

BMJ Open Prognosis of patients with long COVID symptoms: a protocol for a longitudinal cohort study at a primary care referred outpatient clinic in Helsinki, Finland

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To cite: Virrantaus H, Liira H, Posharina T, *et al*. Prognosis of patients with long COVID symptoms: a protocol for a longitudinal cohort study at a primary care referred outpatient clinic in Helsinki, Finland. *BMJ Open* 2023;**13**:e072935. doi:10.1136/bmjopen-2023-072935

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-072935>).

Received 17 February 2023
Accepted 21 September 2023



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ABSTRACT

Introduction After COVID-19, many continue to experience persistent debilitating symptoms, that is, long COVID. Its most prevalent symptoms are chest pain, difficulties with breathing, painful muscles, ageusia or anosmia, tingling extremities and general tiredness. This paper describes the protocol of the Long COVID Cohort Study to assess the prognosis and prognostic determinants of patients with long COVID by implementing patient-reported outcome measures (PROMs), patient-reported experience measures (PREMs) and clinical examinations during a 1-year follow-up.

Methods and analysis This is a prospective, single-site cohort study consisting of administering questionnaires and clinical examinations to adult patients referred to the Clinic for Long-Term Effects of COVID-19 at Helsinki University Hospital (Hospital district of Helsinki and Uusimaa). The referrals are from all healthcare units within HUS and other hospital districts during years 2021–2023. All admitted patients have had laboratory-confirmed COVID-19. The targeted study sample size is 500 participants. The questionnaires are administered at 0, 3, 6 and 12 months. The main outcome variables are the changes in self-reported functional abilities and quality of life. In addition, we will evaluate functional abilities at baseline using neurocognitive evaluation, a 6MWT and a measurement of hand grip strength. The Long COVID Cohort Study will form a quality register for the clinic and characterise the first systematic collection of PROMs, PREMs, questionnaire and clinical examinations related to long COVID in Finland. The Study belongs to a study consortium Long COVID—HORIZON-HLTH-2021-DISEASE-04 that aims to reveal the biomechanisms of long COVID.

Ethics and dissemination This study has been approved by the Helsinki University Hospital research ethics committee board, ID HUS/1493/2021 on 6 March 2021. All study participants sign written informed consent for participation. The study findings will be reported for publication in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The systematic collection of patient-reported outcome measures will add to a patient perspective on these symptoms.
- ⇒ The clinical data benefits the EU Long COVID study consortium and its studies on biomarkers and pathogenesis of the condition by providing a length of clinical outcome measures.
- ⇒ The opportunity to later link the cohort to the national registers in Finland will allow studying the burden of disease, costs and outcomes related to long COVID.
- ⇒ Loss to follow-up could threaten the study's validity, and every effort will be made to reduce this.
- ⇒ The study will be conducted in a university hospital, and some patient selection will therefore occur.

Trial registration number NCT05699512; Pre-results.

INTRODUCTION

In mid-July 2023, there were roughly 1 480 000 confirmed COVID-19 infections in Finland, of which 38% (570 000) were within the Hospital district of Helsinki and Uusimaa (HUS). While the number of hospitalised cases has subsided, COVID-19 is still burdening the healthcare system with its long-term health effects. From the countries with the highest rates of COVID-19 cases, we know that about one-sixth of the patients experience different symptoms after the acute disease^{1 2} and that the prevalence of long COVID in individuals infected with the Omicron variant seems the lowest.³ WHO has defined post COVID-19 condition, also known as long COVID, as symptoms occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually starting within, or persisting for 3 months from the acute infection and,

lasting for at least 2 months, which cannot be explained by an alternative diagnosis.⁴

Symptoms of long COVID affect several organ systems and include fatigue, dyspnoea, atypical chest pain, heart palpitations, cognitive impairment ('brain fog'), myalgia and ageusia or anosmia.¹ In the Dutch population-based lifelines cohort study, the prevalence of long-term symptoms related to COVID-19 was analysed, while correcting for symptoms present before SARS-CoV-2 infection and controlling for the symptom dynamics in matched controls from the population without infection.⁵ Persistent symptoms in COVID-19-positive participants at 90–150 days after the acute infection included chest pain, difficulties with breathing, pain when breathing, painful muscles, ageusia or anosmia, tingling extremities, lump in throat, feeling hot and cold alternately, heavy arms or legs and general tiredness. In 12.7% of patients, these symptoms could be attributed to COVID-19, as 381 (21.4%) of 1782 COVID-19-positive participants versus 361 (8.7%) of 4130 COVID-19-negative controls had at least one of these core symptoms substantially increased to at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint.

It is likely that long COVID symptoms are influenced by several different mechanisms: persistence of chronic inflammation related to COVID-19 or other infectious agents, non-specific effect of hospitalisation, postintensive care syndrome or complications related to comorbidities. Changes in the activity of the autonomous nervous system due to physical and emotional stress, as well as disturbances in coagulation and endothelial function, also play a part.^{6,7} There is data suggesting that the symptoms are worsened by earlier onset depression and anxiety, as well as COVID-19-specific symptom expectation.⁸

In this paper, we describe a cohort study that is launched in the new HUS Clinic for Long-Term Effects of COVID-19. The clinic was established in June 2021 to help patients with persistent symptoms 3 months after a laboratory-confirmed COVID-19 diagnosis, for whom thorough medical evaluation has not revealed any other somatic nor psychiatric disease. The outpatient clinic mainly serves 40% of the Finnish population in the HUS catchment area (population 2.2 million), but has admitted patients from all hospital districts in Finland (population 5.5 million).

We aim to assess the prognosis of long COVID and determine the strength of clinically relevant prognostic factors. The participants in this study are invited to take part in a following EU Horizon-funded study on the biomechanisms of long COVID. We will report the quality of life (QOL), functional capacities, work ability and mental well-being of study participants. We will follow up the participants with electronic surveys and telephone calls up to 12 months. This research supports planning of investigations, treatment and rehabilitation at the clinic. It also creates a knowledge base for the set-up of other clinics in Finland and abroad. Measuring patient-reported outcome measures (PROMs) and patient-reported experience

measures (subjective measurements of patient–doctor concurrence and other factors influencing the treatment experience) can be useful for clinicians, patients and policy-makers to improve the quality of care of long COVID and similar disorders.

METHODS AND ANALYSIS

Design and setting of the study

The Long COVID Cohort Study is a prospective, single-site cohort study conducted at the HUS Clinic for Long-Term Effects of COVID-19, in Helsinki, Finland. The patients admitted to the clinic present cases from the more severe and prolonged spectrum of persistent symptoms after a COVID-19 infection. Patients are referred from other university hospital clinics or primary care.

PROMs questionnaires are sent to patients within a week before or at their first visit to the clinic and then at 3, 6 and 12 months afterwards. The PREMs questionnaires will be delivered at follow-up surveys at 3, 6 and 12 months.

Study population and recruitment procedures

The study population will consist of consecutive adult patients referred to the HUS Clinic for Long-Term Effects of COVID-19. The clinic has a multiprofessional team including physicians with specialities in general and occupational medicine, a psychologist, a social worker, a nurse and psychosomatically oriented physical therapists. The treatment at the clinic is based on the recommendations for rehabilitation of long COVID published by WHO⁹ and includes symptom-based medication, physical therapy and group rehabilitation.

Inclusion criteria are:

- ▶ All patients, age≥18 years, referred to the Clinic for Long-Term Effects of COVID-19 either from other hospital units or primary care.
- ▶ COVID-19 diagnosis≥3 months earlier (confirmed by PCR or antibody testing).
- ▶ Willingness to be enrolled in the study, by signing the informed consent.

Exclusion criteria are:

- ▶ Patients not able to fill out the forms in Finnish.
- ▶ Participation in the study would be unreasonably inconvenient (eg, patients in bed rest).
- ▶ Ongoing drug abuse.

Study phases

The study consists of two phases. At baseline, eligible patients at the HUS Clinic for Long-Term Effects of COVID-19 that meet the inclusion criteria will be identified. Baseline information about ethnicity, previous illnesses, medication and clinical examination will be added to the study data. The consent and information leaflet are sent to the patient with the questionnaires before the first visit.

During the visit, the clinician may answer the patient's questions concerning the cohort study and asks for

another consent for a following study on the pathophysiological biomechanisms of long COVID. Study participants are also invited to join the Biobank at Helsinki University Hospital voluntarily. If the patient does not wish to participate in any of the studies, the questionnaires may still be used for clinical purposes. Participants may also withdraw from participating at any point of the study. To ensure quality of data management, we follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and HUS clinical trials quality procedures, for example, for each variable, we perform range checks to find erroneous data values.

The patients often have been thoroughly examined before their referral to the clinic, but all patients will nevertheless undergo laboratory testing according to national recommendations for fatigue assessment. Consultations of a specialist in infectious diseases and of a neurologist are sought when needed. If clinically warranted, further investigations, for example, spiroergometry, polysomnography, MRI of the brain or further laboratory testing, are performed to rule out other diseases. The data will be entered into pseudonymised form to the HUS electronic Case Report Form (HUSeCRF) database.

Due to prevalent cognitive symptoms in long COVID, neurocognitive assessment will be carried out by a psychologist to evaluate memory, attention, cognitive function and information processing. Physical functions will be measured by a physical therapist using a baseline hand dynamometer (Jamar/Saehan)¹⁰ and a 6 min walking test.¹¹

The second phase consists of follow-up, which will be carried out at 3, 6 and 12 months by digital questionnaire linked to the HUSeCRF system. If the study participants do not reply to the questionnaire in 1 week, they will receive reminders through email and text messages. In case the participants still do not complete the questionnaires, the study nurse will interview them by telephone.

COVID-19 reinfections are monitored by following up on the patient health record and laboratory tests that are carried out. Censoring of study participants on reinfection is not considered necessary, as reinfections are becoming increasingly common since the arrival of the Omicron variant in Finland in December 2021, and based on previous studies, no significant effect on the outcome measures is expected.¹²

The Long COVID EU consortium study

This cohort has a major role in the Long COVID EU consortium study (Long COVID—HORIZON-HLTH-2021-DISEASE-04). Patients in this clinical cohort are invited to donate blood and stool samples for the biomechanistic studies. The clinical and prognostic data will be analysed together with the biomechanistic results.

Outcome measures

Main outcome measures of this study are self-reported functional ability and QOL on a scale of 1–10, and functional ability measured using WHO Disability Assessment

Schedule V.2.0 (WHODAS V.2.0) (see below). The outcome measures and their timing have been marked in table 1. The European Health Interview Survey-Quality of Life 8 item index (EUROHIS-QOL-8) and 15-dimensional (15D) measures (see below) will be used as other outcome measures for stratification of the patients according to baseline health-related quality of life (HRQOL). As long COVID is a symptom-based disorder with only partly uncovered mechanisms,^{7 13} it is a challenge to determine intensity of the disorder or how to define when a patient has recovered. That is why we have chosen several questionnaires measuring QOL and HRQOL.

Both open-ended questions and validated questionnaires will be used in the study. Before the first visit, patients receive the clinic's four-page preliminary survey on demographics, education, social situation (including detailed information on work-status and social benefits), health behaviour, medical history and vaccination status (for SARS-CoV-2 and influenza viruses). We also use open-ended questions that include:

- ▶ What are your main symptoms that weaken your functional abilities?
- ▶ When did these symptoms occur for the first time?
- ▶ What are your expectations for the care at the clinic?
- ▶ What are the activities that you would pursue if your symptoms were in control?
- ▶ What means do you have to control or alleviate the symptoms?
- ▶ What medical or non-medical treatments or therapies have you previously tried for your long COVID symptoms? Did they help?
- ▶ Who is your primary care physician?

The baseline preliminary survey includes the following validated questionnaires:

- ▶ WHODAS V.2.0 covers 36 questions and 6 domains of functioning, including cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating and staying alone), getting along (interacting with other people), life activities (domestic responsibilities, leisure, work and school) and participation (joining in community activities).¹⁴
- ▶ EUROHIS-QOL-8 is an 8-item index, a shortened version of the WHO Quality of Life Instrument.¹⁵
- ▶ 15D is a generic, comprehensive, self-administered instrument for measuring HRQOL among adults. It combines the advantages of a profile and a preference-based, single index measure.¹⁶ A set of utility or preference weights is used to generate the 15D score (single index number) on a 0–1 scale. The 15D compares favourably with other preference-based generic instruments and is widely used at Helsinki University Hospital.
- ▶ Somatic Symptom Disorder B Criteria Scale¹⁷ is a brief self-report questionnaire used to assess the B criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) somatic symptom

**Table 1** Outcome measures and their assessment time schedule

Assessment method	Baseline, 0 months	3 months	6 months	12 months
Main outcome measures				
Self-reported functional ability on VAS 0–10	x	x	x	x
Self-reported quality of life on VAS 0–10	x	x	x	x
Functional ability: WHO Disability Assessment Schedule V.2.0	x	x	x	x
Other measures				
Medical history/anamnesis	x			
Clinical findings at consultation	x			
Laboratory and radiological examinations	x			
Neurocognitive evaluation	x			
Physical functions: hand grip strength and 6 min walking test	x			
Quality of life: European Health Interview Survey-Quality of Life 8 item index	x	x	x	x
Health-related quality of life: 15 dimensional	x	x	x	x
Symptom burden: Somatic Symptom Disorder—B criteria scale and Patient Health Questionnaire-15, a modification of the Bodily Distress Syndrome (BDS) Checklist with 35 symptoms	x	x	x	x
Depression: Patient Health Questionnaire-9	x	x	x	x
Anxiety: Generalized Anxiety Disorder 7-item scale	x	x	x	x
Insomnia: Insomnia Severity Index	x	x	x	x
Work ability: work ability assessment (subjective, three-step) and Work Ability Index, self-assessed current work ability on a scale of 0–10	x	x	x	x
Psychosocial functioning: daily functioning in three subdomains (work, social life, home) on a scale of 0–100	x	x	x	x
Resilience: Resilience Scale-14	x	x	x	x
Patient-Reported Experience Measure (PREM) Questionnaire, right after each visit	x			
PREM questionnaire, extensive version		x	x	x

VAS, visual analogue scale.

disorder,¹⁸ that is, the patients' perceptions of their symptom-related thoughts, feelings and behaviours.

- ▶ Patient Health Questionnaire-15 (PHQ-15) is a somatic symptoms subscale derived from a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument for common mental disorders.¹⁹
- ▶ PHQ-9 is the depression module of the self-administered version of the PRIME-MD diagnostic instrument. It scores each of the nine DSM-IV criteria as '0' (not at all) to '3' (nearly every day).²⁰
- ▶ General Anxiety Disorder-7 is one of the most frequently used diagnostic self-report scales for screening, diagnosis and severity assessment of anxiety disorder.²¹
- ▶ Insomnia Severity Index is a short (five questions) self-reported assessment of how severely insomnia has been impairing functional ability within the previous month.²²

- ▶ The first of the two work ability self-assessing tools includes the question: 'regardless of whether you are at work or not at the moment, please assess your current work ability. Are you (1) totally able to work, (2) partially disable to work or (3) totally disable to work. This question is based on the Health 2000²³ population survey in Finland.²³
- ▶ The other tool is the first question in Work Ability Index, which evaluates self-assessed current work ability on a scale of 0–10.²⁴ The question is, 'current work ability compared with highest work ability ever; assume that your work ability at its best has a value of 10 points. How many points would you give your current work ability? (0 means that you currently cannot work at all) (10 work ability at its best)'.²⁴
- ▶ The assessment of psychosocial functioning is made by asking about daily functioning in three subdomains (work, social life and home) on a scale of 0–100.²⁵ The

subdomain ‘work’ also covers the alternatives ‘job search’ and ‘academic studies’.

- ▶ Resilience Scale-14 (RS-14) is a short version of RS (Resilience Scale) that was developed to measure an individual level of resilience, understood as a relatively stable personal resource, being a positive personality trait that can be activated or used as personal competence and acceptance of self and life, all of which facilitate personal adaptation, that is, coping with change or misfortune.²⁶ The translation of the RS-14 to Finnish has been validated.²⁷

Patients are also asked to circle the symptoms present during the last 3 months in a 35-symptom table, including 5 typical symptoms in 7 domains: cardiopulmonary, gastrointestinal, muscles and joints, general symptoms, and depressive, nervous and cognitive reactions. The table was adapted from a Danish clinician’s handbook on how to diagnose functional disorders and medically unexplained symptoms,²⁸ and it is based on an analysis of 978 patients.²⁹

Cognitive and emotional functioning

The evaluation consists of the following psychological assessment methods:

- ▶ Verbal fluency test.³⁰
- ▶ Wechsler Adult Intelligence Scale, Fourth edition (block design, similarities, digit span).³¹
- ▶ Wechsler Memory Scale (logical memory, immediate and delayed).³²
- ▶ Trail Making Test A and B.³³
- ▶ Boston naming test.³⁴
- ▶ Computerized Neurocognitive Screening Vital Signs: verbal memory test, visual memory test, symbol digit coding, finger tapping test, Stroop test, shifting attention test, continuous performance test (CPT), four-part CPT, non-verbal reasoning.³⁵
- ▶ Psychologist interview on cognitive symptoms and history.

Physical functions

The testing is performed under the supervision of the Clinic’s physical therapist and includes the following:

- ▶ A hand grip strength measurement in kilograms using a Jamar/Saehan baseline hand dynamometer,¹⁰
- ▶ A 6 min walking test (6MWT)¹¹ with blood pressure, pulse, SpO₂ measuring and symptom evaluation before and after the test, measuring for distance walked in metres.
- ▶ Peak expiratory flow measurement.

PREM questionnaires

In addition to PROMs, we collect PREMs which measure the patient’s experience of the treatment at the clinic. PREM questionnaires are given immediately after each visit to the clinic, and at 3, 6 and 12 months. At the follow-ups, the questionnaire is slightly more extensive. The baseline questionnaire includes the following five questions:

- ▶ Are you satisfied with the treatment you received at the Long COVID Clinic?
- ▶ Are your symptoms now: milder, the same or more severe than before coming to the clinic?
- ▶ Did you concur with your doctor about the treatment plan?
- ▶ How do you feel you are able to cope with your illness after the treatment?³⁶
- ▶ Would you come back to the clinic?

The follow-up questionnaire includes those same five questions plus self-reported functional ability and QOL on visual analogue scales (VAS) 1–10, and another two questions:

- ▶ What treatment or rehabilitation methods have you used after your visit to the clinic?
- ▶ What kind of feedback would you like to give to the clinic?

In a future study, these PREMs will be compared with the prognosis to see whether they carry prognostic value. The study hypothesis is, the more positive the treatment experience is to each patient, the better the prognosis. This will allow us to assess the associations between outcomes and the patient–doctor relationship.

Sample size

The study will include all consecutive patients at the clinic who meet the inclusion criteria and have given their consent. The estimation is that within 1 year, 150–200 patients are examined at the clinic. We expect a 10% rejection rate. The study embarked in June 2021. Since we did not have predefined hypotheses and this is a descriptive cohort, we did not perform power calculations. The aim is to recruit 500 participants to the cohort to meet the sufficient case rate. This means that the recruiting process will most likely continue throughout year 2023 and the follow-up period throughout year 2024.

Plan of statistical methods

The demographic and clinical variables (sex, age, body mass index, ethnicity, medical history including previous diagnoses and management details) will be extracted from patient health records. The initial clinic appointment will serve as the baseline for the study. However, patients’ first appointments may occur on any date from 3 months following the acute COVID-19 infection. This is considered in the analyses by stratification of the patients according to time in days since positive PCR testing for SARS-CoV-2 virus. The number of days is used as an effect modifying factor.

Study participants will also be stratified by performing hierarchical cluster analysis on the main symptoms, by measuring functional ability with WHODAS V.2.0 and by stratifying patients into tertiles (high-medium-low functional ability).

To analyse the trends of functional abilities and QOL outcomes and identify the factors influencing them, linear mixed model analyses will be performed. It allows us to obtain robust estimates even in the presence of



missing data. In the models, we will include time, the prognostic factor of interest and its interaction with time as fixed effects. Participants are treated as random effects. Additional covariates will be considered if confounding is suspected. We estimate a 60% attrition rate, although efforts are made to reduce attrition (see 'Study phases'). The non-compliance to follow-up is not expected to be linked to a systematic reason. However, if there is a differential response to follow-up related to the study participants' conditions, follow-up data may be biased.

It is possible that study participants with specific characteristics (for instance, more severe conditions or non-concurrence with the treatment plan) do not return the follow-up questionnaire because of their fatigue or other restraints, or that participants who have recovered before the end of the 1-year follow-up fail to answer questionnaires due to reduced disease-related motivation. There is also the possibility of survival bias. We will therefore run logistic regression analyses to examine the associations between patient characteristics and early study dropout. If any predictors of attrition are identified, the information will be used as a basis for subsequent sensitivity analyses and, if required, for adjusting the main statistical analyses.

Study duration and timeline

The study will have an overall duration of approximately 42 months and will be considered in any case completed 12 months after the recruitment target is achieved. The study embarked on 1 June 2021 and is expected to be completed at the end of year 2024.

The study timeline is the following:

Months 1–32: selection and enrolment of study participants and database implementation.

Months 3–44: follow-up (3, 6 and 12 months) and database implementation.

Months 32–44: analysis of data and final dissemination of results.

Patient and public involvement

The questionnaires and open-ended questions in the preliminary and follow-up surveys have been carefully chosen to reflect the symptoms of long COVID as described by patients all over the world from the first year of the COVID-19 pandemic. We did not, however, include any specific patients or study participants in the planning of the study.

Ethics and dissemination

This study has been approved by the Helsinki University Hospital research ethics committee board, ID HUS/1493/2021 on 6 March 2021. All study participants will sign written informed consent for participation. The study findings will be reported for publication in peer-reviewed journals. Any modifications to this protocol that impact study procedures or analysis will result in an amendment to the protocol and ethics application.³⁷

Financial burden

The costs are related to personnel, postal expenses and analysis costs. These costs will be covered by the grant by which the study has been supported (see 'Funding' for details).

Study guidelines

We have used the SPIRIT reporting guidelines as guidance for the setting up of the study.³⁸ We will use the Strengthening the Reporting of Observational Studies in Epidemiology guidelines when reporting the results of the study.³⁹

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Acknowledgements The authors wish to express their gratitude to the personnel at the Clinic for Long-Term Effects of COVID-19 and to the study participants. We would also like to thank our EU Consortium partners Judith Rosmalen, Rebekka Schnepfer and Gunther Meinschmidt for their comments during the process of writing this study protocol.

Contributors HL had the idea of the study and wrote the original study plan, which this study protocol is based on. HV wrote the manuscript. TP participated in designing the manuscript and provided some of the cited articles. HL, HV, AS and TP were the clinicians at the Long Covid Clinic at HUS, and they collected the informed consents. MVa and MVe planned the statistical methods. AM served as design expert. TM conducted the neurocognitive evaluation. HL reviewed the manuscript for intellectual content. All authors provided feedback on the drafts and critically revised and approved the final manuscript.

Funding This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057553 and from the State Research Funds (HUS) in Finland (TYH2022218).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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