID-19. In this report, we excluded studies with less than 100 participants due to power considerations. We also excluded systematic reviews.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (JH, SQ) reviewed the studies in full text, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. A group of experts in the field provided feedback for the study

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inclusion process, methodological approach and results presentation (KG, HLG). Studies with follow-up longer than three months are reviewed in detail, while studies with shorter follow-up are listed in a table. This rapid review includes a formal quality assessment with the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies only for six-month follow-up studies (1), but without grading of the certainty of evidence. Therefore, the results should generally be interpreted with caution.

Peer review

Kirsten Gravningen, Hanne Løvdal Gulseth, Ernst Kristian Rødland, (senior medical officers, Norwegian Institute of Public Health), supported the identification of research priorities, the identification of review criteria, assisted in shaping inclusion criteria, and critically reviewed the draft before publication.

Results

Description of studies

Results of the literature search

We identified 2491 unique references through the systematic literature searches in MEDLINE, WHO COVID-19 Global literature on coronavirus disease database and a neural network search of Microsoft Academic. JH screened all probable titles and abstracts in Rayyan (2) and EPPI reviewer (3). After all MEDLINE references were screened we built a Machine Learning Model in EPPI reviewer 4 based on identified includes/excludes from title and abstract screening. The model was applied to the references of WHO COVID-19 Global literature on coronavirus disease database. The model considered 884 references as below 30% likely relevance, we excluded these references without human screening. We identified a total of 52 studies as relevant for full human text screening, 33 studies remained after full text screening. To identify further relevant studies, we performed a neural network search in Microsoft Academic Graph based on the included 33 full texts. The previously applied Machine Learning model was applied to the references from the neural network search, 202 references were below 30% likely relevance and excluded without human screening. Searching using neural network strategies identified ten selectable studies in addition to those studies identified by more traditional searches in databases. In total, we read 65 references in full text, of which 43 articles matched our inclusion criteria. Figure 1 shows a graphical representation of our search and screening methodology.
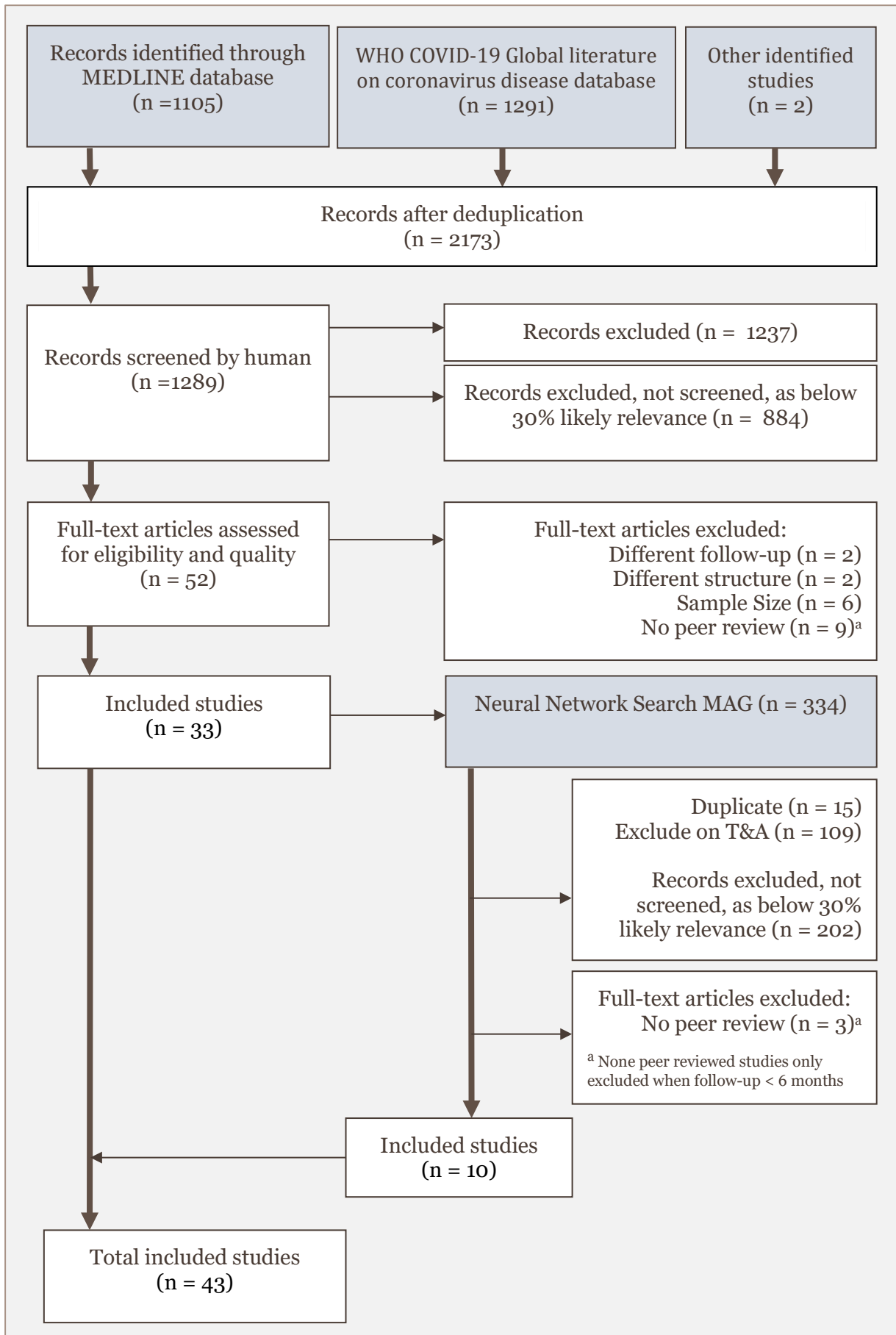
Figure 1. Flow diagram of search strategy and study inclusion

Included studies

On full text screening we included 43 studies (table 1) and excluded 22 studies not matching our inclusion criteria.

Table 1. Overview of included studies (grouped by follow-up length)

First author	Country	Participants (n)	Study type	Study population	Publication status	Follow-up length group
Han et al. (4)	China	114	ambidirectional cohort study	hospitalised	published	>6m
Huang et al. (5)	China	1733	prospective cohort study	hospitalised	published	>6m
Hopkins et al. (6)	UK	454	descriptive Survey	mixed	published	>6m
Nguyen et al. (7)	France	125	retrospective cohort study	unclear	published*	>6m
Stavem et al. (8)	Norway	451	cross-sectional mixed-mode survey	non-hospitalised	published*	>6m
Taboada et al. (9)	Spain	138	cross-sectional study	hospitalised	pre-print	>6m
Klein et al. (10)	Israel	112	descriptive Survey	mixed	published*	>6m
Pilotto et al. (11)	Italy	165	retrospective cohort study	hospitalised	pre-print	>6m
Davis et al. (12)	International	3 762	international Survey	mixed	pre-print	>6m
Ayoubkhani et al. (13)	UK	47 780	registry study	hospitalised	pre-print	>6m
Skyrud et al. (14)	Norway	1 257 831	registry study	mixed	pre-print	>6m
Garrigues et al. (15)	France	279	questionnaire via phone	hospitalised	published*	3-6m
Guler et al. (16)	Switzerland	113	multicentre prospective cohort	hospitalised	published**	3-6m
Sonnweber et al. (17)	Austria	145	prospective, multicentre, observational study	hospitalised	published**	3-6m
Lerum et al. (18)	Norway	103	prospective cohort study	hospitalised	published**	3-6m
Xiong et al. (19)	China	538	telephone follow-up survey	hospitalised	published	3-6m
Petersen et al. (20)	Faroe Islands	180	Questionnaire via phone	Non-hospitalised	published**	3-6m
Afshar et al. (21)	US	594	nationwide prospective cohort study	non-hospitalised	published	1-3m
Arnold et al. (22)	UK	131	prospective cohort study	hospitalised	published	1-3m
Boscolo-Rizzo et al. (23)	Italy	202	cross-sectional survey-based study	non-hospitalised	published	1-3m
Carfi et al. (24)	Italy	179	observational study	hospitalised	published	1-3m
Caronna et al. (25)	Spain	130	prospective study	ambulant care	published	1-3m
Carvalho-Schneider et al. (26)	France	150	descriptive clinical follow-up	hospitalised	published	1-3m
Cellai et al. (27)	US	551	telemedicine follow-up	non-hospitalised	published	1-3m
Jacobs et al. (28)	US	183	prospective cohort study	hospitalised	published	1-3m
Mandal et al.(29)	UK	384	prospective cohort study	hospitalised	published	1-3m
Mazza et al.(30)	Italy	402	unstructured clinical interview	mixed	published	1-3m
Panda et al.(31)	India	225	prospective cohort study	hospitalised	published	1-3m
Pizzini et al. (32)	Austria	109	prospective, multicenter, observational study	hospitalised/ ICU	published	1-3m
Smet et al.(33)	Belgium	220	outpatient follow-up study	hospitalised/ ICU	published	1-3m
Tomasoni et al. (34)	Italy	105	Cross sectional study	hospitalised	published	1-3m
Weerahandi et al. (35)	US	161	prospective single health system observational cohort study	hospitalised	published	1-3m
Parente-Arias et al. (36)	Spain	151	observational cohort study	hospitalised	published	1-3m
Chiesa-Estomba et al. (37)	France	751	prospective survey-based study	hospitalised	published	1-3m
Shima et al. (38)	Iran	100	cohort study	hospitalised	published	1-3m
Poyraz et al. (39)	Turkey	284	cross-sectional survey study	hospitalised	published	1-3m
Munoz et al. (40)	Spain	100	observational study	hospitalised	published	1-3m
Poncet-Megemont et al.(41)	France	139	cross-sectional survey study	hospitalised	published	1-3m
Vaes et al. (42)	Netherlands/ Belgium	1837	survey-based study	mixed	published	1-3m
Van den Borst et al.(43)	Netherlands	124	observational study	hospitalised	published	1-3m
van der Sar - van der Brugge et al. (44)	Netherlands	101	prospective longitudinal cohort study	hospitalised	published	1-3m
Moreno-Perez et al. (45)	Spain	277	prospective cohort study	hospitalised	published	1-3m
Goertz et al. (46)	Netherlands/Belgium	2113	web-based survey	hospitalised/non-hospitalised	published	1-3m

*not peer reviewed, ** accepted manuscript

Quality assessment

We performed quality assessment of included studies with 6-months follow-up with the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Table 2)(1). In absence of a quality assessment tool for registry studies, two registry studies were not assessed. The NIH assessment tool focused on the key concepts for evaluating the internal validity of studies, quality rating can be good, fair or poor methodological quality, based on level of fulfilment of 14 aspects (maximum score is 14 points). One researcher performed quality assessment, controlled by a second author. We set no cut-off for included studies by total quality score. Quality was mixed, ranging from 3-11 points. The peer-reviewed studies were generally of higher methodological quality.

Table 2. Results of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Han (4)	x	x	x	x	-	x	x	-	x	-	x	x	x	x	11
Huang (5)	x	x	x	x	-	x	x	x	x	-	x	-	x	x	11
Hopkins (6)	x	-	x	-	-	-	x	-	-	-	x	-	-	-	4
Stavem (8)	x	x	x	x	-	x	x	-	x	-	x	-	-	x	9
Nguyen* (7)	x	x	-	x	x	x	x	-	x	-	x	-	-	-	8
Taboada* (9)	x	x	x	x	-	x	x	x	x	-	x	-	-	-	9
Klein* (10)	x	x	x	-	-	x	x	-	x	-	x	-	-	-	7
Pilotto* (11)	x	x	x	x	-	x	x	x	-	-	x	-	-	-	8
Davis* (12)	x	-	x	-	-	-	x	-	-	-	-	-	-	-	3

*not peer reviewed

Studies with 6 months of follow-up

Brief summary

We identified 11 studies with a follow-up period of 6 months or longer (4-14). Four studies are published and peer reviewed (4-6, 8), seven are in press or pre-prints and not yet externally peer reviewed (7, 9-14). Two studies from China (4, 5), the UK (6, 13), Norway (8, 14), and one each from France (7), Italy (11), Israel (10) and Spain (9) and one international survey (12). The median follow-up length was mostly 6 months with some variation (41-199 days). Follow-up time was measured from time of discharge, initial symptoms or mixed. Four studies performed clinical follow-ups (4, 5, 9, 11), five studies used postal/phone/online surveys (6-8, 10, 12) and two were registry-based studies (13, 14). Loss to follow up was generally high, range 0-52%. Number of participants ranged from 112 to 1 257 831. Participants were mostly middle-aged, ranging from 16-88 years. Seven studies used a PCR test to diagnose COVID-19 (4-10), and four studies used unspecified methods or self-reporting. The majority of the studies focused on prevalence of symptoms. These studies showed that at least any one symptom persisted until 6 months follow-up. A detailed list of symptoms and proportions of patients affected are shown in Table 3. Fewer studies included analysis for correlating factors between initially registered information and measured outcomes. Findings remain heterogenous, whilst indicating that severity of initial COVID-19 is associated with prolonged symptoms. Echoing this, one study looking at healthcare utilisation found that patients with severe COVID-19 probably consumed more healthcare due to their initial illness, not seen in patients with initial mild COVID-19. Among non-hospitalised patients quality of life scores were similar to the populations norms, at 1.5-6 months post testing positive. Two studies reported changes in radiological findings at 6 months.

Overview of peer-reviewed studies

Han et al. conducted a prospective longitudinal study in Wuhan, which found approximately one-third of 114 initially hospitalised patients showed chest CT findings with pulmonary fibrosis-like changes within 6 months after recovery from severe COVID-19 pneumonia (4). The other two-thirds showed either complete radiological resolution or residual ground-glass opacification or interstitial thickening. The authors found that old age (>50 years old), acute respiratory syndrome, and higher baseline CT lung involvement score were associated with lung fibrotic changes.

Huang et al. conducted a cohort study of 1733 hospitalised patients in Wuhan. The authors found that 6 months after acute infection, COVID-19 survivors most frequently reported fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655)(5). Anxiety or depression was reported among 23% (367 of 1617) of the patients. The authors performed a 6-min walking distance test, finding that many patients lay below the lower limit of the normal range, most impacted were patients with more severe initial presentation. In 107 of 822 participants without acute kidney injury a reduced estimated glomerular filtration rate was found at follow-up. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations. The authors concluded that these patients are the main target population for intervention of long-term recovery.

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Hopkins et al. conducted a 6-month follow-up of 454 respondents to an online survey who self-reported loss of smell at the onset of the COVID-19 pandemic in the UK (6). Of the respondents, 44% reported at least one other ongoing symptom at 6 months. Fatigue was the most prevalent symptom experienced by 23% (n=106) at 6 months. There was a significant improvement in self-rating of severity of olfactory loss where 39% (n =177) of the patients stated they had recovered a normal sense of smell while 12 patients reported complete loss of smell.

Stavem et al. performed a cross-sectional mixed-mode survey of a non-hospitalised, PCR-positive, geographical cohort in the catchment areas of two Norwegian hospitals (8). A total of 451 patients (48 %) responded to the survey. The authors compared prevalence of 23 symptoms during initial illness and at 1.5-6 months. Around 60% of non-hospitalised COVID-19 subjects had no symptoms 1.5–6 months after symptom onset. The authors found an association between symptom load during the acute COVID-19 phase and number of comorbidities with the number of symptoms at follow-up. A supplementary publication by Garratt et al. reports EQ-5D-5 L scores on the same population pool (47). Garratt et al. compared the response-based scores with Norwegian general population norms. The questionnaire was completed by 458 (49%) subjects at a median of 117.5 days after COVID-19 onset. Garratt concludes that EQ-5D index scores (0.82; SD 0.17) did not differ from the general population norms. However, several important dimensions of HRQoL, including aspects of mental health, were lower than general population norms 1.5–6 months after COVID-19 onset.

Overview of non-peer reviewed studies
Nguyen et al. retrospectively identified PCR-confirmed COVID-19 patients who reported anosmia and/or ageusia at the acute phase of infection from a French cohort of 3737 (7). After defining a randomised sample of 200 patients, 125 answered the provided questionnaire. Responding patients were relatively young with a low prevalence of co/morbidities and presented initially with non-severe COVID-19 infection. Mean time between symptom onset and follow-up questionnaire was about 7 months. Thirty (24.0%) patients reported persistent taste and smell disorders 7 months after onset of symptoms. Of them, all reported anosmia at the acute phase and 26 an associated ageusia. Of these 20 (70.0%) reported partial recovery of olfaction sense (smell) and 7/30 (23.3%) no recovery at all, while 10/26 (38.5%) reported partial recovery of gustatory sense (taste) and 3/26 (11.5%) no recovery at all. Female patients were more likely to report persistent symptoms than male patients.

Taboada et al. performed a cross-sectional observational study of 183 hospitalised patients with PCR-confirmed COVID-19 (9). All patients who survived hospital admission were included to assess functional status, and persistent dyspnea (on slight exertion) using a structured interview six months after hospitalization. Among the included patients, 18% were treated at the intensive care unit (ICU). The authors found a generally large proportion of patients had a reduced functional status at six months, 56% reporting at least one unresolved symptom. Six months after hospitalisation, the ICU patients referred a large decrease of their functional status compared with non-ICU patients. Female sex, age, length of hospital stay, mechanical ventilation, and ICU admission were associated with limitations in everyday life.

Klein et al. used phone interviews to follow-up 112 mostly mild, non-hospitalised, and younger COVID-19 RT-PCR-positive adult patients in Israel (10). At six months follow-up, 46% of the

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patients had at least one unresolved symptom, most commonly fatigue (21%), smell and taste changes (14%) or breathing difficulties (9%). The most prolonged symptom experienced was breathing difficulties, in some unresolved after 213 days. Fatigue, breathing difficulties, memory disorders and hair loss, were not typically reported during the 6-weeks follow-ups, while other symptoms such as muscle aches, headache and chemosensory changes usually remained from previous interviews.

Pilotto et al. reassessed 165 COVID-19 patients hospitalised in Italy (11). For the assessment at 6 months follow-up, the authors applied a structured standardised clinical protocol. Patients displayed a wide array of neurological symptoms, with fatigue (34%), memory/attention deficit (31%), and sleep disorders (30%) the most frequent. Subjects reporting neurological symptoms were affected by more severe respiratory COVID-19 parameters during hospitalisation. On neurological examination, 37.4% of patients exhibited neurological abnormalities; cognitive deficits (17.5%), hyposmia (15.7%) and postural tremor (13.8%). Patients with cognitive deficits at follow-up were comparable for age, sex and pre-admission comorbidities but experienced more severe respiratory COVID-19 and longer hospitalisation.

Davis et al. conducted an international web-based survey, via online COVID-19 support groups and social media, of suspected and confirmed COVID-19 cases with illness lasting over 28 days (12). Prevalence of 205 symptoms in 10 organ systems were estimated in their cohort, with 66 symptoms traced over seven months. 3 762 respondents from 56 countries completed the survey, 2 961 (78.9%) were women. The most frequent symptoms reported after month 6 were: fatigue (77.7%) post-exertional malaise (72.2%), and cognitive dysfunction (55.4%). Most had not returned to previous levels of work by 6 months. The study scored lowest among all quality-assessed studies, indicating poor methodology and low internal validity.

Ayoubkhani et al. performed an observational, retrospective, matched cohort study in England (13). 47 780 individuals (mean age 65 years, 55% male) in hospital with COVID-19 and discharged alive by 31 August 2020 were matched to controls on demographic and clinical characteristics. The authors analysed rates of hospital readmission, all-cause mortality, and diagnoses of respiratory, cardiovascular, metabolic, kidney and liver diseases until 30 September 2020. Readmissions and deaths per 1,000 person-years in COVID-19 cases were observed, and 3.5 (3.4 to 3.6) and 7.7 (7.2 to 8.3) times greater, respectively, than in controls. Rates of post-discharge multi-organ dysfunction were elevated in individuals with COVID-19 compared with those in the matched control group, the authors suspect extrapulmonary pathophysiology. Diabetes and major adverse cardiovascular events were particularly common, both when considering all post-discharge events and only incident cases. The absolute risk of post-discharge adverse events was greater for individuals aged ≥70 years than <70 years, and for individuals of white ethnic background than in the non-white group.

Skyrud et al. analysed data on all persons tested for the SARS-CoV-2 in Norway March 1st to November 1st, 2020 (N=1 257 831). The authors used a difference-in-differences design to contrast the monthly health care use before and after testing (14). Their findings suggest that non-hospitalised COVID-19 patients have no increase in complaints leading to increased health care utilisation beyond two months after their test date. For specific health care utilisation for conditions affecting internal organs, they found that mild COVID-19 impacted the primary healthcare use for respiratory conditions at 0-3 months after having tested positive (786%

increase). Similarly, severe COVID-19 increased the number of visits due to respiratory (337-3316% increase), circulatory (166-205% increase), endocrine/metabolic/nutritional (168-791% increase) conditions as well as visits due to general/unspecified conditions (48-431% increase) in outpatient and inpatient specialist care between 0-3 months after being tested. Only severe COVID-19 impacted outpatient specialist care between 4-6 months, for respiratory and circulatory conditions (199-246% increase) and general/unspecified conditions (40% increase).

Table 3. Overview of peer-reviewed and non-peer reviewed studies with 6-month follow-up, reporting prevalence of symptoms on follow-up. A selection of symptoms as provided by the authors, in some instances authors used overlapping terms, some symptoms were not clearly defined. Proportion of patients experiencing a symptom on follow-up, more than 30% red, between 30 and 10% orange, less than 10% yellow. Red shaded background indicates non peer-reviewed studies.

	Han et al.	Huang et al.	Hopkins et al.	Stavem et al.	Taboada et al.	Nguyen et al.	Klein et al.	Pilotto et al.	Davis et al.
Country	China	China	UK	Norway	Spain	France	Israel	Italy	International
Participants included (n)	114	1733	454	451	183	125	112	165	3,762
Age	54 (12)	median age: 57 (IQR 47–65)	40 (range 19-77)	mean 49.7 (SD 15.2)	Mean 65.9 (14.1)	median 36 (range 16 - 85)	Mean 35 ± 12 SD	64.8 + 12.6	Na
Sex (male %)	70	52	25	44	60	55	64	70	21
COVID-19 confirmation	PCR	PCR	mixed	PCR	PCR	PCR	PCR	unclear	mixed
Follow-up from	Discharge	Discharge	unclear	Positive-PCR test	Discharge	Initial symptoms	Initial symptoms	Discharge	unclear
Follow-up length	175 ±20 days	median 186 (175–199)	6 months	median 117 days (IQR 41–193)	6 months	7 months	6 months	6 months	7 months
Hospitalised/ Non-hospitalised	hospitalised	hospitalised	mixed	non-hospitalised	hospitalised	unclear	mixed	hospitalised	mixed
Lost to follow up	0%	30%	38%	52%	25%	38%	22%	20%	NA
Publication status	published	published	published	published	in press	in press	pre-print	pre-print	pre-print
Symptoms									
Any symptom		76% (1265/1655)	44.5% (193/454)	40% (266/445)	56% (102/183)		46% (48/112)		65.2%
Neurologic									
Anosmia		11% (176/1655)		12% (56/445)			13% (15/112)		
Ageusia		7% (120/1655)		10% (45/445)			7% (8/112)		
Anosmia & Ageusia					24% (30/125)		6% (7/112)	17% (25/165)	
Confusion/changed consciousness				2% (10/445)			5% (6/112)	13% (21/165)	58%
Dizziness		6% (101/1655)							
Headache		2% (33/1655)	15% (67/454)	6% (29/445)			4% (4/112)	10% (17/165)	
Numbness/ tingling									
Gait disturbance								11% (18/165)	
Abnormal movements								10% (17/165)	
Respiratory tract									
Expectorate	10% (11/114)			2% (8/445)					
Abnormal pulmonary diffusion	26% (27/104)								
Sore throat or difficult to swallow		4% (69/1655)		5% (21/445)					
Rhinorrhea			5% (21/454)						
Blocked nose			5% (23/454)						
Musculoskeletal									
Muscle weakness or fatigue		63% (1038/1655)							
Joint pain		9% (154/1655)		9% (42/445)					
Myalgia				8% (35/445)			5% (5/112)	30% (50/165)	43%
Cardiopulmonary									
Dyspnea	14% (16/114)		11% (50/454)	16% (73/445)	10% (19/183)		9% (10/112)		40%
Palpitations		9% (154/1655)							
Chest pain		5% (75/1655)							
Dry cough	6.1% (7/114)		7% (33/454)	6% (27/445)					
Dizziness/ Hypotension								12% (20/165)	
Systemic & other									
Fever			5% (22/454)						
Malaise									73%
Fatigue			23% (106/454)				20% (23/112)	34% (56/165)	80%
Hair loss		22% (359/1655)							
Diarrhoea				2% (7/445)			3% (3/112)		
Vomitting				2% (8/445)					
Diarrhoea or vomiting		5% (80/1655)							
Gastrointestinal upset			6% (25/454)						
Urinary dysfunction								14% (23/165)	
Skin rash		3% (47/1655)		2% (7/445)					
Chills				1% (4/445)					
Blurring, loss of vision								20% (33/165)	
Psychosocial									
Anxiety or depression		23% (367/1617)						26% (43/165)	
Sleep difficulties		26% (437/1655)						31% (51/165)	
Radiologic									
Lung fibrotic changes	35% (40/114)								

Predicting factors for symptoms at 6 months

Whereas most studies have predominantly focused on prevalence of symptoms, fewer studies included analysis for identifying correlating factors between initially registered information and measured outcomes. For most studies this was not the primary objective, nonetheless some authors collected data robust enough to provide early insights into factors associated with prolonged illness of COVID-19.

The multivariable negative binomial regression analysis by Stavem et al. showed that two or more comorbidities and more than six initial symptoms correlated with number of symptoms at follow-up (8). Marital status, educational level, smoking status, and BMI did not show any correlation.

Huang et al. grouped hospitalised patients into three severity groups: Scale 3: mild, not requiring supplemental oxygen (n=439), Scale 4: moderate, requiring supplemental oxygen (n=1172), severe, Scale 5–6: requiring high-flow nasal cannula for oxygen therapy or non-invasive ventilation/invasive mechanical ventilation (5). Levels of anxiety and depression were similar for scale 4 versus scale 3 with an odds ratio 0.88 (0.66–1.17), but higher for scale 5-6 versus scale 3 OR 1.77 (1.05–2.97). For fatigue or muscle weakness OR was 0.74 (0.58–0.96) for scale 4 versus scale 3 and 2.69 (1.46–4.96) for scale 5–6 versus scale 3. Women had an OR 1.80 (1.39–2.34) for anxiety or depression, and OR 1.33 (1.05–1.67) for fatigue or muscle weakness compared with men. Age was positively associated with fatigue or muscle weakness, 17% higher (OR 1.17, 1.07–1.27) per 10-year increase of age. No significant association of age with anxiety or depression was observed (5).

Han et al. identified the following independent predictors for lung fibrotic-like changes at 6 months in their multivariable analysis: age >50 years (OR: 8.5, 95% CI: 1.9-38), heart rate >100bpm at admission (OR: 5.6, 95% CI: 1.1-29), duration of in-hospital stay ≥17 days (OR: 5.5, 95% CI:1.5-21), and acute respiratory distress syndrome (OR: 13, 95% CI: 3.3-55), non-invasive mechanical ventilation (OR: 6.3, 95% CI:1.3-30), and total CT score ≥18 (OR: 4.2, 95%CI: 1.2-14) on initial CT (4).

Taboada et al., not peer-reviewed yet, compared outcome of patients admitted to the ICU as well as standard hospital care patients (9). The authors collected information on functional limitations of included patients predating hospital admission. Female sex, age, length of hospital stay, mechanical ventilation, and ICU admission were associated with limitations in the functional status. A higher incidence of ICU patients reported a decrease in their functional status compared with not ICU patients (81.3% vs 40.4%). A decrease in two grades of the functional status was also reported more frequently in ICU patients (56.3% vs 6%). Limitation in their everyday life was referred in 56.4% of ICU patients compared with 17.9% in non-ICU patients. Sex, age, length of hospital stay, comorbidity and need for ICU admission were included as independent variables in their multivariate logistic regression model. Age (OR = 2.6, 95% CI: 1.2–5.7), and length of hospital stay was associated with higher risk of limitations in the functional status. Dyspnea on slight exertion was reported in only 19 patients (10.4%), however ICU patients more frequently recounted dyspnea compared with not ICU patients (37.5% vs 4.6%).

Across the four studies, looking at predicting factors for length of symptoms, more severe initial presentation and need for complex treatment were associated with length of symptoms. Taboada et al. additionally found an association with female sex and limitations in the functional status, Huang et al. found an association with female sex and anxiety or depression. The Norwegian study of non-hospitalised patients did not find any correlation between marital

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status, education level, smoking status, and BMI and presence of symptoms. Neither did Huang et al. find an association with anxiety or depression with education, smoking status and age.

Impact on healthcare use and adverse events at 6 months

Two studies, yet not peer-reviewed, looked at nationally collected registry data to analyse changes on the population level (13, 14). A Norwegian study used a difference-in-differences design to contrast the monthly health care use before and after testing. The other study is an observational, retrospective, matched cohort study of individuals in hospital with COVID-19 using Hospital Episode Statistics and Admitted Patient Care records for England to detect adverse events from background level incidents.

Skyrud et al. used data from the Norwegian emergency preparedness register (Beredt C19) to analyse all-cause and cause-specific utilisation of primary and specialist care (14). The Beredt C19 register joins information on all testing for COVID-19, all electronic patient records from all hospitals in Norway, all consultations with all general practitioners and emergency primary health care, and information on age, sex, country of birth, and date of death. The authors found no impact of mild COVID-19 on deteriorated health or increased health care use that persisted beyond 2 months after having tested positive. For patients that had severe COVID-19 the health care use after 0-3 months increased, particularly for respiratory, circulatory, endocrine/metabolic/ nutritional and general/unspecified conditions. Circulatory, respiratory conditions and general/unspecified conditions were the only potential post- severe COVID-19 conditions leading to increased long-term health care use at 4-6 months.

Ayoubkhani et al. performed an observational, retrospective, matched cohort study of individuals in hospital with COVID-19 in England using data from several registries, the Hospital Episode Statistics, Admitted Patient Care records, General Practice Extraction Service, Data for Pandemic Planning and Research dataset, and Death registrations data from the Office for National Statistics. Individuals identified with COVID-19 were matched on baseline demographic and clinical characteristics with non-COVID-19 patients. All individuals were followed-up from index date to 30 September 2020 or date of death for severe adverse events, information on adverse events were identified from diagnoses made in primary care and in hospitals (13). Readmissions and deaths per 1,000 person-years in COVID-19 cases were observed, and 3.5 (3.4 to 3.6) and 7.7 (7.2 to 8.3) times greater, respectively, than in controls. Rates of post-discharge multi-organ dysfunction were elevated in individuals with COVID-19 compared with those in the matched control group. Diabetes and major adverse cardiovascular events were particularly common, both when considering all post-discharge events and only incident cases. The absolute risk of post-discharge adverse events was greater for individuals aged ≥70 years than <70 years, and for individuals of white ethnic background than in the non-white group

Radiological findings at 6 months

Han et al. reported that compared with the initial CT scans, a significant increase in the CT score for fibrotic-like changes was observed in all patients at 6 months follow-up (4). Nonetheless, significant decrease in the CT scores for total lesions, ground glass opacities, and consolidation were observed in all patients. Compared with the initial CT scans, the incidence rate of nodules or masses (17% vs 1.8%), interlobar pleural traction (17% vs 7.9%), pulmonary atelectasis (11% vs 3.5%,), and bronchiectasis (24% vs 7.0%) were significantly higher in the follow-up scans, while pleural effusion was completely resorbed (0 vs 6.1%). The subgroup of 40 patients who exhibited lung fibrotic-like changes at six months follow-up, 2/40 (5%) showed the fibrotic-

like changes on initial CT scans. Another subgroup of 43 patients who demonstrated complete resolution of CT abnormalities, 20/43 (47%) patients showed resolution at 3 months, and the remaining 23/43 (53%) showed resolution at the 6-month follow-up.

In Huang et al., 353 participants completed chest HRCT at follow-up (5). The median CT scores increased with initial severity during hospitalisation. The consolidations found in the acute phase were nearly fully resolved at follow-up. After multivariable adjustment, participants with high initial severity showed an OR 4.60 (95% CI 1.85–11.48) for diffusion impairment, compared with participants with mildest severity. Risk of diffusion impairment with initial moderate severity was not significant. The percentage change of CT score from acute phase to follow-up was higher among participants with moderate and severe COVID-19 than in those with mildest presentation. Women had an OR 2.22 (95% CI 1.24–3.98) for diffusion impairment, compared with men. Age was positively associated with diffusion impairment and negatively associated with percentage of CT score changed, with the risk of diffusion impairment OR 1.27, (95% CI 1.02–1.60) per 10-year increase of age, and percentage of CT score 4% (1.37–6.64) lower per 10-year increase of age.

Studies with 3-6 months of follow-up

Brief summary

We identified six studies with 3-6 months of follow-up; one each from Norway (18), France (15), Switzerland (16), Denmark (17), China (19) and the Faroe islands (20), four prospective observational cohort studies (16-18, 46), and three phone surveys (15, 19, 20). The sample size ranged from 120-538, with most participants being middle aged. All but one study included hospitalised COVID-19 patients (20). The study participants across all the studies had PCR-confirmed COVID-19 diagnosis. The majority of the studies focused on prevalence of symptoms. These studies showed that at least any one symptom remained during follow-up. Most studies reported high prevalence of dyspnoea and fatigue irrespective of the time of follow-up. Three studies reported prevailing sleep disturbances (15, 17, 19). Two studies reported the loss of hair (15, 19). Two studies analysed quality of life on follow-up, finding that life quality remained compromised, to some extend more in ICU patients (15, 18).

Garrigues et al. performed a phone survey of 120 hospitalised COVID-19 patients, ICU and general ward patients (15). The authors assessed patients for persistent symptoms and health-related quality of life from a single-centre after 100 days of admission. They used a phone questionnaire to collect post-discharge clinical symptoms, degree of breathing difficulties, professional and physical activities, and attention, memory and/or sleep disorders. Health-related quality of life was assessed using the EQ-5D-5L questionnaire. After a mean of 110.9 days, the most frequently reported persistent symptoms were fatigue (55%), dyspnoea (42%), loss of memory (34%), and concentration and sleep disorders (28% and 30.8%, respectively). A similarly reduced quality of life was found in both ICU (mean EQ-VAS: 71.7, EQ-5D index: 0.82) and standard care patients (mean EQ-VAS: 69.9%, EQ-5D index: 0.86).

Guler et al. conducted a national multicentre prospective cohort study in Switzerland with the objective to assess lung function on follow-up (16). A total of 113 COVID-19 patients were included and grouped into mild/moderate or severe/critical COVID-19. Overall, average pulmonary function was normal in patients after mild/moderate COVID-19. Severe/critical disease was associated with impaired pulmonary function, reduced scores in six minute-walking-test, and exercise-induced oxygen desaturation. The authors concluded that four months post SARS-CoV-2 infection, severe/critical COVID-19 was associated with significant functional and radiological abnormalities, potentially due to small airway and lung parenchymal disease.

Sonnweber et al. conducted a prospective, multicentre, observational study among 145 hospitalised COVID-19 patients in Denmark (17). The authors systematically evaluated the cardiopulmonary damage in subjects recovering from COVID-19. Most participants had pre-existing comorbidities (77%) with cardiovascular and metabolic diseases being the most frequent. On 100 days follow-up, 41% of all subjects had persistent symptoms, including dyspnea (36%), night sweat (24%), sleep disorders (22%), or hyposmia/anosmia (19%), but with decreasing frequency compared to the acute phase. Severe symptoms on longest follow-up, such as a severely impaired performance or severe dyspnea were only found in 2% and 4% respectively. Overall, a marked and continuous improvement of all assessed symptoms was observed. Only a minority of subjects showed cardiac impairment. Sequential follow-up

evaluations at 60 and 100 days after COVID-19 onset demonstrated a vast improvement of both, symptoms and CT abnormalities over time.

Lerum et al. aimed to describe self-reported dyspnoea, quality of life, pulmonary function, and chest CT findings three months after hospital admission for COVID-19 (18). A total of 103 discharged COVID-19 patients from six Norwegian hospitals were consecutively enrolled in their prospective cohort study. Approximately half of all participants reported dyspnoea on exertion three months after hospital admission for COVID-19. One fourth of the participants had chest CT opacities and reduced diffusion capacity. Admission to ICU was associated with pathological CT findings, which were not reflected in increased dyspnoea or impaired lung function. The assessment of quality of life with the EQ-5D-5L score found that participants were experiencing a decrease in quality of life, both among ICU patients (EQ-5D index scores (SD): 0.61 (0.23)) and non-ICU patients(EQ-5D index scores (SD): 0.72 (0.19)). Patients admitted to ICU were more impacted in their usual activities than participants admitted to regular wards only.

Petersen et al. performed a questionnaire-based telephone survey 125 days after their initial symptoms in the Faroe Islands (20). The authors analysed long lasting symptoms in 180 mainly non-hospitalised COVID-19 patients. After a mean of 125 days, at least one persisting symptom was reported by 53% of participants. The most prevalent persistent symptoms were fatigue, loss of smell and taste, and joint pains. A third of patients reported one or two symptoms, and 19% three or more symptoms. Severe persistent symptoms were reported by 9%. At follow-up symptoms persisted significantly more frequently among individuals in the age group 50-66 compared with the youngest groups. No differences were found in presence or severity of symptoms regarding hospitalization, sex, smoking, self-reported medication use, or chronic diseases overall, or for each of the most prevalent diseases.

Xiong et al. conducted a longitudinal study based on a telephone survey of 538 COVID-19 survivors 3 months after discharge from hospital in Wuhan, China (19). A cohort of volunteers without COVID-19 from the urban area was selected as controls. Participants were mainly middle aged, and median time from discharge from hospital to follow-up was 97.0 days. Clinical sequelae were common, including general symptoms (49.6%), respiratory symptoms (39%), cardiovascular-related symptoms (13%), psychosocial symptoms (22.7%) and alopecia (28.6%). Most patients who reported these symptoms improved, but 6.5% 0f survivors reported no improvement at all. Based on a univariate analysis, sequelae were more common in female subjects, except for high resting heart rate. In an additional exploratory analysis, dyspnoea during hospitalization was associated with subsequent physical decline/fatigue.

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Table 4. Overview of peer reviewed studies with 3-6-month follow-up, reporting prevalence of symptoms on follow-up. A selection of symptoms as provided by the authors, in some instances authors used overlapping terms, some symptoms were not clearly defined. Proportion of patients experiencing a symptom on follow-up, more than 30% red, between 30 and 10% orange, less than 10% yellow.

	Garrigues et al.	Sonnweber et al.	Lerum et al.	Xiong et al.	Petersen et al.
Country	France	Denmark	Norway	China	Faroe Islands
Participants included (n)	120	145	103	538	180
Age years	Mean 63.2 (±15.7)	Mean 57 (14)	Median 59 (49-72)	Median 52.0 (41.0-62.0)	Mean 39.9 (±19.9)
male % (Sex)	62.5% (75/120)	57% (82/145)	52% (54/103)	45.5% (245/538)	46% (88/180)
COVID-19 confirmation	PCR	PCR	PCR	PCR	PCR
Follow-up from	Admission	Post-Diagnosis	Admission	Discharge	Initial symptoms
Follow-up length	110.9 days	100 days	3 months	97.0 (95.0-102.0) days	125 days
Loss to follow-up	NA	24%	0%	24%	4%
Hospitalised/ Non-hospitalised	Hospitalised	Hospitalised	Hospitalised	Hospitalised	Non-hospitalised
Symptoms					
Any symptom		41% (60/145)		50% (267/538)	47% (84/180)
Neurologic					
Anosmia	13% (16/120)	19 % (27/145)			24% (43/180)
Ageusia	11% (13/120)				16% (29/180)
Cognitive dysfunction					
Dizziness				3% (14/538)	
Memory loss	34% (41/120)				
Attention disorder	26.7% (32/120)				
Headache					7% (13/180)
Respiratory tract					
Expectorate					
Exertion dyspnea/ dyspnea	41.7% (50/120)	36 % (52/145)	54% (37/69)		8% (14/180)
Sore throat or difficult to swallow				3% (17/538)	3% (5/180)
Musculoskeletal					
Muscle weakness or fatigue	42% (50/120)			23% (152/538)	
Joint pain				8% (41/538)	11% (25/180)
Myalgia				5% (24/538)	7% (13/180)
Cardiopulmonary				13% (70/538)	
Resting heart rate increase				11% (60/538)	
Newly diagnosed Hypertension				1% (7/538)	
Chest pain	11% (13/120)			12% (66/538)	5% (9/180)
Dry cough/ cough	17% (20/120)			7% (38/538)	5% (9/180)
Systemic & other					
Fatigue	55% (66/120)			28% (152/538)	24% (43/180)
Hair loss	20% (24/120)			29% (154/538)	
Diarrhoea					4% (7/180)
Vomiting					
Skin rash					2% (5/180)
Chills				5% (25/538)	6% (11/180)
Night sweats		24% (35/145)			
Sweating				24% (127/538)	
Psychosocial				23% (122/538)	
Anxiety				7% (35/538)	
Depression				3% (23/538)	
Sleep difficulties	31% (37/120)	22 % (32/145)		18% (95/538)	
Radiologic					
Lung fibrotic changes					
GGO			25% (25/103)		
Parenchymal bands,			19% (19/103)		

Predicting factors in studies 3-6 months

Four studies analysed predicting factors for duration of symptoms (16-18, 20). Age was found in three studies to correlate with length or severity of lasting symptoms (17, 18, 20). Severity of COVID-19 was found to correlate with functional impairment, and radiological changes (16).

Petersen et al. age-stratified analysis revealed a statistically significant difference in occurrence and number of symptoms between different age groups, with longer symptoms in the elderly (20). No differences were found in presence or severity of symptoms with regard to hospitalisation, sex, smoking, self-reported medication use, or chronic diseases overall, or for hypertension, asthma, hypercholesterolemia, or diabetes type 2.

The analysis by Sonnweber et al. revealed that the severity of acute COVID-19 and patient recovery was associated with age, gender, and pre-existing diseases such as cardiovascular diseases, pulmonary diseases, diabetes mellitus type 2, and malignancy (17).

Radiological findings at 3-6 months

Guler et al. reported that typical radiological follow-up sequelae of COVID-19 included uni-or multi-lobular hypo-attenuated areas, ground-glass opacities, linear/curvilinear densities, reticulations, honeycombing, traction bronchiectasis with architectural distortion in various locations as well as pneumatoceles (16).

According to Sonnweber et al., CT scans unveiled persisting lung pathologies in 63% of patients, mainly consisting of bilateral ground-glass opacities and/or reticulation in the lower lung lobes, without radiological signs of pulmonary fibrosis(17). Although the extent of consolidations and bronchial dilations almost completely resolved, and the mean extent of ground glass opacities significantly decreased. Contrary, reticulations only gradually improved.

Lerum et al. reported persistent ground glass opacities on CT-scans present in one fourth of the participants, while one in five had parenchymal bands, indicating early progression to fibrosis(18). Participants admitted to ICU during hospital admission had higher prevalence of persistent CT abnormalities.

Studies with 1-3 months of follow-up

We identified 26 studies with 1-3 months of follow-up. The majority of the studies analysed hospitalised patients. Nineteen studies are from Europe, 4 from the US, and one each from India, Iran and Turkey. Due to prioritisation of longer follow-up studies, we did not review these studies in detail.

Table 5. Overview of studies with 1-3 months of follow-up (alphabetical order)

Author	Country	Participants (n)	Study design	Hospitalised / non-hospitalised
Afshar et al. (21)	US	594	nationwide prospective cohort study	non-hospitalised
Arnold et al. (22)	UK	131	prospective cohort study	hospitalised
Boscolo-Rizzo et al. (23)	Italy	202	cross-sectional survey-based study	non-hospitalised
Carfi et al. (24)	Italy	179	Observational study	hospitalised
Caronna et al. (25)	Spain	130	prospective study	Ambulant care
Carvalho-Schneider et al. (26)	France	150	descriptive clinical follow-up	hospitalised
Cellai et al. (27)	US	551	telemedicine follow-up	non-hospitalised
Chiesa-Estomba et al. (37)	France	751	prospective survey-based study	hospitalised
Goertz et.al	Netherlands/ Belgium	2113	Web-based study (Facebook)	Mixed
Jacobs et al. (28)	US	183	prospective cohort study	hospitalised
Mandal et al.(29)	UK	384	prospective cohort study	hospitalised
Mazza et al.(30)	Italy	402	unstructured clinical interview	mixed
Moreno-Perez et al. (45)	Spain	277	prospective cohort study	hospitalised
Munoz et al. (40)	Spain	100	Observational study	hospitalised
Panda et al.(31)	India	225	prospective cohort study	hospitalised
Parente-Arias et al. (36)	Spain	151	observational cohort study	hospitalised
Pizzini et al. (32)	Austria	109	prospective, multicenter, observational study	hospitalised/ ICU
Poncet-Megemont et al.(41)	France	139	cross-sectional survey study	hospitalised
Poyraz et al. (39)	Turkey	284	cross-sectional survey study	hospitalised
Shima et al. (38)	Iran	100	cohort study	hospitalised
Smet et al.(33)	Belgium	220	outpatient follow-up study	hospitalised/ ICU
Tomasoni et al. (34)	Italy	105	Cross sectional study	hospitalised
Vaes et al. (42)	Netherlands/ Belgium	1837	survey-based study	mixed
Van den Borst et al.(43)	Netherlands	124	Observational study	hospitalised
van der Sar - van der Brugge et al. (44)	Netherlands	101	prospective longitudinal cohort study	hospitalised
Weerahandi et al. (35)	US	161	prospective single health system observational cohort study	hospitalised

Discussion and conclusion

We included 43 studies. We looked at three different lengths of follow-up; longer than six months follow-up (11 studies) which was our main focus, 3-6 months (7 studies), and 1-3 months (26 studies). Due to few studies with 6 months follow-up or more, we also included non-peer reviewed studies for this period (7 studies). Our approach reflects the early stage of research, and emphasises that current findings need to be seen critically. Our findings represent an overview of the limited available evidence rather than a synthesis of findings.

For six months follow-up, we identified 11 studies, of which only four studies are peer reviewed. We identified seven European, two Chinese, one Israeli study and one international survey. Only four studies performed clinical follow-ups, and seven studies used a PCR test to diagnose COVID-19. Included participants were mostly middle-aged. Loss to follow up was generally high. Most studies focused on prevalence of symptoms. These studies showed that at least one symptom remained at 6 months of follow-up. Most commonly reported symptoms were dyspnoea, fatigue and smell and taste abnormalities. Fewer studies included analysis of correlating factors between initially registered information and measured outcomes. Findings remain heterogeneous, whilst indicating that severity of initial COVID-19 is associated with prolonged symptoms. Echoing this, one study looking at healthcare utilisation found that patients with severe COVID-19 probably consumed more healthcare due to their initial illness, not seen in patients with initial mild COVID-19. Similarly, one study found that among non-hospitalised COVID patients at 1.5-6 months post quality of life scores were similar to population norms.

We identified six studies with 3-6 months follow up, all of which were peer-reviewed. Five studies came from Europe, and one from China. All but one study included PCR confirmed hospitalised COVID-19 patients. There is high heterogeneity across the studies. Four studies conducted clinical follow-ups, in addition to self-reported symptoms. One study only looked at the pulmonary function. Two studies compared COVID-19 ICU vs. non-ICU patients concluding that there were few differences in the symptoms at follow-up. All studies reported lasting symptoms in included patients on follow-up. Most common symptoms were dyspnoea, fatigue, anosmia and sleeping problems. The most consistent predicting factors for symptom duration were age and severity of COVID-19.

We were able to gain first insights into long-lasting effects of COVID-19. Our broad inclusion criteria, limited only to a threshold of 100 participants or more, allowed us to find as many large relevant studies as possible. However, the identified studies validity of results to the Norwegian setting is probably limited at this time. The majority of included participants were hospitalised, and do not reflect the general population. We performed quality assessment of included studies

with 6 months follow-up, finding that quality remains mixed. We did not grade the certainty of evidence, which is why the results from this review should still be interpreted with caution.

The included studies were heterogeneous in terms of statistical methods and procedures. Most studies suffered from large loss to follow up, and were prone to recall bias. The majority of studies did not include matched controls, which is a strong limitation in evaluating COVID-19 specific effects. Due to lack of controls, it remains uncertain how far prevailing symptoms are specific to COVID-19 or more generally attributable to a period of illness. Equally, pandemic related infringements on personal liberty, lockdowns and changes to pre-pandemic lifestyle might also be factors underlying reporting of some symptoms. These factors are not limited to patients who have had COVID-19, but apply to the whole population. The long-termed effects of COVID-19 and long-termed effect of the pandemic situation are difficult to single out in un-controlled studies.

Patients who have been admitted to intensive care unit with COVID-19 seem to be at greatest risk for developing long COVID, but without controlled studies it remains unclear to what extent their symptoms are COVID-19 specific or reflects more general consequences of intensive care. It is well-known that many patients who are admitted to intensive care units after invasive medical treatment experience post-intensive care syndrome (PICS). PICS shares many similarities with long presenting COVID-19. In line with some studies on long COVID, typical risk factor for PICS are older age, female sex and disease severity (48). Furthermore, the majority of studies focused on the prevalence of symptoms, but it remains unclear to what extent these symptoms affect activities of daily living and quality of life.

Only one study assessed changes in healthcare utilisation for patients before and after COVID-19. The large prevalence of symptoms in mild COVID-19 patients over time is not reflected in respective changes of healthcare utilisation. Interestingly, for more severe COVID-19 patients this inconsistency is not apparent. This might indicate that patients with mild COVID-19 continue to experience symptoms, but not to the extent that they consider medical help as necessary. It could also be that there is an over-reporting of symptoms, possibly due to loss to follow up and recall bias. With the currently available data, still too much uncertainty remains to reach a clear conclusion.

There was also large variability in the way different symptoms were categorised. Differences in reporting also represent differences in target population and characteristics, as for example ethnical groups in one location my not be representative for another location. The existing heterogeneity impairs direct comparison of risk estimates across studies, and hence meta-analysis was not feasible. It should be noted that causal relationships cannot be confirmed or refuted based on the included study designs.

Conclusion

Based on 43 studies of mixed quality and limited representativeness we have found that; Hospitalised COVID-19 patients report prevailing symptoms long after infection, with a large proportion continuing to experience one or more symptoms at six months of follow-up. Severe COVID-19 illness, requiring intensive treatment, correlates with longer and more functional limitations on follow up. It appears that patients with more severe COVID-19 require more

healthcare services and are more affected by adverse effects over time. Due to an over representation of hospitalised patients with severe COVID-19 in the reviewed studies, the findings are not considered representative for those with milder symptoms. The long-term impact of COVID-19 on the quality of life in the general population remains unclear.

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Appendix

Appendix 1; Search strategy

Search: 2021-01-26
Ovid MEDLINE(R) ALL January 01, 2021 to January 26, 2021

#	Query	Results
1	chronic covid*.ti,ab,kf.	8
2	long covid*.ti,ab,kf.	53
3	persistent covid*.ti,ab,kf.	10
4	(Post acute covid* or postacute covid*).ti,ab,kf.	20
5	(Post covid* adj3 (illness* or syndrome* or symptom*)).ti,ab,kf.	38
6	(Prolonged adj3 covid*).ti,ab,kf.	56
7	or/1-6	178
8	(chronic adj3 (complication* or infect* or symptom* or syndrome*)).ti,ab,kf.	87977
9	(Long-haul* OR longhaul*).ti,ab,kf.	873
10	((long-term or longterm) adj3 (complication* or consequence* or outcome*)).ti,ab,kf.	107129
11	(Persistent adj3 (infecti* or symptom* or syndrome*)).ti,ab,kf.	25675
12	(Prolonged adj3 recovery).ti,ab,kf.	2504
13	sequelae*.ti,ab,kf.	65210
14	or/8-13	282589
15	exp Coronavirus/	45480
16	exp Coronavirus Infections/	49711
17	(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.	111302
18	((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	4261
19	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.	96949
20	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	39990
21	or/15-20	117249
22	21 and 20191201:20301231.(dt).	97953
23	14 and 22	966
24	7 or 23	1105

Search: 2021-01-29
WHO COVID-19 Global literature on coronavirus disease

TW:(long-covid OR "long covid" OR long-haul* OR "long haul" OR "long hauler" OR "long-haulers" OR "lingering complications" OR "long term complications" OR "longterm complications" OR "long-term complications" OR "persistent complications" OR "prolonged complications" OR "sustained complications" OR "lingering effects" OR "long term effects" OR "longterm effects" OR "long-term effects" OR "persistent effects" OR "prolonged effects" OR "sustained effects" OR "lingering symptoms" OR "long term symptoms" OR "longterm symptoms" OR "long-term symptoms" OR "persistent symptoms" OR "prolonged symptoms" OR "sustained symptoms" OR "post-covid syndrome" OR "post covid syndrome" OR survivors OR survivorship OR "post-covid syndrome" OR "post covid syndrome" OR survivors OR survivorship) OR SU:time

Results: 1291