Patient-reported outcomes and lung function after hospitalization for COVID-19 (PROLUN)

1. Background

1.1 COVID-19 and its clinical course

The first cases of Coronavirus Disease 2019 (COVID-19) emerged in early December 2019 in Wuhan, Hubei, China [1]. The outbreak rapidly spread throughout the region and to other parts of the world [2,3]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Since SARS-CoV-2 is a novel virus, none in the human population have established humoral immunological defense [4]. This contributes to the pandemic spread of the virus in the population. There is very limited evidence on immunity after infection with SARS-CoV-2 [4]. Currently, it is not known whether the immune reaction, including development of specific IgG-antibodies, in response to COVID-19 is associated with long-term outcomes.

Symptoms and disease severity of COVID-19 vary greatly, from asymptomatic infection to mild illness to severe or fatal illness. While most patients experience none or only minor upper respiratory symptoms, up to 15% may require hospital admissions, of whom 5% receive intensive care unit (ICU) treatment, and 3% develop disease similar to acute respiratory distress syndrome (ARDS), requiring mechanical ventilation [2].

In a recent report of hospitalized patients, dyspnea developed in 22 (55%) of 40 patients, and all patients had pneumonia with abnormal findings on chest CT. Complications included ARDS (29%), RNAaemia (15%), acute cardiac injury (12%) and secondary infection (10%). In total, 32% of the patients with pneumonia were admitted to an ICU and 15% died [1]. In those developing ARDS, mechanical ventilation using lower tidal volumes and lower inspiratory pressures are recommended, as is prone positioning for 12-16 h/day for those with severe ARDS [5].

Norway rapidly became one of the earliest countries with a high number of infected individuals per capita [6]. As of March 2020, the Norwegian health authorities recognize that there is a high risk of a national COVID-19 epidemic, in which up to 2.2 million people may contract the virus and possibly 733.000 people may become ill [6]. As of 22 March 2020, 2361 people have been verified with COVID-19 in Norway, with a mean age of 47.1 years; 173 are hospitalized and 38 have or have had ICU care [7]. The National Institute of Public Health expects the number of affected people to increase rapidly [6].

1.2 COVID-19 and interstitial lung disease

Interstitial lung diseases (ILD) are a heterogeneous group of pulmonary diseases characterized by inflammation and fibrosis of the lung parenchyma [8]. While some patients with ILD only experience minor symptoms including cough and exercise dyspnea, others will progress to severe disease with substantially reduced lung function, severe dyspnea, hypoxemia, reduced health-related quality of life (HRQoL) and high rates of mortality [8]. ILD may produce a wide range of unspecific radiological features including patchy consolidations, bronchial wall thickening, honeycombing, traction bronchiectasis, nodules,

cysts, as well as reticular and ground-glass opacities (GGO) [9]. Pulmonary function tests (PFT), including spirometry, plethysmography and diffusion tests, allow for the identification of restrictive ventilatory defects, a hallmark of ILD [10].

A study of 110 survivors of the SARS-CoV-1 outbreak in 2002–2003 found that after 6 months 30% had abnormal chest radiographs, and various lung function parameters were reduced in up to 15% of patients [11]. Furthermore, SARS-CoV-1 survivors exhibited significant decrements in HRQoL and exercise capacity. Other studies reported organizing diffuse alveolar damage (DAD) with increased fibrosis, squamous metaplasia and multinucleated giant cells in SARS-CoV-1 patients with longer-standing disease (>10 days) [12–14].

The underlying mechanisms for the aforementioned lasting lung injuries have not been fully elucidated. However, studies on long-term lung injury after ARDS may shed some light on the pathophysiology. ARDS is a disease of multifactorial etiology characterized histologically by DAD, which can be differentiated into two major temporal phases [15]:

1) An early exudative phase which is characterized by inflammatory edema in the airspaces, hyaline membrane formation and microvessel injury.

2) A fibroproliferative phase, in which the tissue defense response attempts to resolve cellular debris and edema to restore the original lung parenchyma.

Although histological, radiological and biochemical evidence suggest that both phases coexist from the onset of ARDS, the fibroproliferative phase appears to become the predominant feature after approximately 7 days [15–18]. In some individuals, this phase progresses to varying degrees of fibrosis with reduced HRQoL and persistent radiological changes in approximately 25% of the patients [16,19]. Moreover, about 25% of ARDS patients have reductions in PFT after 6 months with little change during 5 years of follow-up [20]. Additionally, the pulmonary stress of mechanical ventilation is a well-documented risk factor for developing unremitting fibrotic pulmonary changes [19].

1.3 COVID-19 and radiological findings

According to a study by Shi *et al*. COVID-19 pneumonia manifests with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral GGO that progressed to, or co-existed with, consolidations within 1–3 weeks [21]. Most patients showed bilateral lung involvement, with lesions mainly located peripherally and subpleurally with diffuse distribution. The predominant pattern was GGO with ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura. These imaging characteristics are non-specific and bear some resemblance to those of SARS-CoV-1 and MERS-CoV infections [21].

Among 21 patients in another study by Chung *et al*., GGO were observed in 12 patients (57%) and consolidation was observed in six (29%) [22]. The extent of disease on CT scans shows a marked increase from the subclinical period through the first and second weeks after symptom onset, then decreases gradually during the third week [21].

Moreover, there is a high incidence of subclinical CT changes in cases with COVID-19. Inui *et al*. have described more GGO over consolidation and milder extension of disease on CT in patients with asymptomatic SARS-CoV-2 infection compared to symptomatic cases

[23]. The typical pattern of CT images in subclinical SARS-CoV-2 infected patients is unilateral, multifocal, predominantly GGOs [21].

Shi *et al*. also found that serial CT imaging of patients can help to monitor disease changes by reflecting therapeutic effects that may be associated with COVID-19 outcomes [21]. The most common pattern of evolution throughout series of CT scans was initial progression to a peak level, followed by radiographic improvement [21]. None of the CT features of COVID-19 are specific or diagnostic, and COVID-19 pneumonia shares CT features with other non-infectious conditions that present as subpleural air-space disease [21].

As COVID-19 is a new disease, there is little information about radiological changes over time and the association with clinical variables, and other outcomes, such as pulmonary function, physical functioning and patient-reported outcomes. More information about radiological patterns will be available as findings from larger series and follow-up studies are presented. As claimed in a recent comment, more research is needed into the correlation of CT findings with clinical severity and progression, the predictive value of baseline CT or temporal changes for disease outcome, and the sequelae of acute lung injury induced by COVID-19 [24].

1.4 COVID-19 and cardiac function

Pre-existing cardiovascular disease (CVD) increases vulnerability to severe COVID-19 infection [2,25]. In addition, COVID-19 can worsen underlying CVD and trigger new cardiac complications. In a study from Wuhan, China, a third of those hospitalized with COVID-19 in a study from Wuhan, China, had underlying CVD (hypertension, coronary heart disease, or cardiomyopathy), and 28% had acute myocardial injury [26].

In patients without previous history of CVD, SARS-CoV-2 may affect the cardiovascular (CV) system with short-term and potential long-term consequences for CV health [27,28]. Possible mechanisms of SARS-CoV-2 responsible for CV complications have been reported are for example the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) with alteration of ACE2 signaling pathways, systemic inflammation with high circulatory levels of proinflammatory cytokines and prothrombotic milieu, impaired myocardial oxygen demand-supply and electrolyte imbalance [27–29]. Further, adverse effects of antiviral drugs, corticosteroids and other therapies aimed at treating COVID-19 can also have harmful effects on the CV system. It is possible that patients with COVID-19 could suffer from cardiac injury, myocarditis, heart failure or arrhythmia.

The clinical effects of hospitalization for pneumonia have been linked to a 50% higher risk of CVD than those not hospitalized for pneumonia with up to 10-year follow-up [30]. Heightened systemic inflammatory and pro-coagulant activity can persist in survivors of hospitalization for pneumonia long after resolution of the index infection. Therefore, pneumonia may be a risk factor for CVD. In survivors after SARS-CoV infection CV abnormalities, as well as altered lipid and glucose metabolism were present in 40%, 68% and 60%, respectively, at 12-years follow-up [31]. Long-term follow-up data concerning the survivors of respiratory virus epidemics are in general scarce but suggest long-term CVD consequences. COVID-19 survivors could experience similar adverse CV outcomes.

1.5 COVID-19 and patient-reported outcomes

The traditional goal for intensive care is to reduce acute mortality. However, acute life-threatening illnesses may also cause severe sequela with great impact on patients' quality of life. Therefore, attention has recently been directed to how acute, life threatening illness and treatment in ICU affects patients' and their relatives' health and HRQoL [32].

It is well-known that age and disease severity are associated with the level of functioning after acute critical illness [33]. However, comparison of results between studies is difficult because of differences in case-mix, study designs and questionnaires, as well as different time of follow-up, and variations in treatment between countries [34]. There has also recently been growing interest in serious psychological sequela after ICU treatment, including posttraumatic stress disorder (PTSD) [35–38] PTSD is a chronic and debilitating mental condition that develops in response to catastrophic life events. Significant PTSD symptoms have been reported in 44% of critical illness survivors [39]. Furthermore, there is evidence that depressive symptoms may be prevalent after intensive care treatment, whereas studies on clinically significant anxiety symptoms are sparse [40]. Studying these symptoms after ICU treatment in patients with COVID-19 is crucial, since they may be modifiable contributors to decline in function and quality of life

The COVID-19 epidemic leads to quarantine and social isolation in the general population, which may have important psychological impacts. About 5% of the general population of Wuhan, China suffered from symptoms of acute posttraumatic stress about 1 month after the outbreak [41]. It is unknown how hospitalization for COVID-19 impacts long-term HRQoL and psychological outcomes including PTSD, or whether this is dependent on whether ICU-treatment.

Non-respiratory symptoms are frequently reported during COVID-19. Symptoms such as anosmia, headache, fatigue or sleepiness are reported in Norwegian patients with SARS-CoV-2 (www.koronastudien.no, 16.05.2020). Currently, it is not known whether non-respiratory symptoms may persist and influence HRQoL.

2. Objectives

2.1 General objectives

The main objectives of this cohort study are to provide follow-up data on persistent lung or cardiac injury, self-reported pulmonary symptoms and symptoms of anxiety, depression and PTSD following hospitalization for COVID-19, and their association with clinical variables and biomarkers during hospitalization.

2.2 Predetermined hypotheses

- Only COVID-19 patients who were admitted to ICU have persistent clinical and radiological signs of pulmonary fibrosis after 12 months.
- The proportion of COVID-19 patients with symptoms of anxiety, depression and PTSD is higher in patients admitted to ICU than in general wards.
- Symptoms of anxiety, depression and PTSD and HRQoL improve from 3 to 12 months after hospitalization for COVID-19.

2.3 Specific objectives

Primary outcomes

1 a) The prevalence of restrictive lung function impairments and reduced gas diffusion after hospitalization for COVID-19.
1 b) The prevalence of interstitial lung findings 3 months and 1 year after hospitalization for COVID-19; GGO, reticular and linear pulmonary findings, scaring and fibrosis, nodular changes, consolidations, peripheral or central zonal dominance, apical or basal zonal dominance.

Secondary outcomes
2 a) Explore the associations between baseline characteristics during COVID-19 hospitalization and sustained reduced PFT and radiological signs of ILD.
2 b) Assess the predictive value of surfactant protein A and D and antibody titer for sustained reduced PFT.
2 c) Explore the associations between novel serum and plasma biomarker levels during hospitalization for COVID-19 and reduced PFT or radiological signs of pulmonary fibrosis.
2 d) Assess the cardiopulmonary fitness, prevalence of cardiac dysfunction and arrhythmias following ICU- and non-ICU treatment for COVID-19, and their associations with baseline characteristics.
2 e) The prevalence and time course of anxiety, depression, chronic insomnia and PTSD following hospitalization for COVID-19, according to ICU treatment.
2 f) The prevalence and time course of upper respiratory symptoms, chronic sinusitis, anosmia and fatigue.
2 g) Explore the associations between baseline characteristics and persistent symptoms of anxiety, depression and PTSD.
2 h) Assess the HRQoL and changes in HRQoL following hospitalization for COVID-19, according to ICU treatment, age and gender.
2 i) Assess the 10-year mortality and prevalence of pulmonary disease following hospitalization for COVID-19.

3. Design, materials and methods:

3.1 Study design and inclusion

The proposed project is a prospective, multicenter cohort study from 2-6 weeks to 10 years after hospital discharge for COVID-19 infection. All patients ≥18 years of age discharged alive with a diagnosis code of "U07.1", U07.2", "J12.X viral pneumonias" and living within the catchment areas of six large Norwegian university hospitals are eligible. The hospitals are Akershus University Hospital (Ahus), Oslo University Hospital (OUH) Ullevål and Rikshospitalet, Østfold Hospital (SØ), Haukeland University Hospital (HUS) and St.Olav Hospital (St.Olav). Hospitalization is defined as time from hospital admission to discharge of ≥8 hours. Participants in competing studies with the similar outcomes are not eligible.

Eligible patients will be identified through the following sources:
1) Patients to be discharged from one of the hospitals.
2) Participants in the biomarker-study: "Mekanismer bak sykelighet og dødelighet ved Covid-19" (REK 117589, Ahus) have consented to receive new invitations for follow-up studies.

3) Participants in the quality registry "Covid OUS" at OUS approved 13. March 2020 (20-07119). The register contains all patients hospitalized with confirmed SARS-CoV-2 and contains prospectively collected clinical data and laboratory parameters from day of admission.
4) Regular (weekly) extraction of diagnosis codes from the hospital information systems will provide the study group with a list of discharged patients with COVID-19 not covered by source 1-3 above.
An invitation to participate in the project will be delivered directly to eligible persons identified from source 1 above, while eligible persons identified from sources 2-4 above will receive an invitation by mail within 6 weeks of discharge.

We aim to use a digital consent form through the TSD-platform (University of Oslo). For patients who do not want to use a digital consent form, a paper consent form will be attached to the information letter.

3.2 Patient flow and data collection:
Completion of the digital or paper consent form will indicate the start of the follow-up period. This will enable the study group to obtain information from the electronic medical record file at the involved hospitals regarding the COVID-19-hospitalization, which will constitute the baseline data (Table 1).

Table 1. Baseline variables obtained from the electronic medical record

Clinical measures	**Medical history**	**Treatment**
NEWS	Charlson comorbidity index	Medication
qSOFA	Cardiovascular/pulmonary	Non-invasive ventilation
CURB-65	History of lung function	ICU
Vital parameters	Clinical frailty scale	**COVID-19 symptoms**
Laboratory measures	History of psychiatric disease	Symptom type and initiation
Clinical hematological and biochemical tests	**Radiological exams**	Travel history
Arterial blood gas	Chest radiograph	
Microbiological results	History of chest CT-scans	

NEWS: National Early Warning Scale, qSOFA: quick Sequential Organ Failure Assessment; CT: Computer tomography.

The first patient follow-up (T0) is questionnaire-based and will be provided digitally through Nettskjema in TSD following completion of the consent form. This package will include validated questionnaires for evaluation of pulmonary symptoms (Dyspnea-12 [42] and mMRC [43,44]), HRQoL (RAND-36 and EQ-5D-5L [45,46]), screening tools for anxiety (GAD-7 [47]), depression (PHQ-9 [48]) or PTSD (PCL-5 [49]). Participants may also opt to receive paper questionnaires by mail.

The clinical follow-ups (T1 and T2) will be performed 2–4 months and 11-13 months after hospital discharge, respectively. The T1 visit will consist of a common set of

examinations related to the primary outcome for all centers: Low-dose chest CT scan, PFTs, pulse oximetry, blood samples (table 2) as well as information about smoking status, work status and current medication. Spirometry, gas diffusion test and whole-body plethysmography will be performed according to the European Respiratory Society recommendations. Antibody measurement against SARS-CoV-2 in serum or plasma samples will be tested using enzyme linked immunosorbent assays (ELISA) and/or chemiluminescence technology following the manufacturers' (Roche) protocols and recommendations from the National reference laboratory on corona virus. At the time of T1 and T2, patients will also respond to the same questionnaire as at T0, with addition of fatigue (Chalder fatigue questionnaire, FQ). The collection of these questionnaires will be partly performed by the National COVID-19 pandemic registry, and partly by Nettskjema or mail. The T2-visit will consist of PFTs and a second low-dose CT-scan for those who had pathological findings on the CT-scan at T1. The patients will complete questionnaires as T1. The common set of examinations and patient-reported outcomes are summarized in Table 2.

Table 2. Examinations and patient-reported outcomes/questionnaires administered in the study

Data collection	**Number of items**	**T0**	**T1**	**T2**
Patient reported outcomes				
Dyspnea				
Dyspnea-12	12	X	X	X
Modified MRC dyspnea scale	1	X	X	X
Health-related quality of life				
RAND 36	36	X	X	X
EQ-5D-5L	6	X	X	X
Psychological symptoms or distress				
GAD-7	7	X	X	X
PHQ-9	9	X	X	X
PTSD Checklist for the DSM-5	20	X	X	X
Chalder fatigue questionnaire	12		X	X
Case report forms				
Smoking habit			X	X
Education and work status			X	X
Current medication			X	X
Clinical examinations				
Pulmonary function tests				
Spirometry			X	X
Gas diffusion			X	X
Oximetry			X	X

Whole-body plethysmography			X	X
Chest CT scan			X	X[1]
Blood samples[2]			X	X
Additional substudy examinations[3]				
Echocardiography			X	X
Cardiopulmonary exercise test			X	X
Long-term ECG			X	X
Nocturnal oximetry			X	
Oscillometry			X	X
CT paranasal sinus			X	
Upper respiratory tract questions and diagnostic interview for chronic insomnia			X	X

MRC: Medical Research Council; PTSD: Post-traumatic stress disorder
[1]if clinically indication; [2]Hemoglobin, leukocytes, thrombocytes, creatinine, lactat dehydrogenase, ferritin, D-dimer, N-terminal pro-B-type natriuretic peptide, troponin T, SARS-CoV-2 antibody titer. [3] Ahus will perform all substudies; OUS, St.Olav and SØ will also perform cardiology substudies; HUS will perform oscillometry.

In addition to the common set of examinations and patient-reported outcomes, the protocol enables substudies relating to biomarkers, additional PFT and cardiology; Oscillometry, cardiopulmonary exercise test, long-term electrocardiography and echocardiography.

The study group will follow the cohort for 10 years with respect to extract new incidents of pulmonary events and mortality.

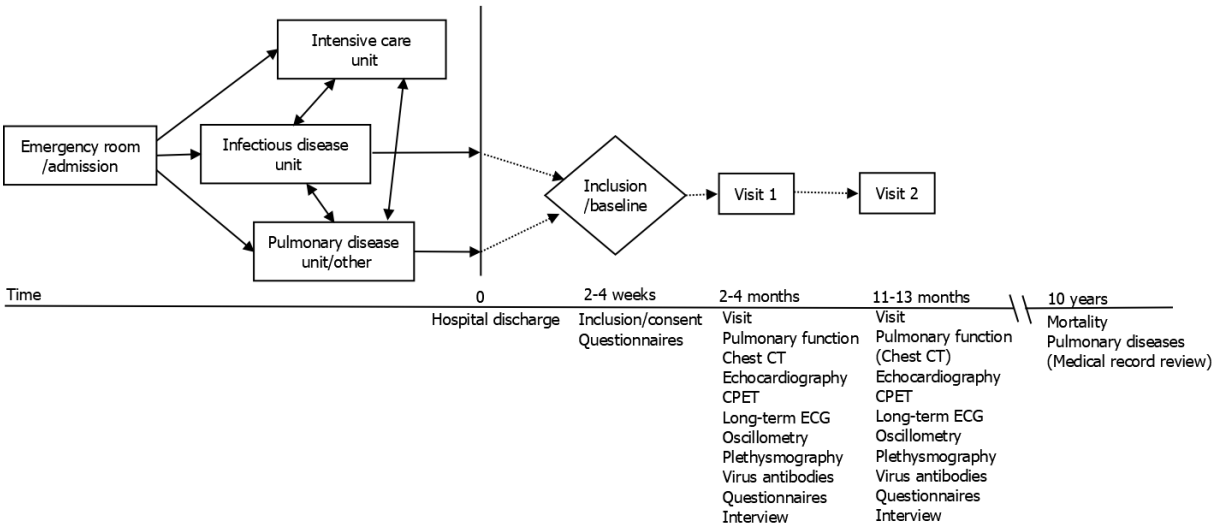

Figure 1. PROLUN study, flow-chart.

3.4 Linkage to other databases

The proposed project aims to link the database to information from the MSIS-database regarding the clinical information of the COVID-19 infection (time course of infection, etc.).

For participants who were included in baseline studies during the hospital admissions we can link our database to the biomarker results and the existing biobank. We will collaborate with the national COVID-19 pandemic registry, which will collect several of the same patient reported outcomes at similar time points as this study. To avoid that the participants need to complete the same questionnaires twice, we will obtain data of the following questionnaires from the national COVID-19 pandemic registry: EQ-5D, RAND-36, GAD-7, PHQ-9, Chalder fatigue questionnaire at 3 and 12 months. The pandemic registry will also collect questionnaires at 6 and 24 months, which we also will apply to link to our study.

3.5 Sample size considerations

To estimate whether the sample size is adequate for the primary outcomes are difficult to calculate, as the COVID-19 pandemic represents an unprecedented medical situation. The most important factor to evaluate the primary outcome is to ascertain that the included sample is similar to the general population. We believe that this will be the case in our study provided that the majority of patients from Norway's major university hospitals are invited to participate. The catchment areas of these hospitals also cover the geographical areas with the most reported patients with COVID-19 so far.

The Norwegian Health Institute of Public Health (NIPH) assumes that 42% of the population will contract the coronavirus, and that approximately 14% will develop COVID-19 [6]. Furthermore, NIPH projects that 0.42% will need hospital admission and 0.11% will require treatment in intensive care units (ICU). The mortality rate for all infected patients is expected to be below 1%, but higher among hospitalized (5-10%). The hospitals have district hospital functions for approximately 1.580 000 individuals. Thus, based on the estimates from NIPH, the cumulative number of COVID19-associated admissions to the participating centers through first year of COVID-19 may measure up >5000, of which >1000 in the ICU. We estimate a participation rate of 50-60% of the invited patients, a total cohort size of 1000. To show a 15% improvement in quality of life during follow-up, a sample size of approximately 200 is sufficient (α=0.05, 1-β =0.80).

The COVID-19 pandemic represents an extraordinary medical situation and there is an urgent need for scientific data to help inform governments and health care providers who are trying to tackle the outbreak. We therefore propose to perform the study in two work-packages (WP):

In WP1 we will include only the first consecutive 100 participants, in an attempt to rapidly provide preliminary answers to the study´s primary outcomes (1a – 1b) while the pandemic is still active. Analyses in WP2 will include all included participants, and allow us to do more sophisticated statistics to answer both our primary and secondary outcomes (2a – 2g).

3.6 Statistical analyses:

Descriptive statistics will be presented as mean and standard deviation, alternatively as median and interquartile range as appropriate. Relevant analyses for evaluation of secondary outcomes may be multiple linear regressions with outcome variables described in 2.3 as dependent variables. Continuous outcome variables will also be dichotomized according to clinically relevant cut-offs (restrictive lung function, established cut-offs of questionnaires)

and multiple logistic regressions performed. Finally, Cox proportional hazards regression analyses may be used to examine the associations between baseline variables and long-term outcomes.

4. Time schedule and dissemination of results:

We will initiate the study immediately after approval from the ethical committee and data protection officer, estimated March 30th, 2020. Due to very low number of new admissions in May, the steering committee has decided in a protocol update of 22.05.2020 to end study inclusion at June 1 2020, at a timepoint where the necessary sample size as described in 3.5 has been reached.

5. Ethical and data protection considerations

The project will seek approval by the regional ethical committee and the local data protection officer prior to study start. All participants must sign the consent based on written study information.

A low dose CT protocol of approx. 2 mSv without the use of contrast enhancement will be applied. This dose corresponds to the annual background radiation exposure or equivalent to the radiation exposure during a flight over the Atlantic Ocean. An additional CT low-dosis of paranasal sinuses for participants at Ahus will involve additional 0.8-1 mSv. The protocol is safe and without any overexposure for the participants.

If a patient presents radiological abnormalities, reduced lung function, alarm symptoms or hypoxemia at visit 1, the patient will be referred to the relevant outpatient clinic. In particular, pulmonary nodules may be detected on the chest CT scan. The Department of Radiology has established guidelines on how to follow-up such findings. All study visits will be in addition to any other clinical visits planned or performed during the study period.

The TSD (Service for Sensitive Data) service is designed for storing and post-processing sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Reaserch Act". TSD is developed and maintaned by USIT at the University of Oslo. Storage in TSD makes use of a dedicated portion of the storage facility "Astrastore" provided by NorSTore, the Norwegian data infrastructure provider. Furthermore, a PGP encrypted version of the UiO web-questionnaire (Nettskjema), interfaced with the governmental ID-portal for login, allows secure data harvesting, time-point studies and strong identification of the respondents. The TSD also provide secure and protected data storage of the images performed in the study. Transfer of images from the different sites will be by direct upload of encrypted image files to TSD or through a secure/encrypted PACS line (as used routinely for transfer of images between hospitals) to Ahus for subsequent upload to TSD.

The 3-month control may start at the time of an ongoing large-scale COVID-19 epidemic. We will seek to perform the visit 1 (at 3-4 months) at geographical sites not interfering with routine hospital work, including LHL-hospital Gardermoen.

6. Personnel, partners and resources

The study is initiated and led by the Pulmonary Research Group at Ahus, with Gunnar Einvik (MD, PhD) as the national primary investigator (PI). The conduction of the study will be

organized with a national steering group, as well as local study groups. Scientifically, the study will consist of three substudies in addition to the main study.

The national steering committee consist of Einvik, associate professor Haseem Ashraf (MD, PhD), professor Knut Stavem (MD, MPH, PhD), professor Charlotte Ingul (MD, PhD) and the local PI's from the other hospitals. The steering committee will be responsible for approving any further changes of the protocol, applications for funding and for the publication plan.

Collaboration has been established with researchers in other institutions. Professor Toril Dammen leads the research group "Psychological aspects of somatic disease" at Department of Behavioural Science at University of Oslo, and will collaborate regarding psychological outcome data. Anne Edvardsen (BLS, PhD) leads the pulmonary research group in Landsforeningen for Hjerte- og Lungesyke (LHL)-Hospitals, and is responsible for the Norwegian translation of Dyspnea-12. Professor Charlotte Ingul (Nord University, NTNU), cardiologist (consultant LHL-hospital) and anesthesiologist, will collaborate regarding the cardiovascular sub-study. The Department of Microbiology at Ahus with researcher Anita Blomfeldt will collaborate regarding the antibody titer analyses. The department of ear-nose and throat disorders at Ahus with researcher Harald Hrubos-Strøm will collaborate regarding the upper respiratory tract symptoms and CT paranasal sinuses. John Solheim is a patient representative of LHL will participate which will contribute as the user representative in this project and has reviewed the revised protocol and patient information.

Ass. professor Ashraf has received an unrestricted grant from Boehringer Ingelheim to support the conduction of the CT-scans. The sponsor will have no influence on the study conduction or publications. Personnel costs are covered by the departments of the researchers involved.

7. Dissemination plan

We will seek to publish results from the cohort study in open-access, peer-reviewed international medical journals and at national or international conferences. We have the following suggestions for papers from the cohort study:

WP #1:

- 3-month descriptive analysis of radiological outcomes in COVID-19 patients.
- 3-month respiratory function and dyspnea in COVID-19 patients.
- 3-month cardiac function at rest and during exercise in COVID-19 patients

WP#2

- 1-year pulmonary radiological outcome in COVID-19 patients.
- 1-year clinical outcome in patients hospitalized with COVID-19 infection.
- The clinical course of psychological symptoms and HRQoL during 2 years after hospitalization with COVID-19 infection.
- The association between biomarkers during COVID-19 infection and persistent ILD after 1 year

- Long-term mortality and respiratory morbidity after hospitalization with COVID-19 infection.
- 1-year cardiac function at rest and during exercise in COVID-19 patients

Additional papers may be suggested by collaborating partners during the study period and evaluated by the national steering committee before initiation of the analyses.
For papers using patient-reported outcomes, a substudy scientific group of Stavem, Dammen, Edvardsen and Einvik are responsible. The substudy of radiological examinations is led by Ashraf, while the cardiology substudy is led by Ingul.
In papers using data from other sources (section 3.4), those that have contributed considerably to the paper may be eligible for co-authorship according to the Vancouver protocol.

8. Protocol changes

8.1 Protocol version 1.1 29.03.2020
Section 3.1 has been updated with a description of usage of the participant list of "Mekanismer bak sykelighet and dødelighet ved Covid-19" to identify eligible patients.
Section 6 has been updated with information of an external sponsor, as well as minor text revisions.

8.2 Protocol version 2.0 08.04.2020
Multicenter
The protocol has been updated with the inclusion of several study sites. In addition to Ahus, OUS Ullevål and Rikshospitalet, SØ, HUS and St.Olav are collaborating in inclusion of patients. Concurrently, section 3 has been revised to describe the change in number of participants, and section 6 has been revised to describe the changes in the organization of the project.

Data collection
Table 2 has been updated with a description of planned examinations. In particular, novel examinations that are not obligatory for all sites have been added; Whole-body plethysmography, oscillometry and cardiopulmonary exercise test for lung function evaluation, echocardiography and long-term electrocardiography for cardiac function evaluation. Finally, the protocol have been updated with blood samples analysed at T1 and T2 regarding antibody against corona-virus. Accordingly, sections 1.1, 1.4, 2.1, 2.3 and 9 have been updated to describe the rationale and objectives for these new examinations.

Dissemination plan
We have added chapter 7 to describe the planned manuscripts from this project, as well as the procedure for later suggestions for new manuscripts.

8.3 Protocol version 2.1 22.05.2020
Title
The acronym was changed to avoid association with other use of the acronym PROLIFE.

Examinations
We have added a paragraph in section 1.5, and accordingly a novel secondary aim 2f, to describe upper airway outcomes. The examinations related to this outcome are questions to the patients at T1 (anosmia, nasal symptoms, sleepiness/insomnia) and CT-scan of paranasal sinuses. These will only be applied at site Ahus.
Whole-body plethysmography and blood samples have been made common for all sites.

Linkage to the national pandemic registry
In section 3.4 and table 2, the rationale for linkage to the novel national pandemic registry has been added. This registry was not initiated when the initial protocol was submitted. Accordingly, some of the questionnaires previously administered in this study will be obtained from the national pandemic registry.

End of inclusion
The end of inclusion date has been changed to June 1 2020 (section 3.4)

Inclusion/exclusion criteria
The ICD-codes described in the initial protocol were erroneous, the correct codes is described in section 3.1. After the initial protocol was drafted it has been evident that another ongoing study on the same sites also will perform PFT and pulmonary CT scans. We will not include the same participants in both studies, thus an additional exclusion criterion has been added in 3.1.

Data management
Section 5 is updated with a description on how images from CT-scans and echocardiography will be uploaded into TSD.

9. References

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