Long-Term Health Outcomes After Hospitalization for COVID-19

Julia C. Berentschot

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Long-Term Health Outcomes After Hospitalization for COVID-19

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Chapter 1

General introduction

COVID-19 pandemic

In December 2019, the first case of coronavirus disease 2019 (COVID-19), identified in Wuhan, China, was reported to the World Health Organization (WHO).[1,2] COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that primarily affects the respiratory system but can cause multi-organ dysfunction. The virus spreads mainly through small liquid particles expelled from an infected individual's mouth or nose, ranging from respiratory droplets to smaller aerosols. These particles are easily transmitted through talking, coughing, sneezing, or breathing, enabling SARS-CoV-2 to spread rapidly worldwide.[1,2] Early insights into its full genome sequence enabled scientists to develop a diagnostic reverse transcription polymerase chain reaction test, which became the standard for diagnosing COVID-19. The number of confirmed COVID-19 cases grew exponentially, with the first confirmed case in the Netherlands reported at the end of February 2020. SARS-CoV-2 shows similarities with earlier coronaviruses, including SARS-CoV-1 (2002) and Middle East Respiratory Syndrome (MERS, 2012), which are of zoonotic origin and have caused severe disease in humans. However, the scale and impact of COVID-19 far exceed those of previous outbreaks. On March 11, 2020, the WHO officially declared COVID-19 a pandemic. The pandemic has been characterized by multiple waves, each dominated by different variants of SARS-CoV-2. Global and national guidelines were implemented to slow the transmission of the virus, including face masks, lockdowns, and offering vaccinations.[3] As of January 2025, over 776 million people worldwide have been infected with SARS-CoV-2.[4] Notably, this number likely underestimates the true prevalence due to undocumented and asymptomatic cases.

Clinical manifestation and hospitalization for COVID-19

COVID-19 presents diverse clinical manifestations, ranging from an asymptomatic infection to critical illness or even death.[5] Most individuals experience a mild to moderate SARS-CoV-2 infection, with the most common symptoms being fever, cough, shortness of breath, fatigue, and loss of smell or taste.[1,6] However, COVID-19 has led to a sudden and substantial rise in hospitalizations worldwide, overwhelming hospital capacity and disrupting routine care delivery.

In the Netherlands, as of March 30, 2023, over 143.000 COVID-19-related hospitalizations have been reported, of which about 14% required admission to an intensive care unit (ICU).[7] Many patients hospitalized for COVID-19 required oxygen supplementation due to hypoxemia, while more severe cases needed advanced respiratory support. Among the severely ill patients, some developed critical complications, such as acute respiratory distress syndrome or multi-organ failure, necessitating ICU admission.[2] Moreover, venous thromboembolism, particularly pulmonary embolism, was frequently observed in patients hospitalized with COVID-19.[8]

COVID-19 can cause dysregulation of the immune system and an excessive inflammatory response.[9] Throughout the pandemic, evolving knowledge of effective treatments has shaped the development of living guidelines for managing patients hospitalized with COVID-19. Several treatments have been

recommended over time to combat the disturbances caused by SARS-CoV-2, particularly in patients requiring supplemental oxygen.[10,11] For instance, steroids and immunomodulatory therapies were recommended to reduce the excessive inflammatory response and antivirals to inhibit viral replication. Research has shown that older age, male sex, and pre-existing comorbidities are associated with increased risk of worse in-hospital outcomes in patients hospitalized for COVID-19.[12-14]

Long-term health outcomes of COVID-19

Insights from SARS-CoV-1 and MERS have shown that patients can develop long-term health problems, including pulmonary abnormalities, fatigue, impaired cardiorespiratory fitness, mental health problems, and reduced quality of life.[15,16] Early reports similarly indicated that many patients experienced lasting health effects in the weeks or months after hospitalization for COVID-19. It is known that patients can experience long-term physical, cognitive, and psychological impairments after critical illness and intensive care unit (ICU) treatment, collectively referred to as post-intensive care syndrome (PICS).[17] Therefore, long-term health problems were expected to be most prominent in patients with severe or critical COVID-19. However, it became clear that persistent health problems can develop regardless of the severity of acute COVID-19. The symptoms were widespread and potentially limitless, affecting physical, cognitive, and psychological domains.[18] Various terms have been proposed to describe this condition, including "long COVID", "Post-COVID-19 Condition", and "Post-Acute COVID-19 Syndrome", which are often used interchangeably.[19,20] In this thesis, we use the term long COVID, which is more commonly used among patients and also recognized by the WHO. The most recent definition, as described by the National Academies of Sciences, Engineering, and Medicine,[20,21] describes long COVID as an infection-associated chronic condition characterized by single or multiple symptoms that occur after SARS-CoV-2 infection and persist for at least 3 months. It can present as a continuous, relapsing and remitting, or progressive disease state, affecting one or more organ systems, with symptoms and conditions ranging from mild to severe. As many patients develop long COVID, it is essential to deepen our understanding of the long-term health effects of COVID-19 in order to optimize aftercare strategies for this new population.

COVID-19 aftercare

The rapid surge in COVID-19 cases and frequent hospitalizations challenged the clinical resources available. Patients were to be discharged from the hospital as soon as possible, either to their home environment or to inpatient rehabilitation facilities. Severely affected patients requiring prolonged hospitalization were typically referred to more intensive, multidisciplinary rehabilitation at discharge, including in- or outpatient medical rehabilitation or rehabilitation in a skilled nursing facility. Patients who were sufficiently independent at hospital discharge were discharged home, with or without the support of community-based rehabilitation, such as physical therapy.

Many hospitals routinely followed up with patients after discharge, typically monitoring pulmonary sequelae (e.g., pulmonary function testing and chest radiology) and gaining insights into the post-acute health effects of COVID-19.[22-24] Medical specialists and general practitioners played a vital role in secondary triage, facilitating referrals for tailored aftercare.

COVID-19 aftercare pathways were predominantly guided by clinical expertise and opinion rather than evidence-based guidelines.[25] Gaining insights into these aftercare pathways, along with evaluating aftercare from both the perspectives of patients and healthcare professionals, could help optimize aftercare strategies.

The CO-FLOW study

As the first COVID-19 wave emerged in the Netherlands, we recognized the urgent need to study the long-term health outcomes of this novel disease. We considered that assessing various health outcomes over time and gaining insights into aftercare pathways could provide valuable knowledge and help optimize COVID-19 aftercare. The rapid and substantial increase in hospitalizations during the early phase of the pandemic, along with early reports of persistent symptoms and knowledge of PICS, prompted us to focus our research on patients hospitalized for COVID-19. Our research group designed the multicenter prospective cohort study "COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system" (CO-FLOW) from a combined pulmonology, rehabilitation, and intensive care perspective, conducted in Rotterdam–Rijnmond–Delft region in the Netherlands.

The study comprehensively evaluated objectively assessed and patient-reported health outcomes for up to 2 years after hospital discharge, with the follow-up period later extended to 3 years. We aimed to study systematically: 1] trajectories of physical, cognitive, and psychological outcomes; 2] patient flows, healthcare utilization, perspectives of patients and healthcare professionals on aftercare; 3] effects of physical, cognitive, and psychological outcomes on participation and health-related quality of life (HRQoL); and 4] predictors of long-term health outcomes, healthcare utilization, and patient satisfaction with aftercare. As our knowledge evolved, we expanded our research to deepen our understanding of the long-term health outcomes after hospitalization for COVID-19. For instance, the CO-FLOW study was extended with a 3-year follow-up to continuously monitor health outcomes, retaining most patient-reported outcome measures (PROMs) and adding a questionnaire on post-exertional malaise (PEM), which had emerged as a distinct feature of long COVID. We later added two sub-studies to explore 1) immunological abnormalities in patients with long COVID and their association with fatigue, building on previous studies that have linked abnormalities in the immune system to long COVID, and 2) a clinical randomized controlled pilot trial of a home-based computerized cognitive training program to explore its effect on long-term cognitive complaints. Lastly, we collaborated with national and international researchers to address emerging research questions. The research presented in this thesis builds upon the findings of the CO-FLOW study.

Figure 1 presents the CO-FLOW study timeline. The study group recruited 650 participants between July 1, 2020, and September 9, 2021; all patients had been discharged from the hospital between March 26, 2020, and May 21, 2021. Study measurements were performed at 3 and 6 months and at 1, 2, and 3 years after hospital discharge. Additionally, we collected data on pulmonary function testing and chest radiology that were assessed as part of routine follow-up care at the participating hospitals. The study was performed by a multidisciplinary team, including two PhD students.

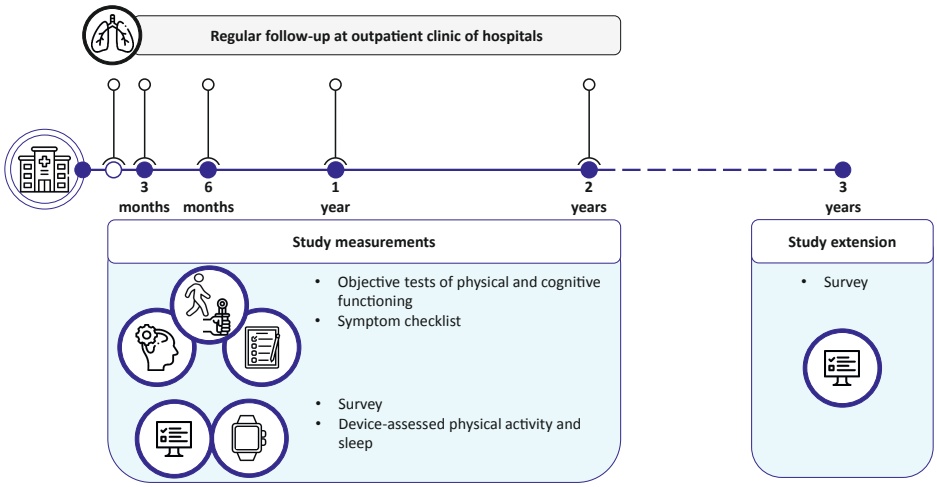

Figure 1. CO-FLOW study timeline.

Interim analyses were conducted throughout the study to contribute to the evolving knowledge of COVID-19. **Figure 2** presents an overview of the CO-FLOW study output. The study findings are featured in two PhD theses, each addressing distinct topics, alongside some joint publications.

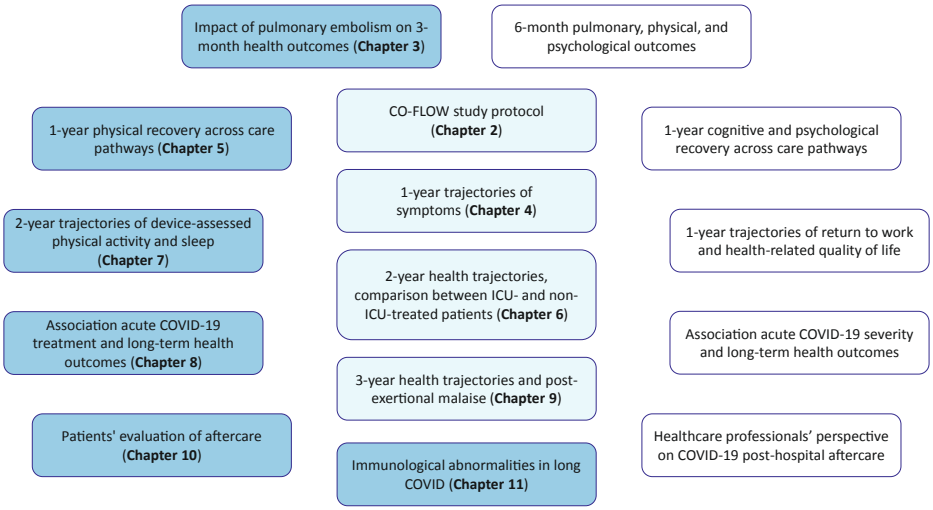

Figure 2. Overview of the CO-FLOW study output.
Each block represents the topic of a scientific publication. Boxes highlighted in dark blue correspond to publications presented in this thesis, white boxes represent publications included in the other PhD student's thesis, and light blue boxes indicate joint publications featured in both theses.

Outline of this thesis

This thesis aims to enhance our understanding of long-term health outcomes in patients hospitalized for COVID-19. **Chapter 2** presents the CO-FLOW study protocol. Health outcomes up to 1 year after hospitalization are described in Chapter 3-5. **Chapter 3** describes the impact of pulmonary embolism during hospitalization on health outcomes at 3 months after hospital discharge. **Chapter 4** presents trajectories and clusters of symptoms up to 1 year. **Chapter 5** focuses on trajectories of objectively assessed physical function across aftercare pathways up to 1 year. **Chapters 6 and 7** summarize all CO-FLOW study data up to 2 years after hospital discharge, including comparisons between ICU- and non-ICU-treated patients. **Chapter 6** describes trajectories of health outcomes, including objectively assessed and patient-reported health outcomes, while **Chapter 7** focuses on device-assessed physical activity and sleep, and their association with HRQoL. **Chapter 8** explores the association between COVID-19 treatments during hospitalization and health outcomes up to 2 years after discharge. **Chapter 9** presents the trajectories of patient-reported health outcomes up to 3 years after hospital discharge, focussing on changes in the third year, and the presence of post-exertional malaise at 3 years. **Chapter 10** describes patients' satisfaction and unmet needs regarding COVID-19 aftercare. **Chapter 11** explores immunological abnormalities in patients with long COVID at 3-6 months after hospital discharge and their association with fatigue, one of its most prominent symptoms. Finally, **Chapter 12** provides a general discussion of the main findings of this thesis, methodological considerations, and clinical implications, concluding with recommendations for future research.

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Chapter 2

CO-FLOW: COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system: study protocol of a multicenter prospective cohort study following patients 2 years after hospital discharge

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Abstract

Background First studies indicate that up to 6 months after hospital discharge, coronavirus disease 2019 (COVID-19) causes severe physical, cognitive, and psychological impairments, which may affect participation and health-related quality of life (HRQoL). After hospitalization for COVID-19, a number of patients are referred to medical rehabilitation centers or skilled nursing facilities for further treatment, while others go home with or without aftercare. The aftercare paths include 1] community-based rehabilitation; 2] in- and outpatient medical rehabilitation; 3] inpatient rehabilitation in skilled nursing facilities; and 4] sheltered care (inpatient). These aftercare paths and the trajectories of recovery after COVID-19 urgently need long-term in-depth evaluation to optimize and personalize treatment. CO-FLOW aims, by following the outcomes and aftercare paths of all COVID-19 patients after hospital discharge, to systematically study over a 2-year period: 1] trajectories of physical, cognitive, and psychological recovery; 2] patient flows, healthcare utilization, patient satisfaction with aftercare, and barriers/facilitators regarding aftercare as experienced by healthcare professionals; 3] effects of physical, cognitive, and psychological outcomes on participation and HRQoL; and 4] predictors for long-term recovery, health care utilization, and patient satisfaction with aftercare.

Methods CO-FLOW is a multicenter prospective cohort study in the mid-west of the Netherlands with a 2-year follow-up period. Measurements comprise non-invasive clinical tests and patient reported outcome measures from a combined rehabilitation, pulmonary, and intensive care perspective. Measurements are performed at 3, 6, 12, and 24 months after hospital discharge and, if applicable, at rehabilitation discharge. CO-FLOW aims to include at least 500 patients who survived hospitalization for COVID-19, aged ≥ 18 years.

Discussion CO-FLOW will provide in-depth knowledge on the long-term sequelae of COVID-19 and the quality of current aftercare paths for patients who survived hospitalization. This knowledge is a prerequisite to facilitate the right care in the right place for COVID-19 and comparable future infectious diseases.

Trial Registration The Netherlands Trial Register (NTR), https://www.trialregister.nl. Registered: 12-06-2020, CO-FLOW trialregister no. NL8710.

Background

From the beginning of 2020 the world has been overwhelmed by coronavirus disease 2019 (COVID-19), a new respiratory infectious disease that was first discovered in China at the end of 2019. Hospitalization, including Intensive Care Unit (ICU) treatment, is frequently needed. Hospitalized patients have to deal with mild to severe illness, often without the support of family and loved ones. This new disease and surreal situation are expected to cause severe and long-lasting physical, cognitive, and psychological sequelae, affecting participation and health-related quality of life (HRQoL). Little is known yet about the long-term sequelae of COVID-19, and therefore, the European Academy of Rehabilitation Medicine warned for the unknown aftershocks of the pandemic and called for action.[1]

Many factors will play a role in the potentially severe long-term sequelae after hospital discharge. Since recent years it has come to the attention that ICU treated patients can experience a combination of long-term physical, cognitive, and psychological sequelae, known as the Post-Intensive Care Syndrome.[2,3] COVID-19 has unique features in that ICU length of stay is relatively long and that patients are frequently immobilized in prone position with (high pressure) mechanical ventilation.[4] After ICU, patients with COVID-19 can experience musculoskeletal, neurological, and psychological impairments.[5-7] Furthermore, the viral pneumonia may cause permanent lung injury. Secondarily, ventilator induced damage will occur in a large proportion of patients, leading to permanent pulmonary function decline, necessitating respiratory rehabilitation or even long-term oxygen support.[8] A large proportion of the severely ill patients experiences thrombotic complications such as pulmonary embolism or ischemic brain infarction, which can result in long-term morbidity (e.g. chronic thrombo-embolic pulmonary hypertension, and cognitive and motor impairments).[9]

Although long-term sequelae of COVID-19 are expected to be most prominent in ICU treated patients, also hospitalized patients without ICU treatment may experience long-term impairments in several areas.[10-12] Likewise, many of these patients are severely ill, are immobilized for a relatively long period, may experience complications, are often restricted in having visitors, are confronted by isolation measures, and may develop permanent pulmonary damage. Such a unique situation could, besides affecting physical function,[13] potentially result in cognitive and psychological impairments such as anxiety, concentration problems, and post-traumatic stress.[14]

Rehabilitation, with its multidisciplinary approach (rehabilitation medicine, physical/sports therapy, occupational therapy, psychology, social work, dietetics, speech/language therapy), is the cornerstone of management of the consequences of COVID-19. Minimizing the effects of potential long-term impairments on participation (including return to work, leisure activities, and social relationships) and HRQoL are essential rehabilitation goals.

The sudden COVID-19 pandemic forced quick development of aftercare paths for this new patient group. These aftercare paths comprise 1] community-based rehabilitation; 2] in- and outpatient medical rehabilitation; 3] inpatient rehabilitation in skilled nursing facilities; and 4] sheltered care

(inpatient). However, whether these newly developed aftercare paths provide patients with the right care in the right place is unknown yet. For instance, the trajectory of recovery after hospitalization for COVID-19 and its predictors remain unknown to date, and outcomes beyond 6 months are still scarce.[11,15-18] Studies in survivors from other coronavirus pneumoniae (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) suggest long-term sequelae lasting for months or even years.[19-22] Early studies in COVID-19, mostly with a cross-sectional design, indicate that a broad range of sequelae may occur up to 6 months after hospitalization, varying from pulmonary impairments and residual radiological abnormalities to impairments in cardiorespiratory and neuromuscular fitness, and symptoms such as dyspnea, fatigue, anxiety, depression, and sleep disturbances.[11,15,23,24] However, how long these symptoms will last and to what extent recovery will occur is still unclear.[25]

Besides in-depth knowledge on the trajectories of physical, cognitive, and psychological recovery, insight in the aftercare paths is needed, such as patient flows across the different paths, healthcare utilization, patient satisfaction with aftercare, and barriers/facilitators regarding aftercare as experienced by health care professionals. This knowledge will further facilitate optimization of the aftercare paths for COVID-19 and comparable future infectious diseases, and will build on the relatively underexamined post-ICU recovery and effectiveness of rehabilitation.[26]

Given the above, the newly developed aftercare paths for COVID-19 urgently need to be evaluated.[27] Evaluation should be performed prospectively in the short, medium, and long term, on a broad range of sequelae and predictors, participation, HRQoL, and aftercare paths. CO-FLOW, with its combined rehabilitation, pulmonary, and ICU perspective, offers this holistic and long-term (2 years) follow-up approach.

Aims

The aim of the CO-FLOW study is to gain in-depth knowledge on the long-term sequelae in patients who survived hospitalization for COVID-19 and to further develop the aftercare paths for COVID-19 and other comparable future infectious diseases. More specifically, CO-FLOW aims, by following the outcomes and aftercare paths of all COVID-19 patients after hospital discharge, to systematically study over a 2-year period: 1] trajectories of physical, cognitive, and psychological recovery; 2] patient flows, healthcare utilization, patient satisfaction with aftercare, and barriers/facilitators regarding aftercare as experienced by healthcare professionals; 3] effects of physical, cognitive, and psychological outcomes on participation and HRQoL; and 4] predictors for long-term recovery, health care utilization, and patient satisfaction with aftercare.

Methods

Eligibility criteria

All COVID-19 patients who survived hospitalization in one of the hospitals in the Rotterdam–Rijnmond–Delft region, which is in the mid-west of the Netherlands, are eligible if they fulfill the

following in- and exclusion criteria. Inclusion criteria: 1] COVID-19 diagnosis (based on positive polymerase chain reaction or multidisciplinary team decision based on symptoms and computed tomography (CT) or positive serology); 2] requiring and surviving hospitalization; 3] within 6 months (but preferably within 3 months) after hospital discharge; 4] patient or relative has sufficient knowledge of Dutch or English language. Exclusion criteria: 1] age < 18 years; 2] incapacitated subjects.

Sample size

A formal sample size calculation was not performed, because we did not focus on a single outcome to base our power calculation on in this multiple outcome prospective cohort study. The original sample size estimation was ≥ 335 patients, estimated on the number of patients hospitalized in the first wave of the COVID-19 pandemic in the Rotterdam-Rijnmond region. Due to the ongoing COVID-19 pandemic this was later extended to ≥ 500 patients, including patients from the second and third wave.

Study design

The CO-FLOW study has a prospective multicenter cohort design, in which outcomes are studied from a combined rehabilitation, pulmonary, and ICU perspective. Participating institutions are hospitals (n=7, among which an academic hospital), a rehabilitation center, a skilled nursing facility, and a sheltered care facility, all in the region Rotterdam-Rijnmond-Delft. Since July 1st 2020, patients are included after hospital discharge and followed until 2 years thereafter throughout the continuous health care chain.

Measurements are performed at 3, 6, 12, and 24 months after hospital discharge. Patients admitted to inpatient medical rehabilitation or to a skilled nursing facility after hospital discharge undergo an additional measurement at discharge. Measurements comprise (non-invasive) clinical tests and patient reported outcome measures (PROMs), and are predominantly part of regular care; **Table 1**. During study visits, additional non-invasive measurements are performed by a trained researcher or research assistant. These measurements are performed when patients visit their own hospital for their regular follow-up after hospital discharge. The length of this regular follow-up period depends on the severity of disease and is based on the decision of the treating physician. After patients are discharged from regular care, they are invited to visit Erasmus MC, University Medical Center Rotterdam, for the remaining study visits. In case patients are not willing or able to come to Erasmus MC, a research assistant visits them at home to perform the study measurements.

Outcome measures

Outcome measures concern A] trajectories of recovery; B] predictors from a rehabilitation, pulmonary, and ICU perspective; and C] aftercare paths.

A] Trajectories of recovery

Physical function

Pulmonary function: spirometry measuring forced vital capacity (FVC), forced expiratory capacity at the first second of exhalation (FEV1), and diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin (DLCOc) results are collected, if tests are performed during aftercare. The Global Lung Function Initiative Network (GLI) reference values were used to express percentages of predicted values, the z-scores and the lower limit of normal (LLN);[28,29] Radiographic abnormality: chest X-ray and CT-scan results are collected, if performed during aftercare; Neuromuscular fitness: hand-held dynamometry with Jamar hydraulic dynamometer (Lafayette Instrument Company, USA) to assess maximum grip strength (patient squeezes the dynamometer three times with each hand);[30,31] Medical Research Council (MRC) to manually assess muscle strength in the upper and lower limb;[32] Cardiorespiratory fitness: 6-min walk test (6MWT), a submaximal exercise test measuring the distance walked in 6 min over a 30 m (mainly) or 20 m walkway, depending on the test location. Secondary outcomes include exercise-induced changes in saturation, heart rate, and perceived fatigue and dyspnea (Borg scale);[33] 1-min sit-to-stand test (1MSTS) in which the number of successfully standing up from a chair without using hands for support is counted during 1 min;[34] Body mass index (BMI): height and weight measurement. Fat-free mass: arm circumference.[35,36]

Mobility: De Morton Mobility Index (DEMMI), an observation test to assess problems with mobility, balance, movement, and daily activities in the elderly.[37]

Physical activity, sedentary behavior, and sleep: GENEActiv wrist watch (Activinsights, Kimbolton, UK), a small and light-weight tri-axial accelerometer. This watch is worn on the dominant wrist for 7 consecutive days to objectively assess physical (in)activity and sleep behavior in daily life.

Cognitive function

Subjective: Cognitive Failure Questionnaire (CFQ) to assess the frequency of experienced cognitive failures in everyday life, such as absent-mindedness, slips and errors of perception, memory, and motor functioning.[38,39]

Objective: Montreal Cognitive Assessment (MoCA), a rapid screening instrument for cognitive dysfunction, assessing different domains: visuospatial/executive function, attention, concentration, working memory, language, short-term memory, and orientation.[40] If indicated, patients receive additional cognitive tests as part of regular care only: Location Learning Test (LLT),[41] Trail Making Test (TMT),[42] Stroop Test,[43,44] Letter-Digit Substitution Test (LDST),[45] Digit Span,[46] and Letter and Category Fluency.[47,48]

Psychological function

Mood: Hospital Anxiety and Depression Scale (HADS), a general measure of emotional distress containing two subscales: anxiety and depression.[49]

Post-Traumatic Stress Syndrome: Impact of Event Scale-Revised (IES-R), assessing traumatic consequences that (senior) patients may experience after treatment in the hospital or ICU, comprising the domains of intrusion, avoidance, hyperarousal, and a total subjective stress IES-R score.[50]

Secondary measures

Independency in activities of daily life is measured with the Barthel Index (BI);[51] Self-reported physical activity with the International Physical Activity Questionnaire (IPAQ-short form) targeting vigorous, moderate, and light activities;[52] Self-reported physical fitness with the International Fitness Scale (IFIS), a questionnaire assessing general physical fitness, cardiorespiratory fitness, muscular strength, speed-agility, and flexibility;[53] Fatigue with the Fatigue Assessment Scale (FAS), a simple and short self-administered questionnaire to indicate chronic fatigue;[54] Health-related quality of life with the SF-36 and the 5-level EuroQoL-5D (EQ-5D-5L) questionnaires. The SF-36 questionnaire is a multidimensional instrument for measuring general health condition, referring to limitations in functioning due to physical and/or emotional limitations.[55] The EQ-5D-5L consists of the 5-level EQ-5D index (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale (EQ-VAS);[56] Burden of disease with the Assessment of Burden of Corona (ABC) tool, an innovative tool that measures and visualizes integrated health status. An important part of the tool is the ABC scale, which is largely based on the Clinical COPD Questionnaire, and consists of five domains (symptoms, functional state, mental state, emotions, and fatigue);[57] Self-reported COVID-19 symptoms with the COVID-19 Symptom Checklist, developed for the purpose of the study, that screens novel symptoms since the onset of COVID-19; Sleep quality with the Pittsburgh Sleep Quality Questionnaire (PSQI) to assess subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction;[58] Participation with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P), assessing participation in daily life activities in three scales: frequency, restrictions, and satisfaction;[59] and Recovery with the novel Core Outcome Measure for Recovery, assessing the absence of symptoms related to the illness, the ability to do usual daily activities, and the return to state of health as prior to COVID-19.[60]

B] Predictors for long-term recovery

Patient characteristics: age, sex, education, marital status, socio-economic status, cultural background, pre-injury employment and living situation, comorbidity, smoking, alcohol use (all questionnaire developed for the purpose of the study), pre-morbid physical activity class (Saltin-Grimby Physical Activity Scale, SGPALS),[61] and coping (Coping Inventory for Stressful Situations, CISS).[62,63]

Clinical characteristics (electronic patient records): laboratory biomarkers and hyperinflammation (serum creatinine, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula, C-reactive protein, ferritin, alanine aminotransferase, hemoglobin, mean corpuscular volume, thrombocytes, lymphocyte count, D-dimer, NT-proBNP, IL-6, presence of IgG and IgM antibodies for COVID-19), duration of hospital and ICU stay, quantity and type of oxygen supplementation, duration of mechanical ventilation, acute physiology and chronic health (APACHE sII score), severity of pulmonary disease (CO-RADS score CT-scan), thrombosis, tracheostomy,

delirium, pulmonary embolism, other complications during hospital stay, readmission and vaccination status, and nutritional status with the Short Nutritional Assessment Questionnaire (SNAQ).[64,65]

C] Aftercare paths

Patient flows: questionnaire developed for purpose of the study and electronic patient records, to investigate patient flows between 1] community-based rehabilitation; 2] in- and outpatient medical rehabilitation; 3] inpatient skilled nursing facility; and 4] sheltered care (inpatient).

Health care utilization: iMTA Medical Consumption Questionnaire (iMCQ) assessing healthcare use.[66]
Productivity losses: iMTA Productivity Costs Questionniare (iPCQ) assessing productivity losses.[67]
Patient-reported experience measure: Satisfaction with COVID-19 Aftercare Questionnaire (SCAQ), a post-hospitalization questionnaire developed for the purpose of this study in co-creation with ex-COVID-19 patients and their relatives; available upon request.
Organization of COVID-19 aftercare: questionnaire to assess the level of organization of COVID-19 aftercare as perceived by healthcare professionals and to explore barriers and facilitators for aftercare experienced by the professionals. This questionnaire was developed for the purpose of this study and available upon request, based on the Care Process Self-Evaluation Tool.[68]

Data management

Measurements are performed by trained research assistants in the participating centers under supervision of qualified researchers. Data is collected in Castor Electronic Data Capture system (Castor EDC), a cloud based clinical data management platform, and the platform 'Gezondheidsmeter.nl'. Surveys including all PROMs are sent to patients through Castor EDC via email, facilitating automatic data storage in the database. Clinical data are collected from electronic patient records by research assistants. Also, we use the Erasmus MC COVID Research (EraCoRe) database for collection of outcomes collected during regular care.

Statistical analyses

A] Trajectories of recovery

The course of physical, cognitive, and psychological recovery over time will be analyzed using linear mixed models (LMM) and/or generalized estimating equations (GEE) analysis for outcomes on an interval scale (linear) and for binary outcomes (logistic), respectively, on an intention-to-treat basis. As part of each model, a covariance matrix is estimated that represents the within-subject dependencies in repeated measurements. Level of recovery at each time point will be included as the dependent variable in the LMM and GEE models. Measurement time (3, 6, 12, and 24 months) is entered as independent variable. In post-hoc analyses, significant recovery over total follow-up and from time point to time point (3, 6, 12 and 24 months) will be identified for each outcome. These analyses will reveal whether overall or partial recovery is reached and which disabilities will persist in the long term. Likewise, trajectories of participation and HRQoL will be studied, including the impact of potential physical, cognitive, and/or psychological disabilities on these outcomes.

B] Predictors for long-term recovery

For this analysis we will develop multivariable prediction models. LMM/GEE models including repeated measurements will be constructed to identify predictors for long-term recovery. Patient characteristics (e.g. age, sex, cultural background) and clinical characteristics (e.g. length of ICU stay, APACHE II score, duration of mechanical ventilation) will be entered as independent variables to the models, with recovery as dependent variables. Significant predictors ($p<0.05$) will be included in multivariable models using a Bonferroni correction, dividing the significance level ($alpha<0.05$) by the number of predictors included in the model. These models will identify independent predictors for recovery, which may facilitate in preventing or treating unfavorable health outcomes in future patients.

C] Aftercare paths

The proportions of patients flows through the different aftercare paths will be calculated. Recovery within and between the different patient flows over time will be analyzed by entering the type of aftercare path as independent variable to the LMM/GEE models. Speed of recovery and (time of) maximum recovery reached will be compared between aftercare paths by studying interactions between paths and time. Comparing trajectories of different aftercare paths and for multiple outcomes may show in which time frames recovery increases most and when it levels off. Models will be adjusted for case mix.

Health care utilization (number of consultations with general practitioner, physiotherapist, occupational therapist, speech and language therapist, psychologist, dietician, pulmonologist, hospitalizations, etc.) will be calculated for each aftercare path. The effect of cumulative treatment time on recovery will be analyzed at each measurement time using the LMM/GEE models. Likewise, effects of diversity on recovery will be studied by adding variables such as age, sex, and cultural background to the LMM/GEE models. These analyses will inform treatment decisions regarding timing, type, and volume of rehabilitation required for optimal outcomes for specific groups of patients. Patient satisfaction with treatments received in each aftercare path and barriers/facilitators experienced by professionals will be studied using descriptive statistics.

Table 1. Overview of study measurements.

	Discharge hospital	**Discharge inpatient rehabilitation**	**3m after discharge hospital**	**6m after discharge hospital**	**12m after discharge hospital**	**24m after discharge hospital**
Patient information/ informed consent	×	×	*			
Patient characteristics		×	*			
Clinical characteristics		EPR[$]	*			
General questions, health care path, recovery		×	×	×	×	×

Table 1. Continued.

	Discharge hospital	Discharge inpatient rehabilitation	3m after discharge hospital	6m after discharge hospital	12m after discharge hospital	24m after discharge hospital
Pre-morbid physical activity class (SGPALS)			×			
COVID-19 Symptom Checklist		×	×	×	×	×
Questionnaires: online or postal mail						
Independency general daily life activities: BI		□	×	×	×	×
Physical activity: IPAQ-short form			×	×	×	×
Physical fitness: IFIS		×	×	×	×	×
Fatigue: FAS		×	□	×	×	×
Mood: HADS		□	□	×	×	×
Post-Traumatic Stress Syndrome: IES-R		□	□	×	×	×
Cognition: CFQ		×	×	×	×	×
Coping: CISS					×	
Health-related quality of life: SF-36, EQ-5D-5L		□	□/×	×	×	×
Burden of disease: ABC-tool			□	×	×	×
Sleep quality: PSQI		×	×	×	×	×
Participation: USER-P			×	×	×	×
Health Care utilization: iMCQ, iPCQ			×	×	×	×
Patient satisfaction with COVID-19 aftercare: SCAQ					×	
Clinical tests at hospital, inpatient rehabilitation, or at home						
Mobility: DEMMI		□	×	×	×	×
Antropometry: body mass index, arm circumference		□	×	×	×	×
Nutritional status: SNAQ		□	×	×	×	×
Cognition: MoCA		□	×	×*	×*	×*

Table 1. Continued.

	Discharge hospital	Discharge inpatient rehabilitation	3m after discharge hospital	6m after discharge hospital	12m after discharge hospital	24m after discharge hospital
Cognition: TMT, LLT a.o.[&]		□	□		□	
Pulmonary function: spirometry[&]		□	□	□	□	□
Radiographic abnormality: CT-scan[&], X-ray[&]			□	□	□	□
Neuromuscular fitness: handgrip strength, MRC*		□	×	×*	×*	×*
Cardiorespiratory fitness: 6MWT, 1MSTS		□	×	×	×	×
Physical activity and sleep: accelerometry			×	*	×	×

*□ = standard care in rehabilitation center or skilled nursing facility or standard care at regular follow-up in hospital; x=study measurement; [$] EPR=Electronic patient record; * if missed or submaximal score at previous assessment; [&] If indicated; when patients are discharged from regular follow-up these measurements are not performed.*

Discussion

Relevance

The CO-FLOW study will provide in-depth knowledge on the unknown long-term aftershocks of the COVID-19 pandemic and the quality of current aftercare paths for patients who survived hospitalization. This knowledge is indispensable to facilitate optimization and personalization of aftercare for the current pandemic, ensuring the right care in the right place. Furthermore, the CO-FLOW study will deliver an experience- and evidence-based aftercare path for a potential future COVID-19 outbreak and comparable infectious diseases. In addition, this will expand our knowledge on the relatively underexamined post-ICU recovery and effectiveness of rehabilitation.

Strengths

Strengths of our study are that 1] CO-FLOW comprises long-term (2 years) monitoring after hospital discharge, with a strong focus on clinical tests; 2] CO-FLOW recruits all COVID-19 hospital survivors, both with and without ICU treatment, which is indispensable because long-term impairments are also expected in patients without ICU treatment; 3] patients are followed over all aftercare paths. This also concerns patients who have been discharged from regular care; 4] CO-FLOW applies a holistic approach focusing on physical, cognitive, and psychological outcomes, participation (including return to work, which is an important outcome in the younger patients), HRQoL, and a wide range of predictors of long-term recovery, among which diversity.

Limitations

Some limitations have to be mentioned: 1] The CO-FLOW study only focusses on a part of the Netherlands, the Rotterdam–Rijnmond–Delft region. This one-region approach facilitates fast implementation of measurement infrastructure and long-term integral monitoring of all patients who survived hospitalization, including patients who have been discharged from regular care. Knowledge, expertise, and infrastructure of the CO-FLOW study is transferable to other regions and countries to facilitate organization and optimization of aftercare; 2] A control group of patients without COVID-19 is not included in CO-FLOW which hampers interpretation of outcomes; 3] For most of our outcome parameters, no pre-morbid information is available. This hampers interpretation of recovery, particularly in patients with co-morbidity.

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Chapter 3

The impact of pulmonary embolism on health outcomes of COVID-19 at 3 months after hospitalization

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Abstract

Background COVID-19 patients frequently experience pulmonary embolism (PE), but its long-term consequences remain uncertain.

Objectives To assess the impact of PE in COVID-19 patients on health outcomes at 3 months after hospitalization.

Methods In this multicenter cross-sectional study, we aggregated data from existing databases to evaluate the impact of PE on health outcomes at 3 months after hospitalization. We assessed 1) questionnaires on health-related quality of life (HRQoL, 5-level EuroQol 5-dimensional questionnaire [EQ-5D-5L]), anxiety, depression, cognitive failure, and posttraumatic stress disorder; 2) pulmonary function tests (diffusing capacity of the lungs for carbon monoxide [DLCO] and spirometry); and 3) radiological abnormalities. We developed 3 models to assess the association between PE and the EQ-5D-5L index and the percentage of predicted DLCO (DLCO%): a crude model (model 1), adjusted for age, sex, and presence of comorbidities (model 2), and model 2 additionally adjusted for intensive care unit admission (model 3).

Results We included 465 patients who had been hospitalized for COVID-19, of whom 102 (21.9%) had developed a PE during admission. Patients with PE had poorer EQ-5D-5L index values, more impairment in pulmonary functions, and more frequent radiological abnormalities than patients without PE. Symptoms of anxiety, depression, cognitive failure, and posttraumatic stress disorder did not differ between the 2 groups. In model 2, PE was associated with lower EQ-5D-5L index and lower DLCO%. After additionally adjusting for intensive care unit admission, the association between PE and lower EQ-5D-5L index (mean difference = -0.069, [95%CI -0.12 to -0.017]) remained, but not between PE and DLCO%.

Conclusion Our findings suggest that PE in COVID-19 patients is associated with reduced health-related quality of life at 3 months after hospitalization. While PE may be a marker of COVID-19 severity, its presence during hospitalization could indicate potential long-term health issues, which may be considered during follow-up care.

Introduction

Hospitalized COVID-19 patients are at risk of thrombotic complications, with acute pulmonary embolism (PE) as the most frequently occurring.[1,2] A meta-analysis has shown a high incidence of PE in hospitalized COVID-19 patients, with an incidence of 17% in nonintensive care unit (ICU) patients and 26% in ICU patients.[2] While previous studies have focused on predictors for PE and acute clinical outcomes in COVID-19 patients with diagnosed PE,[3,4] there is limited data on the long-term impact of PE on health outcomes in this population.[5]

In non-COVID-19 patients, PE survivors often experience long-term health sequelae. These include new-onset or increased dyspnea, functional impairment, and decreased cardiopulmonary reserve, and are reported in up to 50% of PE survivors.[6-8] This so-called post-PE syndrome is associated with increased frailty, symptoms of anxiety and depression, and reduced health-related quality of life (HRQoL).[8-12] In severe, but rare, cases, chronic thromboembolic pulmonary hypertension (CTEPH) may develop, leading to a considerable loss of HRQoL and increased mortality.[13]

Many patients hospitalized for COVID-19 experience long-term health effects and different terms have been used to describe this condition, such as "Post-Acute COVID-19 Syndrome," "Long COVID," and "post-COVID-19 Condition." Fatigue and neurocognitive impairment are frequently reported health problems after hospitalization for COVID-19.[14,15] Moreover, COVID-19 patients may experience reduced HRQoL.[16,17]

Based on these considerations, we aimed to assess various health outcomes in patients with and without PE, including patient-reported outcome measures (PROMs), pulmonary function, and radiological abnormalities, 3 months after hospitalization for COVID-19. The primary outcomes were HRQoL and diffusing capacity of the lungs for carbon monoxide (DLCO), other outcomes were considered as secondary outcomes. These primary outcomes were commonly found to be reduced in both non-COVID-19 patients with PE and COVID-19 patients.[8-10,12,16,18-23] Furthermore, we conducted multiple multivariable regression analyses to explore the association between PE and both primary and secondary outcomes.

Methods

Study design and participants

This multicenter observational study was conducted across 4 Dutch academic hospitals: the Erasmus University Medical Center (UMC), Leiden UMC, Maastricht UMC, and Radboud UMC. We retrospectively collected and combined data from pre-existing cohorts of COVID-19 patients in the participating hospitals, as described in detail elsewhere,[24-28] and performed a cross-sectional analysis at 3 months after discharge. These databases had been established as part of routine follow-up procedures or local study procedures; for a detailed description, see **Supplementary Methods S1**. During the first COVID-19 wave in the Netherlands, the participating academic hospitals routinely

offered follow-up around 3 months after discharge. As part of this 3-month visit, patients performed pulmonary function tests, chest imaging, and questionnaires, which we used in the current study.

Eligible patients had been discharged before September 2020 and of whom data were available from at least one of the following: pulmonary function tests, chest computed tomography (CT) scans, or one or more PROMs using questionnaires, all performed as part of the 3-month visit. Ethical approval was obtained from each participating site, and either informed consent had been obtained or an opt-out procedure had been applied. The current study was approved by the Erasmus UMC (MEC-2021-0423).

Data collection

Demographic (age, sex, body mass index, and smoking status) and clinical (comorbidities, laboratory values, diagnosis of PE, chest CT scan abnormalities, admission to ICU, invasive mechanical ventilation, number of days in ICU, number of days in the hospital, and treatment for COVID-19) characteristics during hospital admission were collected from the databases of the pre-existing cohorts using a standardized format provided to the local researchers of the participating hospitals. In these databases, sex was defined based on the information recorded in the electronic patient record, which categorized individuals as male or female, primarily according to their registered biological characteristics. If variables were missing from these databases, local researchers retrospectively collected this information from the electronic patient records. Patients who were classified as having had PE during hospitalization were those who displayed suspected thrombotic complications, and in whom the diagnosis was verified through CT pulmonary angiography (CTa) or clinical assessment. Clinical assessment encompassed PE diagnosis in cases where CTa was omitted due to patients' inability to be transferred to the CT scan. PE was categorized based on the most proximal location in the pulmonary arteries (central, segmental, or subsegmental). All other patients were classified as not having had PE. Data had been deidentified and stored in separate databases, which were merged for this study.

Outcomes

We evaluated HRQoL and DLCO as primary outcomes, while other PROMs, spirometry, and chest radiological abnormalities were considered secondary outcomes.

PROMs

We used PROMs that had been assessed in at least 2 of the participating hospitals. When the same health outcome was assessed by different questionnaires, we used validated cut-off scores to indicate the presence of a specific health complaint and combined the dichotomous outcome of the questionnaires.

HRQoL was assessed with the 5-level EuroQol 5-dimensinal questionnaire (EQ-5D-5L) across all hospitals and consists of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[29] The EQ-5D-5L dimension scores were converted into a single index value ranging from less than 0 (negative values indicating a health state worse than death) to 1 (representing

perfect health). The EQ-5D-5L also includes a vertical visual analog scale (VAS) to assess self-rated general health status on a scale from 0 (worst imaginable health status) to 100 (best imaginable health status). We used age- and sex-adjusted median index values obtained from the Dutch tariff for the EQ-5D-5L as reference values.[30]

We also assessed symptoms of anxiety, depression, PTSD, and cognitive failures. Symptoms of anxiety were assessed with the Hospital Anxiety and Depression Scale[31] (HADS) subscale anxiety (HADS-A) and Generalized Anxiety Disorder[32] (GAD-7) questionnaires. Validated cut-off scores of ≥8 for HADS-A and ≥10 for GAD-7 were used to indicate signs of anxiety. Symptoms of depression were assessed with the HADS subscale for depression[31] (HADS-D) and the Patient Health Questionnaire-9[33] (PHQ-9), with cut-off scores of ≥8 for the HADS-D and ≥10 for the PHQ-9 indicating depression. Symptoms of PTSD were assessed with the PTSD Checklist for DSM-5[34] (PCL-5) and the Impact of Event Scale-Revised[35] (IES-R); in both questionnaires, scores ≥33 indicate clinically significant PTSD. Cognitive failures were assessed using the Cognitive Failure Questionnaire (CFQ), with scores >43 indicating cognitive failure.[36,37]

Pulmonary function

Pulmonary function tests included the assessment of diffusing capacity of the lungs for carbon monoxide (DLCO) in $mmol \cdot min^{-1} \cdot kPa^{-1}$ and spirometry to assess forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in liters, following the guidelines of the American Thoracic Society and the European Respiratory Society.[38] Pulmonary function outcomes are also presented as a percentage of predicted DLCO (DLCO%), FVC (FVC%), and FEV_1 (FEV_1%) values, using references values from the Global Lung Function Initiative Network.[39,40] Abnormal values were defined as those below the lower limit of normal (<LLN; z-score below -1.64).

Radiological abnormalities

Chest CT scans were assessed by experienced radiologists using a standardized assessment. We used the radiological reports to score the presence of distinctive parenchymal abnormalities across 5 categories: ground-glass opacities (GGOs), subpleural lines/bands, bronchiectasis, reticulation/fibrosis, and consolidation.

Statistical analysis

Continuous variables are presented as mean (SD) or as median (IQR). Categorical variables are presented as count (percentage). The normality of variables was assessed using histograms. We compared health outcomes at follow-up between COVID-19 patients with and without PE using 2-sample *t*-test or Mann-Whitney *U* test for continuous variables and Fisher's exact test for dichotomous variables. The median difference and 95% CI between the EQ-5D-5L index and age- and sex-adjusted median Dutch Tariff index values were calculated using the Bonett and Price method, as the distribution of the median Dutch Tariff index values was skewed.[41] *P* values are corrected for multiple comparisons using Bonferroni correction.

Multiple multivariable linear regression analysis and logistic regression analysis for symptoms of anxiety and depression were performed to assess the association between PE and the primary outcomes EQ-5D-5L index and DLCO%, and secondary outcomes including PROMs (anxiety, depression, and cognitive failures) and spirometry (FEV_1 and FVC). A directed acyclic graph was used to identify potential confounders and mediators (**Supplementary Methods S2** and **Supplementary Figure S1**). Three models were explored for each outcome: 1) a crude model containing only PE (model 1); 2) model 1 with age at admission, sex, and the presence of any comorbidity (diabetes mellitus, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, pre-COVID-19 VTE, stroke, active cancer, immunodeficiency or hypertension) as confounders. For DLCO%, we replaced the covariate of any comorbidity with the presence of chronic lung disease; 3) model 2 plus the addition of ICU admission.

We tested the additivity assumption by comparing the complex model, including *a priori* considered interactions, to the model without these interactions using a likelihood ratio test. Multiplicative interactions were added to the final model and separate analyses were performed when the interaction was significant. We used a *P* value threshold for significance of the interaction term of 0.15. Second, the linearity of the relationship between the health outcomes and age was examined using natural splines (splines package, R)[42] and incorporated into the final model if applicable. Results of the multivariable regression analyses are expressed as mean difference (MD) or odds ratio (OR) with 95% CI.

We performed 2 explorative subgroup analyses and one sensitivity analysis. We performed multivariable linear regression analysis to calculate the MD in EQ-5D-5L index and DLCO% for different patient groups. First, regarding potential associations of PE and ICU admission, patients were categorized into admitted to the ICU with (group 1, reference group) and without PE (group 2) and patients without ICU admission with (group 3) and without PE (group 4) and adjusted for sex and age at admission. Second, regarding PE severity, patients were categorized based on the most proximal location of PE: patients without PE (group 1, reference group), patients with subsegmental PE (group 2), patients with segmental or central PE (group 3), and patients with PE based on clinical assessment (group 4). Finally, a sensitivity analysis was performed in which patients with PE based on clinical assessment were excluded. Statistical analyses were performed using IBM SPSS Statistics (v.28) and R software (v.4.2.1).[42]

Results

In total, 465 patients who had been hospitalized for COVID-19 and completed at least one of the outcome measurements at the 3-month follow-up visit were identified. Of those, 102 (21.9%) patients had been diagnosed with PE during hospitalization. The localization of PE was most often segmental (43/102, 42.5%), thereafter subsegmental (40/102, 39.2%), central (11/102, 10.8%), and location unknown or clinically diagnosed (8/102, 7.8%). The median age of patients with PE was 59.5 (IQR, 54.0-66.0) years and 77 (75.5%) were male. Among patients without PE, the median age

was 60.0 (53.0-69.0) years and 236 (65.0%) were male. Other characteristics observed at hospital admission are summarized in **Table 1**. The median follow-up time (days between hospital discharge and follow-up assessment) was similar between patients with PE (85.5 [68.0-102.8] days) and those without (87.0 [68.0-102.0] days).

Table 1. Characteristics of participants enrolled in the study.

Characteristics at baseline	***n***	**Total (*n* = 465)**	**No PE (*n* = 363)**	**PE (*n* = 102)**
Demographics				
Age (y)	465	60.3 ± 12.2	60.5 ± 12.5	59.4 ± 11.0
Male sex	465	313 (67.3)	236 (65.0)	77 (75.5)
BMI (kg/m^2)	414	27.7 (24.9-31.2)	27.8 (24.9-31.7)	27.7 (24.9-30.3)
Smoking status	430			
Never		207 (48.1)	159 (47.2)	48 (51.6)
Former		217 (50.5)	172 (51.0)	45 (48.4)
Current		6 (1.4)	6 (1.8)	0 (0.0)
Medical history				
No comorbidity	464	106 (22.8)	77 (21.3)	29 (28.4)
Diabetes mellitus	426	69 (16.2)	55 (16.1)	14 (16.7)
Cardiovascular disease	426	160 (37.6)	133 (38.9)	27 (32.1)
Chronic kidney disease	426	28 (6.6)	26 (7.6)	2 (2.4)
Chronic liver disease	465	8 (1.7)	7 (1.9)	1 (1.0)
Chronic lung disease	426	91 (21.4)	80 (23.4)	11 (13.1)
Pre-COVID-19 VTE	462	18 (3.9)	13 (3.6)	5 (5.0)
Stroke	462	17 (3.7)	16 (4.4)	1 (1.0)
Active cancer	423	40 (9.5)	35 (10.3)	5 (6.0)
Immunodeficiency	423	41 (9.7)	37 (10.9)	4 (4.8)
In-hospital characteristics				
Laboratory values				
LDH (U/L)	456	366.0 (292.0-473.0)	352.0 (280.5-451.0)	415.0 (335.0-530.0)
Ferritin (µg/L)	318	926.0 (475.8-1686.8)	839.0 (422.0-1671.5)	1269.0 (584.0-1910.0)
D-dimer (mg/L)	253	1.2 (0.7-2.5)	1.1 (0.7-1.9)	2.0 (1.0-5.8)
Chest CT scan abnormalities				
No abnormalities	394	9 (2.3)	7 (2.3)	2 (2.2)
Ground-glass opacities	391	373 (95.4)	283 (95.0)	93 (96.8)
Consolidations	392	266 (67.9)	201 (67.2)	65 (69.9)
Reticulation/fibrosis	321	64 (19.9)	54 (22.5)	10 (12.3)
Bronchiectasis	306	41 (13.4)	30 (13.3)	11 (13.8)
Curvilinear bands	299	36 (12.0)	25 (11.4)	11 (13.9)

Table 1. Continued.

Characteristics at baseline	*n*	Total (*n* = 465)	No PE (*n* = 363)	PE (*n* = 102)
Requiring oxygen supplementation	461	410 (88.9)	317 (88.1)	93 (92.1)
ICU admission	465	217 (46.7)	133 (36.6)	84 (82.4)
Invasive mechanical ventilation	465	199 (42.8)	116 (32.0)	83 (81.4)
Extracorporeal membrane oxygenation	465	5 (1.1)	3 (0.8)	2 (2.0)
Length of ICU stay, d	216	21.0 (12.0-33.8)	16.5 (8.3-29.0)	28.5 (18.0-40.0)
Length of hospital stay, d	347	9.0 (5.0-26.0)	8.0 (4.0-16.0)	32.0 (20.0-46.5)
Treatment				
Hydroxychloroquine	463	228 (49.2)	185 (51.1)	43 (42.6)
Corticosteroids	461	126 (27.3)	86 (23.8)	40 (40.4)
Antivirals	463	56 (12.1)	40 (11.0)	16 (15.8)
Antibiotic agent	460	351 (76.3)	264 (73.3)	87 (87.0)
Antifungal agent	460	124 (27.0)	69 (19.2)	55 (55.0)
Antiplatelet therapy[a]	460	75 (16.3)	61 (17.0)	14 (13.9)

Data are presented as mean with ±SD, median with IQR or as a number with percentage.
BMI, body mass index; CT, computed tomography; ICU, intensive care unit; LDH, lactate dehydrogenase; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]Antiplatelet therapy comprises patients in whom antiplatelet therapy was initiated during hospitalization and patients with chronic antiplatelet therapy that was continued during hospital admission.

PROMs

In total, 405 (87.1%) patients completed at least one questionnaire at follow-up. The EQ-5D-5L dimension scores are presented per group in **Figure 1A**, for categorical outcomes see **Supplementary Table S1**. Patients with PE had a lower mean EQ-5D-5L index value than patients without PE (**Table 2** and **3**) (MD: -0.086 (95% CI: -0.13 to -0.038)). Both groups, those with PE (median difference: -0.18 (95% CI: -0.18 to -0.18) and those without PE (median difference: -0.09 (95% CI: -0.09 to -0.09) exhibited lower index values compared to age- and sex- adjusted Dutch Tariff median index values, with patients with PE showing a more pronounced difference. Regarding other PROMs, symptoms of anxiety, depression, PTSD, and cognitive failures did not differ between patients with and without PE (**Figure 1B** and **Table 2**).

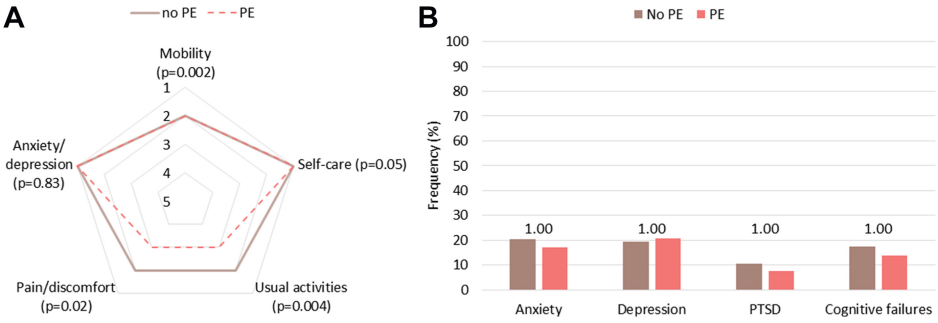

Figure 1. Patient-reported outcomes in COVID-19 patients with and without pulmonary embolism during hospitalization at 3 months follow-up.

Patient-reported outcome measures were assessed around 3 months after hospital discharge. (A) Median group scores across the dimensions of the 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L). Each dimension has five answer levels: no problems (1), some problems (2), moderate problems (3), severe problems (4), and extreme problems/unable to (5). For categorical outcomes for each domain, see ***Supplementary Table S1****. Group differences in 5-level EuroQol 5-dimensional questionnaire scores were assessed using a Mann-Whitney U test and P values are presented, using Bonferroni corrected P values for multiple testing. (B) Frequency of patients with symptoms of anxiety, depression, posttraumatic stress disorder (PTSD), and cognitive failures. Symptoms of anxiety were indicated by scores ≥8 on the anxiety subscale of the Hospital Anxiety and Depression Scale or scores ≥10 on the Generalized Anxiety Disorder questionnaire. Symptoms of depression were indicated by scores ≥8 on the depression subscale of the Hospital Anxiety and Depression Scale or scores ≥10 on the Patient Health Questionnaire-9. Symptoms of PTSD were indicated by scores ≥33 on the PTSD Checklist for DSM-5 (cut-off ≥33) or scores ≥33 on the Impact of Event Scale-Revised. Subjective cognitive failures in everyday life were indicated by scores >43 on the Cognitive Failure Questionnaire. Group differences for symptoms of anxiety, depression, PTSD, and cognitive failures were assessed using Fisher's exact test and P values are presented in the figure, using Bonferroni corrected P values for multiple testing. PTSD, posttraumatic stress disorder.*

Pulmonary function

Diffusion capacity data was available for 379 (81.5%) COVID-19 patients (**Figure 2** and **Table 2**). Patients with PE exhibited lower mean DLCO% values than those without PE (MD: -7.9 [95% CI:-12.3 to -3.5]). The proportion of patients with impaired DLCO (<LLN) was higher among patients with PE (59/89, 66.3%) than those without PE [124/279; 44.4%], OR: 2.5 [95% CI: 1.5 to 4.2]).

Spirometry data was available for 403 (86.7%) COVID-19 patients. Patients with PE had lower mean FVC% and FEV_1% values than those without PE (**Figure 2**). The proportion of patients with impaired FVC values (<LLN) was higher among patients with PE (26/95, 27.4%) than patients without PE (46/290, 15.9%, OR: 2.0 [95% CI: 1.1 to 3.6]) but did not differ for FEV_1 (OR: 1.5 [95% CI: 0.8 to 2.8]).

Table 2. Patient-reported outcome measures, pulmonary function, and chest radiology abnormalities in COVID-19 patients with and without pulmonary embolism (ref) during hospitalization at 3 months follow-up.

Health outcomes at 3 months post-hospitalization	n	Total (n=465)	n	No PE (n=363)	n	PE (n=102)	MD/OR (95% CI)
PROMs							
HRQoL, n	318		236		82		
EQ-5D-5L, index value		0.74 ± 0.19		0.76 ± 0.19		0.67 ± 0.20	MD: -0.086 (-0.13 to -0.038)
EQ-5D-5L, VAS		65.8 ± 18.6		67.4 ± 18.7		61.3 ± 17.7	MD: -6.1 (-1.6 to -10.6)
Anxiety, n	380		298		82		
HADS-A, total score		4.8 ± 4.1		4.8 ± 4.0		4.9 ± 4.4	MD: 0.09 (-1.1 to 1.3)
GAD7, total score		3.4 ± 3.9		3.4 ± 4.3		3.4 ± 3.1	MD: -0.004 (-2.0 to 2.0)
Anxiety (HADS-A ≥ 8 or GAD7 ≥ 10)		75 (19.7)		61 (20.5)		14 (17.1)	OR: 0.8 (0.4 to 1.6)
Depression, n	384		302		82		
HADS-D, total score		4.6 ± 3.9		4.4 ± 3.8		5.0 ± 4.3	MD: 0.5 (-0.6 to 1.7)
PHQ9, total score		5.1 ± 5.1		5.2 ± 5.1		4.7 ± 5.2	MD: -0.5 (-3.6 to 2.6)
Depression (HADS-D ≥ 8 or PHQ9 ≥ 10)		79 (20.6)		63 (20.9)		16 (19.5)	OR: 0.9 (0.5 to 1.7)
PTSD, n	261		197		64		
PCL5, total score		12.1 ± 12.9		12.6 ± 13.3		10.4 ± 11.5	MD: -2.1 (-6.1 to 1.8)
IES-R, total score		16.1 ± 14.8		16.1 ± 14.5		16.1 ± 15.7	MD: 0.005 (-9.2 to 9.2)
PTSD (PCL5 ≥ 33 or IES-R ≥ 33)		26 (10.0)		21 (10.7)		5 (7.8)	OR: 0.7 (0.2 to 2.1)
Cognitive functioning, n	254		189		65		
CFQ total score		27.7 ± 16.8		28.0 ± 16.6		26.7 ± 17.5	MD: -1.3 (-6.2 to 3.6)
Cognitive failure (CFQ > 43)		42 (16.5)		33 (17.5)		9 (13.8)	OR: 0.8 (0.3 to 1.8)
Radiological abnormalities							
No abnormalities	376	30 (8.0)	284	29 (10.2)	92	1 (1.1)	OR: 0.1 (0.002 to 0.6)
Ground to glass opacities	392	269 (68.6)	299	195 (65.2)	93	74 (79.6)	OR: 2.1 (1.2 to 3.8)
Subpleural curvilinear lines/bands	366	184 (50.3)	275	125 (45.5)	91	59 (64.8)	OR: 2.2 (1.3 to 3.7)
Bronchiectasis	366	153 (41.8)	277	99 (35.7)	89	54 (60.7)	OR: 2.8 (1.7 to 4.7)
Reticulation/fibrosis	341	112 (32.8)	261	80 (30.7)	80	32 (40.0)	OR: 1.5 (0.9 to 2.6)
Consolidations	390	47 (12.1)	298	28 (9.4)	92	19 (20.7)	OR: 2.5 (1.2 to 4.9)

Table 2. Continued.

Health outcomes at 3 months post-hospitalization	n	Total (n=465)	n	No PE (n=363)	n	PE (n=102)	MD/OR (95% CI)
Pulmonary function							
Spirometry							
FVC, L	393	3.9 ± 1.1	297	3.9 ± 1.1	96	3.8 ± 1.1	MD: -0.2 (-0.4 to 0.1)
FVC, % predicted	394	93.1 ± 19.1	298	94.8 ± 19.6	96	88.0 ± 16.7	MD: -6.8 (-10.8 to -2.7)
FVC<LLN, n (%)	385	72 (18.7)	290	46 (15.9)	95	26 (27.4)	OR: 2.0 (1.1 to 3.6)
FEV_1, L	398	3.0 ± 0.8	300	3.0 ± 0.8	98	3.0 ± 0.8	MD: -0.08 (-0.3 to 0.1)
FEV_1, % predicted	399	92.7 ± 18.8	301	94.0 ± 19.3	98	88.7 ± 16.6	MD: -5.3 (-9.2 to -1.3)
FEV_1<LLN, n (%)	390	66 (16.9)	293	45 (15.4)	97	21 (21.6)	OR: 1.5 (0.8 to 2.8)
Gas exchange							
DLCO, $mmol \cdot min^{-1} \cdot kPa^{-1}$	369	6.6 ± 2.1	281	6.7 ± 2.1	88	6.2 ± 2.1	MD: -0.5 (-1.0 to -0.01)
DLCO, % predicted	368	75.0 ± 18.9	280	76.9 ± 18.7	88	69.0 ± 18.2	MD: -7.9 (-12.4 to -3.5)
DLCO < LLN, *n* (%)	368	183 (49.7)	279	124 (44.4)	89	59 (66.3)	OR: 2.5 (1.5 to 4.2)

Data are presented as mean with ±SD for continuous variables and as a number with percentage for categorical variables. PROM, patient reported outcome measure; PE, pulmonary embolism; MD, mean difference; OR, odds ratio; FVC, forced vital capacity; LLN, lower limit of normal; FEV_1, forced expiratory volume in 1 second; DLCO, diffusing lung capacity for carbon monoxide; CT, computed tomography; HRQoL, Health-Related Quality of Life; EQ-5D-5L; 5-level EuroQol 5D questionnaire; VAS, visual analog scale; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale with the subscales anxiety; HADS-D, Hospital Anxiety and Depression Scale with the subscale depression; GAD7, General Anxiety Disorder-7; PHQ9, Patient Health Questionnaire-9; PTSD, posttraumatic stress disorder; PCL5, PTSD Checklist for DSM-5; IES-R, Impact of Event Scale-Revised; CFQ, Cognitive Failure Questionnaire.

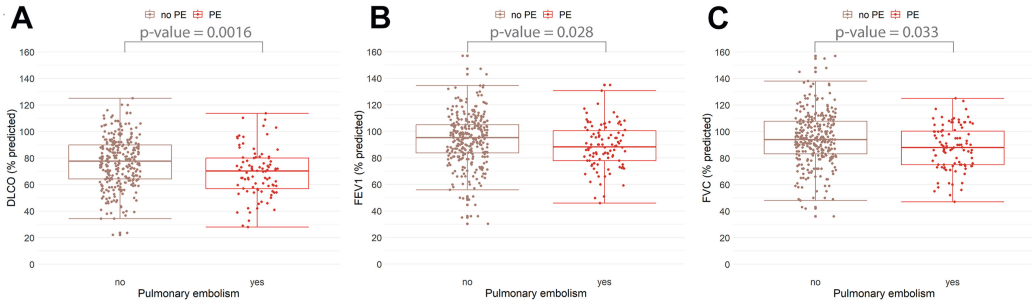

Figure 2. Pulmonary function outcomes in COVID-19 patients with and without pulmonary embolism (PE) during hospitalization at 3 months follow-up.
Pulmonary function tests were performed around 3 months after hospital discharge. The outcomes are presented as percent-predicted values. Group differences in pulmonary function outcomes were assessed using independent t-tests and P values are presented, using Bonferroni corrected P values for multiple testing. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide; PE, pulmonary embolism.

Radiological abnormalities

Information on radiological outcomes was available for 392 (84.3%) COVID-19 patients. Residual abnormalities were more frequently found in patients with PE than those without PE, with GGO being the most common abnormality as shown in **Figure 3** and **Table 2** (OR: 2.1 [95% CI: 1.2 to 3.8]).

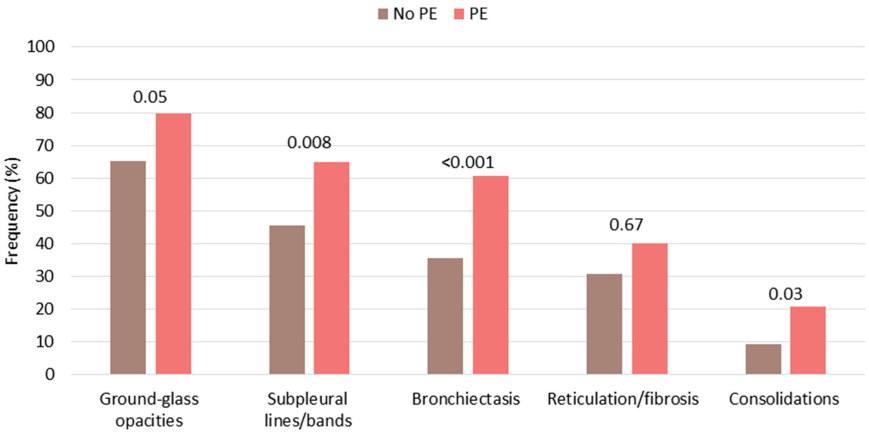

Figure 3. Radiological abnormalities in COVID-19 patients with and without pulmonary embolism during hospitalization at 3 months follow-up.
Chest CT scans were performed around 3 months after hospital discharge. Group differences in radiological abnormalities were assed using Fisher's exact tests and P values are presented, using Bonferroni corrected P values for multiple testing.

Table 3. Mean difference or odds ratio in primary and secondary outcome measures between COVID-19 patients with and without pulmonary embolism (reference) during hospitalization at 3 months follow-up.

Health outcomes at 3 months post-hospitalization	Total (*n* = 465)	No PE (*n* = 363)	PE (*n* = 102)	Crude model (model 1)	Model 2[a]	Model 3[b]
Primary outcome measures						
EQ-5D-5L index value	0.74 ± 0.19	0.76 ± 0.19	0.67 ± 0.20	MD: -0.086 (-0.13 to -0.038)	MD: -0.095 (-0.14 to -0.047)	MD: -0.069 (-0.12 to -0.017)
DLCO (% predicted)[c]	75.0 ± 18.9	76.9 ± 18.7	69.0 ± 18.2	MD: -7.92 (-12.38 to -3.45)	MD: -8.09 (-12.48 to -3.70)	MD: -2.21 (-6.61 to 2.19)
Secondary outcome measures						
Anxiety (HADS-A ≥ 8 or GAD7 ≥ 10)	75 (19.7%)	61 (20.5%)	14 (17.1%)	OR: 0.80 (0.41 to 1.48)	OR: 0.84 (0.43 to 1.58)	OR: 0.71 (0.34 to 1.42)
Depression (HADS-D ≥ 8 or PHQ9 ≥ 10)	79 (20.6%)	63 (20.9%)	16 (19.5%)	OR: 0.92 (0.48 to 1.67)	OR: 0.98 (0.51 to 1.80)	OR: 0.94 (0.46 to 1.85)
Total CFQ score[c,d]	27.6 ± 16.8	28.0 ± 16.6	26.7 ± 17.5	MD: -1.30 (-6.17 to 3.57)	MD: -1.00 (-5.61 to 3.60)	MD: -0.66 (-5.85 to 4.53)
FVC (% predicted)[c]	93.1 ± 19.1	94.8 ± 19.6	88.0 ± 16.7	MD: -6.79 (-11.16 to -2.42	MD: -6.58 (-10.94 to -2.23)	MD: -2.33 (-6.82 to 2.15)
FEV_1 (% predicted)	92.7 ± 18.8	94.0 ± 19.3	88.7 ± 16.6	MD: -5.27 (-9.53 to -1.01)	MD: -5.24 (-9.5 to -0.98)	MD: -2.76 (-7.27 to 1.75)

Data are presented as mean ± SD and mean differences (95% CI) or numbers with percentages and odds ratios for symptoms of anxiety and depression, between patients with vs without diagnosis of a PE during hospital admission. The outcomes were assessed around 3 months after hospital discharge. We used the percentage of predicted value of DLCO, FVC, and FEV_1. Symptoms of anxiety were indicated by scores ≥8 on the anxiety subscale of the HADS or scores ≥10 on the GAD questionnaires. Symptoms of depression were indicated by scores ≥8 on the depression subscale of the HADS or scores ≥10 on the PHQ-9 questionnaires. MD, mean difference; OR, odds ratio; PE, pulmonary embolism; EQ-5D-5L, 5-level EuroQol 5D questionnaire; DLCO, diffusion capacity of the lungs for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; GAD, Generalized Anxiety Disorder; PHQ-9, Patient Health Questionnaire-9; CFQ, Cognitive Failure Questionnaire; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

[a]Model 2 is the crude linear model additionally adjusted for age at admission, sex and presence of one or more comorbidities at admission (y/n). Comorbidities included diabetes mellitus, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, pre-COVID-19 VTE, stroke, active cancer, immunodeficiency and hypertension. For the pulmonary function outcomes, the presence of one or more comorbidities was replaced by the presence of chronic lung disease.

[b]Model 3 is the multivariable linear model 2 additionally adjusted for intensive care unit admission.

[c]Natural splines with 3 degrees of freedom were included in model 3 of FVC, and model 2 and 3 of the CFQ and DLCO.

[d]Weighted linear regression was used in this model.

Association between PE and health outcomes at 3 months follow-up

In all multivariable analyses, the complex model with interactions did not perform better than the model without interactions (**Supplementary Table S2**). In the crude models, we found an association between PE and lower EQ-5D-5L index value as well as between PE and lower DLCO% (**Table 3**). Regarding HRQoL, the association between PE and lower EQ-5D-5L index value remained after adjusting for sex, age, and comorbidity (MD: -0.095 [95% CI: -0.14 to -0.047]) and after additionally adjusting for ICU admission (MD: -0.069 [95% CI: -0.12 to -0.017]). The association between PE and lower DLCO% remained after adjusting for sex, age, and pre-existing lung disease (MD: -8.09 [95% CI: -12.48 to -3.70]) but was mitigated when ICU admission was included in the model (MD: -2.21 [95 CI: -6.61 to 2.19]). Similarly, we found an association between PE and lower FVC% and FEV_1% after adjusting for sex, age and comorbidity (MD: -6.58 [-10.94 to -2.23] and -5.24 [-9.5 to -0.98], respectively), but was mitigated when ICU admission was included in the model (MD: -2.33 [-6.82 to 2.15] and -2.76 [-7.27 to 1.75], respectively) (**Table 3**). No association was found between PE and the presence of secondary outcomes for symptoms of anxiety, depression, and cognitive failures (**Table 3**) in the crude model or after adjusting for the confounders.

Subgroup and sensitivity analyses

First, we explored potential associations of PE and ICU admission with the EQ-5D-5L index and DLCO% (**Figure 4** and **Supplementary Table S3**). Compared with patients with PE admitted to the ICU, patients with PE without ICU admission had similar EQ-5D-5L index values (MD: 0.04 [95% CI: -0.08 to 0.16]), while patients without PE admitted to the ICU (MD: 0.06 [95% CI: 0.004 to 0.12]) or those without PE and ICU admission (MD: 0.12 [95% CI: 0.06 to 0.17]) had significantly higher values. For DLCO% values, compared with patients with PE admitted to the ICU, patients without PE admitted to the ICU had similar DLCO% values (MD: 3.9 [-1.2 to 9.0]), while patients without ICU admission had higher mean DLCO% values (MD: 19.48 [95% CI: 10.3 to 28.6] and MD: 16.86]95% CI: 12.2 to 21.6], respectively).

In the second subgroup analysis, patients were grouped based on the most proximal location of PE (**Figure 4** and **Supplementary Table S4**). Compared with patients without PE, EQ-5D-5L index values were significantly lower in patients with segmental/central PE (MD: -0.09 [95% CI: -0.15 to -0.03]) and patients diagnosed with PE through clinical assessment (MD: -0.19 [95% CI: -0.35 to -0.04] but did not differ significantly from patients with subsegmental PE (MD: -0.07 [95% CI-0.14 to 0.004]). Regarding DLCO%, compared with patients without PE, patients with segmental/central PE (MD: -7.6 [95% CI: -13.2 to -2.1]) and those diagnosed with PE through clinical assessment had significantly lower DLCO% (MD: -19.2 [95% CI: -31.9 to -6.5]) but did not differ significantly from patients with subsegmental PE (MD: -6.3 [95% CI: -13.0 to 0.45]). Differences between patients with subsegmental PE and segmental/central PE in these outcomes were relatively small (**Figure 4** and **Supplementary Table S4**).

To address potential misclassification of the PE diagnosis in patients diagnosed through clinical assessment alone, we conducted a sensitivity analysis excluding these patients (**Supplementary Tables S5** and **S6**). This exclusion did not quantitatively change the results of the main analysis.

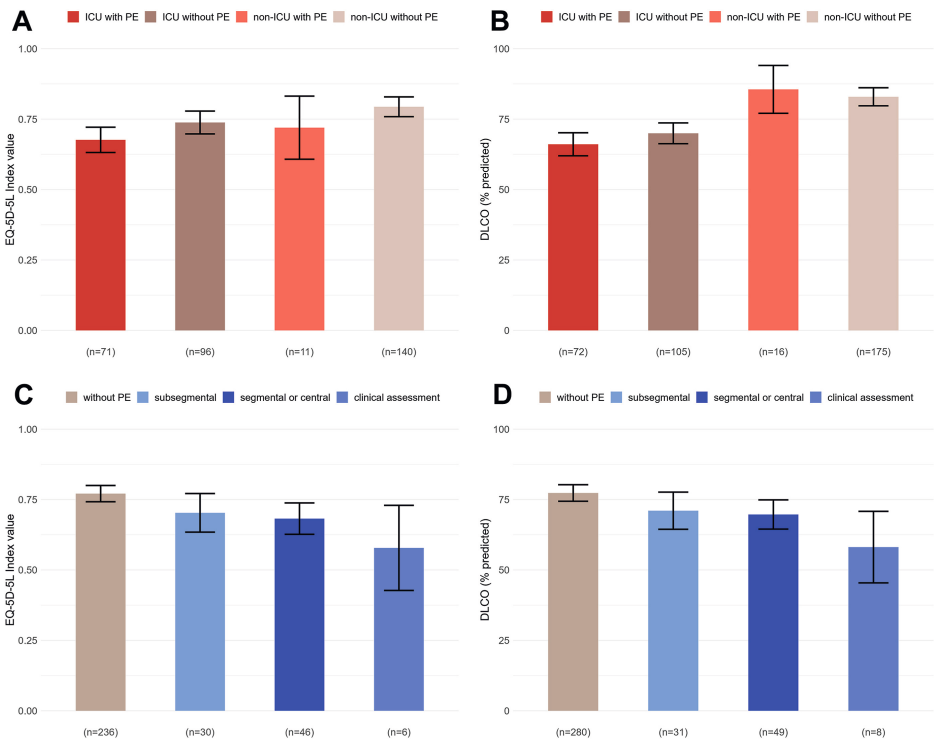

Figure 4. Results of the subgroup analysis.
Bar charts depicting the mean EQ-5D-5L index value (A, C) and percentage of predicted DLCO (B, D), divided in groups of the two explorative subgroup analyses. (A. B) Patients are divided based on admission to the intensive care unit (yes or no) and developing PE (yes or no). (C, D) Patients are divided based on the localization of PE (ie, none, subsegmental, segmental/central or clinical assessment). The bar charts depict the EQ-5D-5L index values (A, C) and DLCO% (B, D) of males with an age at admission of 60, which was the median age of our study population. The whiskers represent the 95% Cis. EQ-5D-5L, 5-level EuroQol 5D questionnaire; DLCO, diffusing lung capacity for carbon monoxide; PE, pulmonary embolism.

Discussion

This study assessed the impact of PE in patients who had been hospitalized for COVID-19 on various health outcomes at 3 months after hospitalization. Overall, COVID-19 patients with PE showed poorer health outcomes at follow-up compared with those without PE. In a more in-depth analysis, our findings indicate that COVID-19 patients with PE were more likely to experience impaired HRQoL and had more impaired DLCO than those without PE, even after adjusting for age, sex, and the presence of (lung) comorbidity. However, after additional adjustment for ICU admission, only the association between PE and HRQoL remained.

Our study contributes to the existing literature on decreased HRQoL among COVID-19 patients.[16,19-21] Previous studies assessing the EQ-5D-5L questionnaire in hospitalized COVID-19

patients found a decline in HRQoL compared with their pre-COVID-19 state in all dimensions except for self-care, yet did not compare patients with and without PE.[19,20] Our analysis revealed that COVID-19 patients diagnosed with PE during hospitalization had more impaired HRQoL than those without PE at 3 months follow-up, overreaching the minimum clinically important difference in EQ-5D-5L index value (ranging between 0.037 and 0.069).[43] Nevertheless, both COVID-19 patients with and without PE showed lower HRQoL than the Dutch tariff for the EQ-5D-5L index value.[30]

Studies in non-COVID-19 patients with PE also indicated lower HRQoL compared with the general population.[8-10,12] However, our observed mean EQ-5D-5L index value of 0.67 ± 0.20 at 3 months follow-up in COVID-19 patients with PE was lower than the reported means in non-COVID-19 patients, ranging from 0.84 ± 0.21 to 0.85 ± 0.22,[10,11] which difference is above the minimum clinically important difference.[17] This observation, in combination with the overall lower HRQoL reported in COVID-19 patients, might indicate that the presence of PE increases the impact of COVID-19 on HRQoL. Of note, previous studies reported inconsistent results on the association between ICU admission for COVID-19 and changes in HRQoL,[17] favoring the impact of PE on reduced HRQoL.

Various reasons, ranging from mechanistic to psychological, have been proposed as important contributors to lower HRQoL in patients with PE. These reasons include complications arising from treatment, rare conditions resulting from inadequately resolved thrombi, eventually leading to chronic thromboembolic with or without pulmonary hypertension (CTEPH or CTEPD), post-PE cardiac impairment due to acute ischemic injury and chronic inflammation, and the more common long-term PE sequelae of deconditioning, dyspnea, functional limitations, and reduced exercise tolerance.[7,9,12,13] These issues can be influenced by decreased physical activity after PE diagnosis and the mental strain arising from sudden illness onset, concerns about treatment-related complications, fears of recurrence and physical discomfort due to pain or dyspnea.[9,12,44] The multifactor nature of the abovementioned factors underlines the complexity of isolating the exclusive impact of PE on HRQoL outcomes in every patient with PE, a complexity even more pronounced in patients with COVID-19 associated PE. Notably, a recent Dutch study found that the occurrence of CTEPH and thrombus resolution in COVID-19 associated PE was similar to non-COVID-19 associated PE.[45] More common long-term PE sequelae such as deconditioning,[44] are more likely to be important contributors to the observed effect in our study.

Although non-COVID-19 patients with PE are generally at risk for symptoms of anxiety and depression,[8-10] the prevalence of these symptoms did not significantly differ between COVID-19 patients with and without PE during hospitalization at 3 months follow-up. These findings suggest that in patients with COVID-19-related PE, the presence of PE may not add to the psychological distress already caused by hospitalization for COVID-19.

Our study confirms prior research suggesting persistent lung injury in COVID-19 patients after hospitalizatio,[22,23] with a higher frequency observed in patients with PE compared with those without PE.[5] Impairment in DLCO was the most notable pulmonary abnormality lung injury among all our COVID-19 patients, affecting 66% of the patients with PE. The magnitude of DLCO impairment has

been associated with the extent of the PE in non-COVID-19 patients with PE.[18] In our study, COVID-19 patients with PE also exhibited more frequent radiological abnormalities at 3 months follow-up, with GGO being the most common, consistent with previous studies.[22,46,47] These pulmonary abnormalities can persist for months or even years after COVID-19 infection, although continuing improvement over time has been noted.[16,23,48,49] Future studies are warranted to gain insight into the trajectories of DLCO impairment across patients with and without PE beyond 3 months follow-up.

Although our findings revealed an association between PE and impaired DLCO, this association disappeared after adjusting for ICU admission. This raises the question of whether ICU admission should be considered as a mediator or a confounding factor in the analysis. If ICU is a mediator, our results might suggest an effect of PE on pulmonary function outcomes. In this case, adjusting for ICU admission will lead to a lower estimate of the total effect of PE on pulmonary function outcomes (**Supplementary Material S2**). Indeed, COVID-19 patients with PE have a higher frequency of ICU admission, although the predictive value of PE has been observed to be only mild.[2] However, ICU admission may also confound the effect of PE on health outcomes, particularly as ICU is considered a risk factor of PE.[50] Therefore, ICU admission itself may contribute to the diagnosis of PE and adjusting for ICU admission is necessary to avoid an incorrect high estimate of the total effect of PE on health outcomes. If ICU admission confounds the causal effect (model 3), our results do not support PE on pulmonary function outcomes.

Similar to ICU admission, PE may not be a cause of decreased health outcomes but may serve as a marker of increased COVID-19 severity. According to the World Health Organization, acute VTE is one of the complications to describe critical disease in COVID-19, and PE has been linked to a procoagulant state that is more pronounced in critically ill COVID-19 patients.[51] To disentangle the effects of PE and ICU admission on the long-term health outcomes, we conducted exploratory subgroup analyses. The results suggest that ICU admission is associated with impaired DLCO, regardless of PE diagnosis during admission, while HRQoL seemed to be reduced in patients with PE. However, our second subgroup analysis did not suggest that the location of initial PE, a potential marker for PE severity, significantly modifies the association between PE and our primary outcomes. Consequently, the decreased health outcomes in patients with PE might be indicative of increased COVID-19 severity. Thus, while PE should not necessarily be viewed as the primary cause of decreased HRQoL following hospitalization for COVID-19, it seems that patients with PE are more likely to experience reduced HRQoL. Therefore, the presence of PE during COVID-19 may still be indicative of potential long-term health issues and may be considered during aftercare.

We acknowledge the complexity of disentangling the specific contributions of PE and COVID-19 severity to the observed health outcomes at 3 months follow-up. For instance, our patients with and without PE also differed in the use of corticosteroids, antifungal agents, and antibiotic agents. The effect of these different treatment policies on the risk of developing PE and subsequent health outcomes in COVID-19 patients is unknown. Nonetheless, our study primarily focused on exploring potential differences in long-term health outcomes between patients with and without PE. The observed differences in HRQoL and DLCO between groups have clinical relevance, providing valuable

insights to patients about their expectations and guiding practitioners in tailoring aftercare. In this context, the debate whether PE merely serves as a proxy for disease severity or independently contributes to lower HRQoL and DLCO might be of secondary importance.

The strength of this study lies in its multicenter design, which involved data collection from 4 academic hospitals in the Netherlands, resulting in a large sample size of patients with and without PE during hospitalization for COVID-19. The large sample size allowed for the correction of confounding factors and investigation of plausible interaction terms and linearity of the relationship between the different health outcomes and continuous variables. The follow-up assessment included comprehensive objective and subjective measures to evaluate the effect of PE on diverse health outcomes. Moreover, the study's large nationwide sample increased the external generalizability. Finally, we tried to reduce confounding by using different models. However, residual confounding remains a potential limitation despite these efforts. One study limitation is the potential misclassification of PE in patients diagnosed through clinical assessment alone. However, the exclusion of these patients, representing only a small minority (7.8%), did not quantitatively alter our results, indicating that the impact of this misclassification on our findings is likely minimal. Another limitation included the small number of non-ICU patients who developed PE, warranting caution in interpreting the subgroup analysis. The observed poorer health outcomes in the PE group may result from increased COVID-19 severity rather than solely the effect of PE. Our data did not allow further investigation, such as a sensitivity analysis for the severity of COVID-19. Further studies are needed to confirm our study findings and evaluate the longer-term impact of PE on health outcomes after hospitalization for COVID-19. Additionally, we included a selected group of patients, namely those who completed 3-month follow-up assessments in one of the 4 academic hospitals and had data available for one of the outcomes. Patients could have different reasons to not participate, eg, inability to visit the outpatient clinic, declining follow-up because of absence or presence of symptoms, or having follow-up scheduled elsewhere. Furthermore, our results might not be fully generalizable to the general COVID-19 population as the study's timeframe is limited to the first wave of COVID-19. Even though the incidence of PE seems to be as high in the second wave as in the first wave,[1] the impact of the different treatment modalities, availability of vaccines, and SARS-CoV-2 variants on the relationship between PE and health outcomes is uncertain. Moreover, to date, the frequency of patients requiring hospitalization for COVID-19 is much lower compared with the first wave. We collected data from pre-existing cohorts of COVID-19 patients in the participating academic hospitals, which lacked some detailed and potentially insightful information, such as information on the presence of chronic thromboembolic disease, thromboembolic resolution, race and ethnicity of participants, anticoagulation status and the specific anticoagulants used by the patients with PE after hospitalization. These factors may affect the HRQoL through the mechanisms previously discussed. Finally, the use of different questionnaires across hospitals might introduce some variability. Nonetheless, validated cut-off scores were used to assess symptoms of anxiety, depression, and PTSD, and the observed frequency of these symptoms align with previous studies.[52,53] These limitations underscore the importance of large longitudinal follow-up studies with extended follow-up durations.

In conclusion, this large multicenter study provides insights into the clinical impact of PE in COVID-19 patients on health outcomes at 3 months after hospitalization during the first wave. Patients with PE had more impaired HRQoL, even after adjusting for ICU admission. PE was not associated with the other assessed health outcomes, or the association disappeared after adjusting for ICU admission. The association between PE and poorer health outcomes remains uncertain, as PE might serve as a proxy for increased disease severity, with poorer outcomes resulting from the severity of COVID-19 itself. Nonetheless, our findings indicate that COVID-19 patients with PE showed clinically significant reduced HRQoL. Therefore, the presence of PE during hospitalization, whether or not being a marker of disease severity, could be indicative of potential long-term health issues and may be considered during aftercare.

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Chapter 4

Symptoms persisting after hospitalisation for COVID-19: 12 months interim results of the CO-FLOW study

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Abstract

Introduction A large proportion of patients experience a wide range of sequelae after acute COVID-19, especially after severe illness. The long-term health sequelae need to be assessed. Our objective was to longitudinally assess persistence of symptoms and clusters of symptoms up to 12 months after hospitalization for COVID-19, and to assess determinants of the main persistent symptoms.

Methods In this multicentre prospective cohort study patients with COVID-19 are followed up for 2 years with measurements at 3, 6, 12, and 24 months after hospital discharge. Here, we present interim results regarding persistent symptoms up to 12 months. Symptoms were clustered into physical, respiratory, cognitive and fatigue symptoms.

Results We included 492 patients; mean±SD age was 60.2±10.7 years, 335 (68.1%) were males, median length of hospital stay was 11 (6.0–27.0) days. At 3 months after discharge 97.0% of the patients had at least one persisting symptom, this declined to 95.5% and 92.0% at 6 and 12 months, respectively (p=0.010). Muscle weakness, exertional dyspnoea, fatigue, and memory and concentration problems were the most prevalent symptoms with rates over 50% during follow-up. Over time, muscle weakness, hair loss and exertional dyspnoea decreased significantly (p<0.001), while other symptoms such as fatigue, concentration and memory problems, anosmia and ageusia persisted. Symptoms from the physical and respiratory cluster declined significantly over time, in contrast to the fatigue and cognitive symptom clusters.

Conclusion The majority of patients experienced COVID-19 sequelae up to 12 months after severe infection. Whereas physical and respiratory symptoms showed slow gradual decline, fatigue and cognitive symptoms did not evidently resolve over time.

Introduction

Acute coronavirus disease 2019 (COVID-19) infection in humans is associated with a heterogeneous range of symptoms including respiratory, musculoskeletal, gastrointestinal and neurological symptoms. In 5–14% of patients the respiratory consequences of COVID-19 are severe, requiring hospitalisation for oxygen supplementation or even prolonged ventilatory support.[1]

Whereas a proportion of patients fully recover, it becomes increasingly clear that a proportion of patients experience a wide range of long-lasting sequelae after acute COVID-19. Different terms are currently used for describing the presence of post-COVID-19 symptoms, such as long COVID, long haulers, post-COVID-19 syndrome, persistent post-COVID and post-acute sequelae of COVID. Although several definitions are in place, persistent symptoms after COVID-19 are regarded as post-COVID-19 syndrome if they persist or present within 12 weeks of the onset of acute COVID-19 and last for at least 2 months, and are not attributable to alternative diagnoses.[2,3] The more recent World Health Organization (WHO) definition of post-COVID-19 condition (PCC) is very similar to this definition, adding that symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness and must persist for at least 2 months.[4] Symptoms may also fluctuate or relapse over time. These post-acute COVID-19 sequelae encompass a wide range of symptoms and organ systems. Common symptoms include fatigue, shortness of breath and cognitive dysfunction.[4]

Although exact overall prevalence of these long-term symptoms remains unclear, it is estimated that between 2.6% and 18.7% of symptomatic patients experience persistent symptoms related to COVID-19 beyond 12 weeks after COVID-19.[5,6] This number increases when patients are more severely affected.[7] A recent systematic review described that more than 50% of all patients (the majority after hospitalisation) experience post-acute COVID-19 sequelae, even up to 6 months after acute infection.[8] Data from a Chinese cohort demonstrated symptoms persistent in over 68% of hospitalised patients at 6 months after disease onset, decreasing to 49% at 12 months,[9] whereas recent European results indicated that 91.7% of patients reported at least one symptom at 12 months.[10]

The nature of the reported symptoms is diverse and ranges from exertional dyspnoea to sensory overload. Although studies have tried to phenotype the patients with residual symptoms, looked into co-occurrence of pairs of post-COVID-19 symptoms or report on assays of symptoms according to various organ systems, it remains unclear how the various domains of symptoms relate to each other and how frequently certain types of symptoms overlap.[11-13]

Currently, most reports on persistent symptoms remain limited to 6 months after infection and little is known regarding the determinants of persistent symptoms. Also, most studies are cross-sectional and studies reporting outcomes across multiple time points are scarce. The aim of the current study was therefore to assess persistence of symptoms and clusters of symptoms up to 12 months after

hospital discharge, to explore how various clusters of symptoms overlap with each other and to assess determinants of the main persistent symptoms after COVID-19.

Methods

Study design

The COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system (CO-FLOW) study is an ongoing multicentre prospective cohort study following COVID-19 patients discharged from hospitals in the Rotterdam-Rijnmond-Delft region in the Netherlands. Detailed description of its protocol can be found elsewhere.[14] In short, up to 2 years after hospitalisation patients with COVID-19 are evaluated at 3, 6, 12, and 24 months after hospital discharge. Here, we present interim results regarding persisting symptoms obtained in the period from July 1st 2020 until December 1st 2021 as part of the CO-FLOW study up to 12 months after discharge. The Medical Ethics Committee of the Erasmus Medical Centre (MC) approved this study (MEC-2020-0487). The trial was registered at The Netherlands Trial Register (NL8710) (https://www.trialregister.nl) on June 12, 2020.

Adult patients (≥18 years of age) were eligible to participate in the CO-FLOW study if they had been hospitalised for COVID-19 (diagnosis based on either positive reverse transcription polymerase chain reaction or a clinical diagnosis combined with positive serology for COVID-19) within the previous 6 months and patient or relative had sufficient knowledge of the Dutch or English language. Incapacitated patients were unable to participate given the study procedures. For this study only participants with at least two study visits were included.

Study Procedures

In principle, all patients that had been hospitalised were offered outpatient follow-up at one of the participating centres. Patients were recruited during outpatient follow-up after discharge in one of the participating centres, at the inpatient rehabilitation centre, or at the skilled nursing facility. All patients provided written informed consent before the start of the measurements. Recruitment of study participants occurred independent of the patient's recovery status; this was largely based on availability of research personnel to recruit patients and to perform study visits. Study visits were synchronised with the patient's regular follow-up for COVID-19 at each of the participating centres if possible. When patients were discharged from regular follow-up, study visits continued in the Erasmus University MC or, if patients were unable to come to the Erasmus University MC, a research assistant performed the study visit at home. During study visits patients performed noninvasive clinical tests, including physical, psychological and cognitive evaluation. At 3-, 6- and 12-month follow-up visits, patients received questionnaires via e-mail or postal mail. Data were stored in Castor EDC (Castor EDC, Amsterdam, The Netherlands).

Outcomes

A new Corona Symptom Checklist was developed for this study on "novel or worsened symptoms since the onset of COVID-19" during the first 3 months of the study, based on the first experiences with post-COVID-19 patients. All questions are answered with "yes" or "no" (see **Supplementary Methods** for complete questionnaire). During the study visits the Corona Symptom Checklist was administered by a research assistant in a face-to-face interview. As the checklist was still under development when the study started amid the beginning of the COVID-19 pandemic, it was introduced at all study visits after 5 August 2020. As the pandemic evolved and knowledge increased regarding PCC, additional questions were added (sensory overload, headache, chest pain) from June 2021 onwards.

As fatigue is considered as one of the most prevalent symptoms in PCC, we chose to report fatigue not based on the checklist results, but on the validated Fatigue Assessment Scale (FAS) that was assessed in all patients since study onset. The FAS is a 10-item self-report questionnaire and is validated in patients with chronic lung disease.[15] The items are scored on a Likert scale ranging from 1 to 5. A total score of ≥22 is considered to represent substantial fatigue and was used to indicate persisting fatigue.[15]

Patient and clinical characteristics were collected at study visits and through electronic patient records. Patient characteristics included age, sex, body mass index (BMI), migration background, pre-COVID educational and employment status, smoking status and comorbidities. Clinical characteristics included baseline laboratory and radiological parameters, complications during hospitalisation including delirium and thrombosis, type and quantity of oxygen support, intensive care unit (ICU) admission, length of stay (LOS) ICU, LOS hospital and COVID-19 directed treatment during hospital admission.

Statistical analyses

We examined descriptive statistics to ensure data met statistical assumptions. Variables were presented as mean with standard deviation (SD), median with interquartile range, or numbers (n) with percentages (%) as appropriate.

Patient-reported symptoms were clustered into one of four clusters according to the nature of the symptom: physical, respiratory, fatigue and cognitive symptom cluster. The physical symptom cluster was composed of the symptoms muscle weakness, balance problems/dizziness, joint pain, tingling/numbness in extremities, hair loss, headache, chest pain, skin rash, vision problems, hoarseness, anosmia, ageusia, stool problems, claudication, hearing problems and miction problems. The respiratory symptom cluster was composed of the symptoms exertional dyspnoea, dyspnoea, cough and phlegm. The fatigue symptom cluster was composed of fatigue and sleeping problems. The cognitive symptom cluster was composed of the symptoms memory problems, concentration problems, sensory overload and anxiety/nightmares. If any of the symptoms in the clusters was present at a time point, persisting symptoms in that cluster were scored as present at that time point. We used generalised estimating equations (GEEs) with an unstructured covariance matrix

to assess persistence of symptoms and symptom clusters over time. GEEs account for correlations between patient follow-up measurements and include all observed outcomes despite incomplete data. For longitudinal analyses, a Bonferroni correction was applied and a p-value <0.002 was considered statistically significant. Difference in the distribution of symptom clusters across sexes were assessed with a Chi-Square test. Lastly, we performed multivariable logistic regression analyses with a backward selection procedure to determine which variables are independently associated with the most prevalent symptom per cluster at 3 months after discharge. The dependent variables were muscle weakness, deconditioning/exertional dyspnoea, fatigue and memory problems. We only reported determinants of symptoms at 3 months after discharge, as symptoms were most prevalent at 3 months after discharge and the majority did not decrease significantly over time. Determinants that were examined were age, sex, BMI, migration background (European, Dutch Caribbean, Asian, Turkish and (North) African), pre-COVID educational (low, middle, high) and employment status (employed, not employed, retired), presence of comorbidity, smoking (never versus ever), BMI and C-reactive protein (CRP) at admission, complications of thrombosis or delirium, oxygen supplementation (none, nasal cannula or mask oxygen supplementation, high-flow nasal cannula, mechanical ventilation), LOS hospital and COVID-19 directed treatment with steroids. The covariates BMI and CRP were imputed with their mean value if missing. Variable elimination from the multivariable models was based on goodness of fit using the likelihood ratio test with a p-value of 0.1, and the final models are presented with adjusted odds ratios (ORs) and 95% confidence interval (95% CI). We also assessed clinical characteristics of patients hospitalised for COVID-19 at 3 months follow-up, which are presented across the number of symptoms clusters affected. As numbers per group/characteristic were limited, differences were not statistically assessed, and these trends should be considered as explorative and hypotheses generating. All analyses were performed using Statistical Package for Social Sciences (SPSS) version 25 (IBM SPSS statistics, SPSS Inc, Chicago, IL, USA) and STATA version 8SE (StataCorp LLC, College Station, Texas, USA) and R version 4.1.1 (R-Foundation) were used for graphs.

Results

Characteristics

Between 1 July 2020 and 1 December 2021 patients were recruited in CO-FLOW. The total number of patients hospitalised for COVID-19 during the recruitment period in the region was 4569 of whom 1199 (26%) died during hospitalisation. The number of patients that had been invited is largely unknown due to logistical reasons. From the 3370 survivors, 650 patients (19% of all survivors) were included in this study, of whom 492 participants underwent at least two study measurements and were included in this interim analysis.

Baseline characteristics are presented in **Table 1**. Patients had a mean age of 60.2±10.7 years, 335 (68.1%) were male and 403 (81.9%) had one or more comorbidities: most commonly obesity, cardiovascular or pulmonary disease. Oxygen supplementation during admission was required by 474 (96.3%) patients, 199 (40.4%) had been admitted to the ICU, with a median LOS in ICU of 17

(9.0–30.5) days, and the median total LOS in the hospital was 11 (6.0–27.0) days. Of all patients, 357 (72.6%) received any COVID-19 directed treatment, of whom 330 (70.8%) received any form of steroids and 54 (11.5%) received directed anti-inflammatory treatment.

To date, 20 patients withdrew from the study or were deceased during follow-up. Up to 54 patients missed one or more study visits. A flowchart of the included patients and study measurements is shown in **Figure 1**.

Persisting symptoms

Table 2 presents the number and proportion of patients with persisting symptoms at each follow-up measurement. At 3 months after discharge, 97.0% of the patients had at least 1 persisting symptom, this proportion of patients declined to 95.5% at 6 months and to 92.0% at 12 months (p=0.010). Presence of a single symptom varied from 9.7% for miction problems to 81.8% for exertional dyspnoea. At all study visits, the most prevalent symptoms were muscle weakness, exertional dyspnoea, fatigue, and memory and concentration problems. These symptoms were reported by >50% of the patients during follow-up; a large number of other persistent symptoms were frequently reported, presented in **Table 2** and **Figure 2**. Symptoms that significantly declined over time were muscle weakness, hair loss, and exertional dyspnoea (p<0.001).

Table 1. Patient and clinical characteristics of patients hospitalised for COVID-19.

	n[a]	All (N=492)
Patient characteristics		
Age, years		60.2 ± 10.7
Sex, male		335 (68.1)
BMI, kg/m^2	437	29.3 ± 5.5
Migration Background	491	
European		373 (76.0)
Dutch Caribbean		61 (12.4)
Asian		25 (5.1)
Turkish		18 (3.7)
(North) African		14 (2.9)
Pre-COVID education	489	
Low		166 (33.9)
Middle		172 (35.2)
High		151 (30.9)
Pre-COVID employment	490	
Unemployed		77 (15.7)
Employed		297 (60.6)
Retired		116 (23.7)

Table 1. Continued.

	n[a]	All (N=492)
Smoking status	491	
Never		211 (43.0)
Former		270 (55.0)
Current		10 (2.0)
Comorbidities		
≥1		403 (81.9)
Obesity (BMI≥30)		190 (38.6)
Diabetes		95 (19.3)
Cardiovascular disease/ hypertension		192 (39.0)
Pulmonary disease		119 (24.2)
Renal disease		46 (9.3)
Gastrointestinal disease		22 (4.5)
Neuromuscular disease		49 (10.0)
Malignancy		56 (11.4)
Autoimmune/inflammatory disease		54 (11.0)
Mental disorder		25 (5.1)
In-hospital characteristics		
PCR confirmed SARS-CoV-2		485 (98.6)
Serology confirmed SARS-CoV-2		7 (1.4)
Laboratory values		
Creatinine, umol/L	471	82.0 (69.0-100.0)
(CKD-EPI) eGFR, ml/min	456	82.0 (66.0-90.0)
CRP, mg/L	467	85.0 (47.0-154.0)
Ferritin, ug/L	284	832.5 (443.5-1613.3)
ALAT, U/L	457	37.0 (26.0-56.0)
Hemoglobin, mmol/L	468	8.6 (7.9-9.2)
MCV, fl	461	89.0 (85.0-91.0)
Thrombocytes, 10^9/L	463	211.0 (159.0-276.0)
Lymphocytes absolute count, 10^9/L	325	0.9 (0.6-1.1)
D-dimer, mg/L	237	1.1 (0.6-380.0)
NT-pro-BNP, pmol/ml	90	18.5 (8.8-48.0)
IL-6, pmol/ml	36	55.5 (28.0-179.0)
Chest x-ray abnormalities	468	
Normal		59 (12.6)
Moderate		99 (21.2)
Severe		310 (66.2)

Table 1. Continued.

	n[a]	All (N=492)
Thrombosis	484	79 (16.3)
Delirium	477	121 (25.4)
Requiring oxygen supplementation	492	474 (96.3)
Requiring high flow nasal cannula	462	150 (32.5)
ICU admission		199 (40.4)
Invasive mechanical ventilation		175 (35.6)
Length of intubation, days	167	14.0 (8.0-27.0)
Tracheostomy	482	64 (13.3)
Length of ICU stay, days	197	17.0 (9.0-30.5)
Length of hospital stay, days		11.0 (6.0-27.0)
COVID-19 directed Treatment	466	
None		109 (23.4)
(Hydroxy)chloroquine		14 (3.0)
Steroids		330 (70.8)
Antivirals		69 (14.8)
Anti-inflammatory (IL-6) treatment		54 (11.6)
Convalescent plasma		8 (1.7)
Monoclonal antibodies		0 (0.0)
Time interval between discharge and follow-up visit		
3 Months visit, days	385	94.7 ± 22.8
6 Months visit, days	483	184.8 ± 27.9
12 Months visit, days	271	368.3 ± 17.3

Data are presented as n (%), mean ± standard deviation, or, for non-normally distributed variables, median (interquartile range). [a]Adjusted n is presented for variables with a total number of patients <492. BMI, Body Mass Index; IL-6, interleukin 6; PCR, Polymerase Chain Reaction, SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2; ICU, Intensive Care Unit.

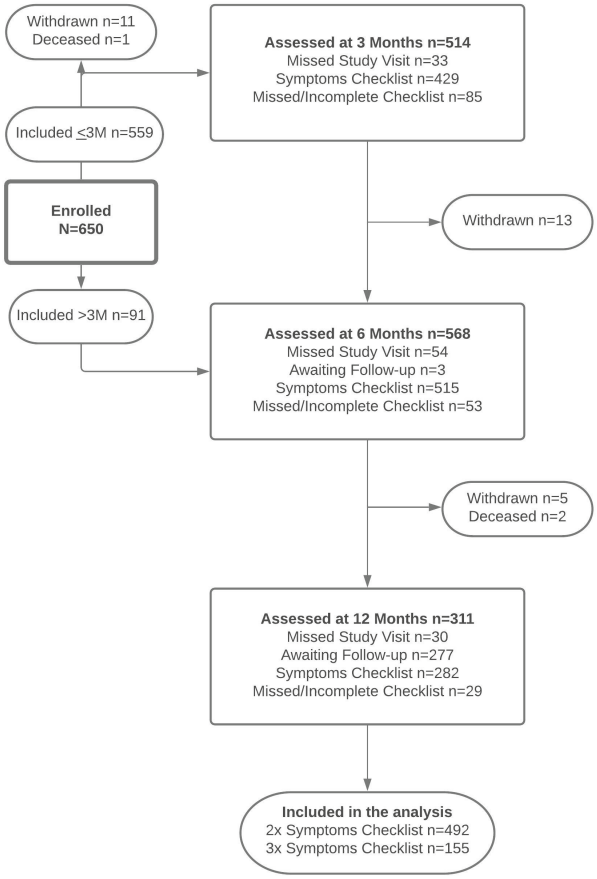

Figure 1. Flowchart of the patients in the CO-FLOW study during the interim analysis.

Table 2. Prevalence of COVID-19 related symptoms at 3-, 6-, and 12-month follow-up in patients after hospitalisation for COVID-19.

	3 months (n=385) n (%)	**6 months (n=483) n (%)**	**12 months (n=271) n (%)**	**p-value**
Physical symptoms				
Muscle weakness	220 (57.1)	234 (48.4)	111 (41.0)	**<0.001**
Balance problems/dizziness	169 (43.8)	213 (44.4)	116 (42.8)	0.922
Joint pain	166 (43.2)	201 (41.6)	111 (41.0)	0.352
Tingling/numbness in extremities	147 (36.8)	163 (33.9)	86 (32.1)	0.291
Hair loss	138 (35.9)	98 (20.3)	35 (12.9)	**<0.001**

Table 2. Continued.

	3 months (n=385) n (%)	6 months (n=483) n (%)	12 months (n=271) n (%)	p-value
Headache#	33 (31.4)	57 (26.1)	29 (18.6)	0.579
Chest pain#	29 (29.0)	40 (18.4)	28 (17.8)	0.069
Skin rash	99 (25.7)	132 (27.4)	82 (30.3)	0.587
Vision problems	97 (25.2)	148 (30.6)	78 (28.8)	0.023
Hoarseness	91 (23.6)	125 (25.9)	57 (21.0)	0.088
Anosmia	84 (21.9)	93 (19.3)	53 (19.6)	0.369
Ageusia	82 (21.2)	94 (19.5)	52 (19.2)	0.185
Stool problems	68 (17.7)	89 (18.5)	41 (15.1)	0.547
Claudication	54 (14.1)	68 (14.1)	27 (10.0)	0.116
Hearing problems	52 (13.5)	70 (14.5)	53 (19.6)	0.059
Miction problems	37 (9.7)	58 (12.1)	34 (12.5)	0.269
Respiratory symptoms				
Exertional dyspnoea	315 (81.8)	345 (71.4)	171 (63.1)	**<0.001**
Dyspnoea#	78 (66.1)	114 (51.8)	83 (52.9)	0.003
Cough	112 (29.0)	119 (24.7)	66 (24.4)	0.329
Phlegm	98 (25.5)	117 (24.2)	67 (24.7)	0.727
Fatigue symptoms				
Fatigue	243 (64.5)	277 (63.1)	156 (60.2)	0.932
Sleeping problems	141 (36.5)	172 (35.6)	96 (35.4)	0.777
Cognitive symptoms				
Memory problems	211 (54.7)	271 (56.1)	158 (58.3)	0.144
Concentration problems	206 (53.4)	249 (51.6)	140 (51.7)	0.826
Sensory overload#	44 (45.5)	93 (43.9)	58 (36.7)	0.503
Anxiety/nightmares	56 (14.5)	72 (14.9)	40 (14.8)	0.785

Data are presented as n (%) indicating the number of patients with symptoms. p-values are based on Generalized Estimating Equation analyses, with follow-up visit as fixed factor and symptom (yes/no) at each follow-up visit as dependent variable. Bonferroni correction was applied for multiple testing, a p-value <0.002 was considered statistically significant (printed in bold). #: symptoms headache, chest pain, dyspnoea, and sensory overload were added in a later stage, resulting in lower total numbers.

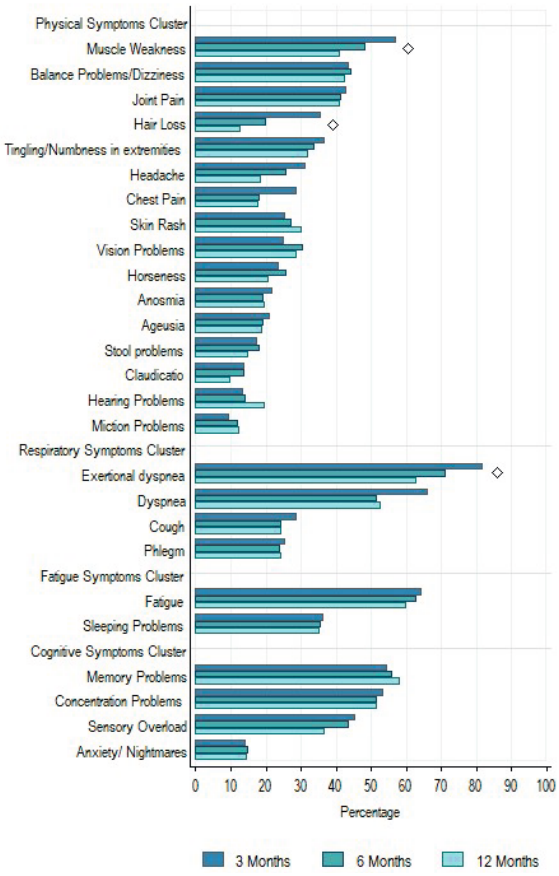

Figure 2. Symptom prevalence over time.
Prevalence of COVID-19-related symptoms at 3-, 6- and 12-month follow-up in patients after hospitalisation for COVID-19, sorted by symptoms cluster and from most to least frequently reported. Data are presented as percentage of patients with symptoms. Symptoms marked with ◊ declined significantly over time based on generalised estimating equation analyses, with follow-up visit as fixed factor and symptom (yes/no) at each follow-up visit as dependent variable.

Symptom clusters

The prevalence of symptoms and the overlap between symptom clusters at 3 months follow-up are shown in **Figure 2**. At 3 months, 90.7% of patients reported at least one symptom from the physical symptom cluster; this declined significantly to 86.8% at 6 months and to 84.5% at 12 months (p=0.025). Respiratory symptoms were reported by 87.3%, 79.1%, and 76.0% of the patients at 3, 6, and 12 months, respectively (p<0.001). In the fatigue symptom cluster, 68.3% of the patients reported a symptom at 3 months, 67.8% at 6 months, and 67.6% at 12 months (p=0.082). A symptom from the cognitive symptom cluster was reported in 71.8% of the patients at 3 months, 70.0% at 6 months, and 74.2% at 12 months (p=0.452).

At 3 months after hospital discharge, 218 (56.3%) reported symptoms in all four symptoms clusters and 292 (75.5%) in three clusters. Symptoms in the physical and respiratory symptom clusters most frequently overlapped (**Figure 3**). The majority of patients with fatigue also experienced cognitive symptoms (86.8%), and vice versa (83.4%). Isolated symptoms were rare but concerned most frequently fatigue in 21 (5.3%) patients or physical symptoms in 18 (4.6%) patients. Females more frequently report symptoms in all four clusters than males (63% *versus* 52%, p<0.001) (**Figure 3**). Fatigue and cognitive symptoms were more frequent in females than in males (80.2% *versus* 68.6%, p=0.002), and 74.5% *versus* 68.6% (p=0.009), respectively), and so were the frequency of respiratory (85.9% versus 85.5%, p=0.022) and physical symptoms (90% *versus* 88.5%, p=0.002).

In **Supplementary Table S1** patient and clinical characteristics of patients hospitalised for COVID-19 at 3 months follow-up are presented across the number of symptom clusters affected. The majority of patients (89%) experienced symptoms in two or more clusters. Several trends can be noticed with increasing number of symptom clusters affected: more in females, patients with non-European background, employment, comorbidities and with lower CRP, lower D-dimer and more severely affected chest radiograph upon admission. No association seems present with LOS, ICU admission and ventilation and with COVID-19 directed treatment.

Determinants of persisting symptoms

Out of the physical symptom cluster, muscle weakness was the most frequently reported symptom at 3 months after hospital discharge. Patients who were female (OR 2.66, 95% CI 1.62–4.37, p<0.001), had a longer LOS hospital (OR 1.04, 95% CI 1.02–1.05, p<0.001)) were more likely to experience muscle weakness at 3 months after hospital discharge, and patients who received steroids as treatment during hospitalisation (OR 0.53, 0.29–0.96, p=0.036 were less likely to experience muscle weakness (**Figure 4**). Out of the respiratory symptom cluster, exertional dyspnoea was the most prevalent symptom. We were unable to perform valid multivariable logistic regression on this outcome given the high prevalence of this symptom (81.5%) at 3 months after hospital discharge.

Fatigue was the most prevalent symptom in the fatigue symptom cluster. Patients who were female (OR 2.76, 1.61–4.76, p<0.001) and/or had comorbidities (OR 2.19, 1.24–3.87, p=0.007) were more likely to develop fatigue symptoms, while patients who were retired (OR 0.38, 0.22–0.65, p=0.001) were less likely to develop fatigue symptoms at 3 months after hospital discharge (**Figure 4**).

At 3 months, memory problems were the most frequently reported symptom in the cognitive symptom cluster. Patients who were female (OR 2.01, 1.30–3.39, p=0.002), had a shorter LOS (OR 0.98, 0.97–0.99, p=0.003), and/or had comorbidities (OR 1.95, 1.12–3.40, p=0.018) were more likely to experience memory problems at 3 months after hospital discharge (**Figure 4**).

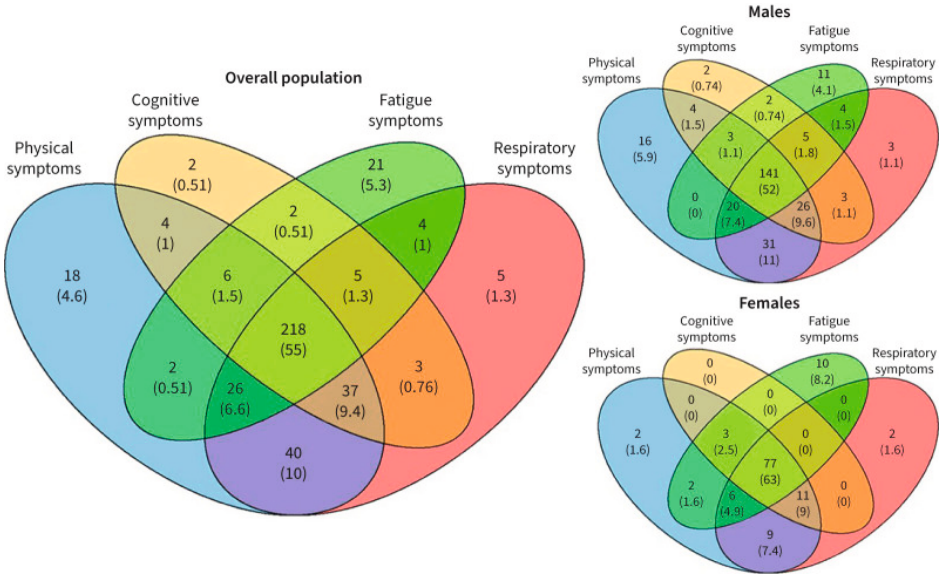

Figure 3. Venn diagrams showing overlap between the symptom clusters (physical symptoms, cognitive symptoms, fatigue symptoms and respiratory symptoms) for the entire cohort, males and females.
Data are presented as n (%) indicating the number of patients with symptoms. Data are presented as n (%) indicating the number of patients with symptoms.

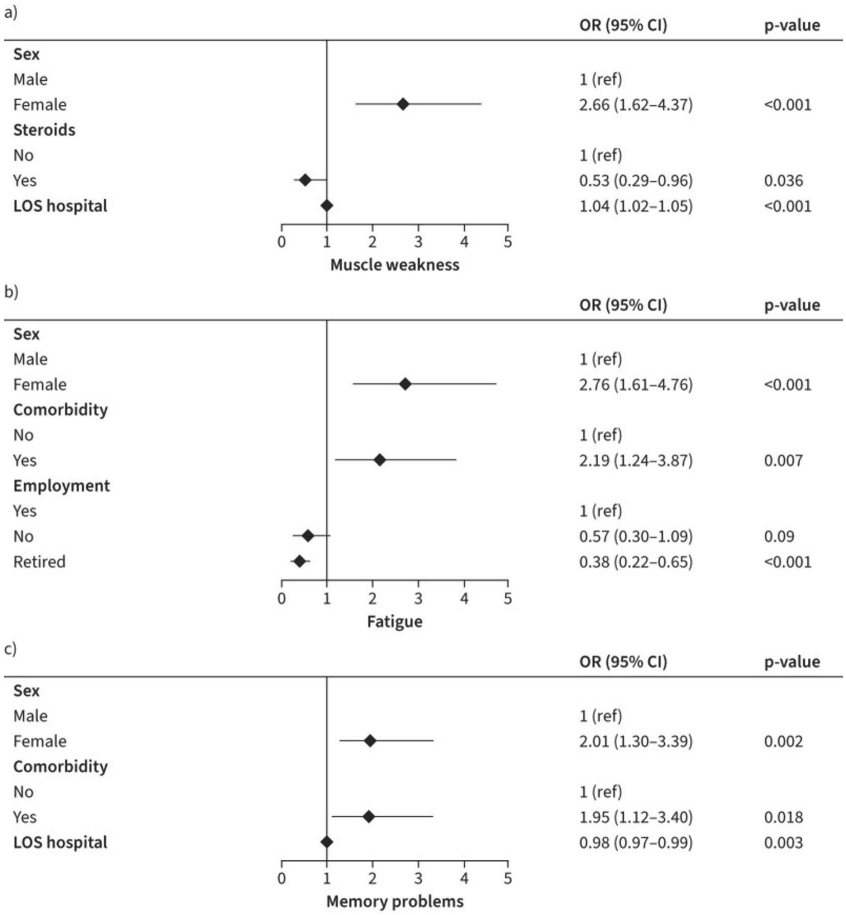

Figure 4. Forest plot of the patient and admission characteristics associated with the most prevalent symptoms for the a) physical, b) fatigue and c) cognitive symptoms clusters obtained by multivariable logistic regression analyses.
LOS: length of stay.

Discussion

Up to 12 months after hospitalisation for COVID-19 over 90% of patients suffer from at least one persisting symptom. Muscle weakness, exertional dyspnoea, fatigue, and memory and concentration problems were the most prevalent symptoms with reporting rates of over 50% of the patients at one of the time points. Although several physical and respiratory symptoms (muscle weakness, hair loss, exertional dyspnoea) declined significantly over time, others – including fatigue and cognitive symptoms – persisted. Our findings support the observation from a recent meta-analysis that the short-term prevalence of persisting symptoms was similar to long-term prevalence of symptoms up to 6 months after hospital discharge.[8] Persisting symptoms are a common feature of COVID-19, especially after hospitalisation but may also occur after mild or even asymptomatic infection. To date, long-term data regarding persisting symptoms at 12 months and beyond are limited. In a cohort study from Wuhan, the proportion of persistent symptoms was shown to decrease from 68% at 6 months to 49% at 12 months after hospitalisation and 55% at 24 months after hospitalization.[9]

Although this finding appears to contradict our findings, their cohort contained only 1% of patients that had received mechanical ventilation compared to 35.6% in our cohort. The severity of acute COVID-19 is increasingly recognised to be associated with a larger proportion and longer duration of persisting symptoms and should thus be taken into account when comparing studies.[16,17] Our study unfortunately shows a much less optimistic picture regarding recovery over time, with a high prevalence of persisting symptoms that is much more in line with other European outcomes that demonstrate numbers of incomplete recovery between 71.1 and 91.7% of patients after severe or critical COVID-19 infection, without evident improvement over time.[10,18] We do have to acknowledge that symptoms may have resided in severity over time or could be in part attributed to other causes, but we did not have data on this. More and longer-term follow-up results will be collected to obtain even more insight into the future outlook of these patients. Also, one has to take into account that our study only addressed hospitalised patients, and sequelae in this group will differ substantially from non-hospitalised patients.

Looking into determinants, female sex was the most important predictor of persistent symptoms. Earlier, we demonstrated a relationship between female sex and increased risk for fatigue up to 6 months after discharge.[7] Now we extend these findings to other symptoms and show that females more frequently experience symptoms from multiple symptom clusters 3 months after hospitalisation. Previous studies have also demonstrated that female sex was associated with an increased number of persisting symptoms.[10,18,19] It is frequently stated that, while acute cases of COVID-19 tend to be most severe in older males, PCC seems to be more frequent in younger females. Age, however, was not found to be a determinant of persistent symptoms in our cohort, nor in other studies after adjustment for confounders.[10,19] Also, it is necessary to bear in mind that there may be a bias in symptoms reporting between males and females.[20] We also found presence of comorbidity to be associated with increased fatigue and memory problems, but this was not found by others.[10] Obesity was previously described as a major risk factor for not fully recovering.[18] It is quite possible that pre-existent health problems make patients more vulnerable to unfavourable

outcome after severe illness. We found that patients treated with steroids during hospital stay were less likely to report muscle weakness during follow-up. This finding seems counter-intuitive at first. A potential explanation for this, although speculative, may be that as COVID-19 is known to cause long-term immunological dysfunction that may relate to (part of) the persisting symptoms, immunomodulation with corticosteroids in the acute phase may positively affect development of some of the symptoms such as muscle weakness. The relationship between in-hospital treatments and long-term outcomes has been little studied and should be addressed in future studies.

Although numbers of acute COVID-19 may eventually decrease with increasing immunity in the population, our findings point out that consequences will be long felt by many. As challenges in vaccination programmes worldwide continue to hinder effective control measures, the number of people with PCC will only continue to increase. Vaccination may play an important role not only to prevent new infections, but also in preventing PCC, as it was recently demonstrated that post-vaccination breakthrough infections are less likely to be associated with symptoms persisting for >28 days.[21]

The best approach to PCC is unclear. As symptoms range from mild to severe and are very diverse in nature, there is no one size fits all treatment possible. Although we grouped symptoms into clusters, there are currently no universally recognised phenotypes, diagnostic criteria, minimal severity scores or diagnostic tests to establish a diagnosis of PCC. Establishing more objective and evidence-based definitions and phenotypes of PCC will be necessary to compare findings across cohorts and settings, and to establish evidence-based interventions. Also, the impact of prior symptoms and prior comorbidity needs to be taken into account, just as the expected effects of hospitalisation.

There are currently many unknowns regarding PCC, including the underlying mechanisms. Current theories on PCC include virus-specific pathophysiological changes, immunological aberrations and inflammatory damage in response to the acute infection and expected sequelae of post-critical illness.[22] Indeed, it is very hard to differentiate between the expected sequelae, such as described in the post-intensive care syndrome, and the sequelae that are specific for COVID-19.[23] Nonetheless, in a large analysis on electronic health records data, key features of long COVID (e.g. breathlessness and fatigue) were more frequently reported after COVID-19 than in matched controls after influenza virus infection.[13] Overall, it is becoming increasingly clear that the sequelae after COVID-19 are more prevalent than after most other types of infections, persist for a long time, and have a major impact on the burden of disease and healthcare.

Our study has several strengths and limitations. We followed a large cohort of patients in a longitudinal design at 3, 6 and 12 months after hospital discharge. Currently, long-term follow-up data are scarce. As the study is still ongoing, data were not complete for the entire cohort; also, the initial patients were generally recruited between 3 and 6 months after hospital discharge, resulting in unequal groups at different time points. We therefore included only participants with data of at least two study measurements and used GEE models to make maximal use of all data and to investigate how symptoms developed over time.

As we included patients at the outpatient clinic after discharge, a selection bias of patients with lingering symptoms cannot be excluded. Therefore, it is useful to have some more insights in the recruitment procedure of participants. All patients that had been hospitalised were offered outpatient follow-up, unless this was logistically not possible. Recruitment of study participants occurred independent of the patient's recovery status. Inclusion in this study was largely based on availability of research personnel to recruit patients and to perform study visits, which was the most limitative step for inclusion. Although consent rate to participation was very high, the exact number of patients approached for participation is unknown, which is a limitation of this study. Our final study cohort was representative of the overall admitted population that received aftercare (data not shown). Nonetheless, the extent of selection bias cannot be quantified.

One inclusion criterion was that patients or their relatives had to be able to communicate in Dutch or English. Therefore, there is underrepresentation of individuals with a migration background in this study compared to the community where this cohort was established. Nonetheless, 24% of the participants in this cohort had a migration background; migration background was not a predictor of residual symptoms in this study. Another limitation is that our results are only generalisable to hospitalised patients and we did not have a control group. Also, we did not have patient scores on the severity of complaints. Even though symptoms may persist for considerable time, the severity may very well decrease over time, as was also shown in other studies.[16] Also, we cannot exclude that symptoms had other aetiology than post-COVID.

To summarise, a large number of post-COVID-19 patients experienced persistent symptoms up to 12 months after hospitalisation for COVID-19. Whereas physical and respiratory symptoms showed slow gradual decline, fatigue and cognitive symptoms did not evidently resolve over time. This finding stresses the importance of finding the underlying causes and effective treatments for PCC on the one hand, and adequate COVID-19 prevention on the other hand. Large and long-term cohort studies are urgently needed to help better understand persistent symptoms after COVID-19 and its biological drivers.

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Chapter 5

Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW)

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Abstract

Background The sudden COVID-19 pandemic forced quick development of care pathways for patients with different needs. Trajectories of physical recovery in hospitalized patients for COVID-19 following different care pathways are unknown. We aimed to assess trajectories of physical recovery and levels of physical function reached within the different care pathways. Additionally, we assessed differences in physical function across care pathways at follow-up visits.

Methods This multicenter prospective cohort study of adults who had been hospitalized for COVID-19 was performed in 10 centers, including 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities), located in the Netherlands. Study visits were performed at 3, 6, and 12 months post-hospital discharge and included assessment of cardiorespiratory fitness (6 min walk test [6MWT], 1 min sit-to-stand test [1MSTST]), muscle strength (maximum handgrip strength [HGS]) and mobility (de Morton Mobility Index [DEMMI]).

Findings We report findings for 582 patients who had been discharged from hospital between March 24, 2020 and June 17, 2021. Patients had a median age of 60.0 years, 68.9% (401/582) were male, 94.6% (561/582) had received oxygen therapy, and 35.2% (205/582) mechanical ventilation. We followed patients across four different rehabilitation settings: no rehabilitation (No-rehab, 19.6% [114/582]), community-based rehabilitation (Com-rehab, 54.1% [315/582]), medical rehabilitation (Med-rehab, 13.7% [80/582]), and rehabilitation in a skilled nursing facility (SNF-rehab, 12.5% [73/582]). Overall, outcomes in 6MWT (14.9 meters [95% CI 7.4 to 22.4]), 1MSTST (2.2 repetitions [1.5 to 2.8]), and HGS (3.5 kg [2.9 to 4.0]) improved significantly ($p<0.001$) from 3 to 6 months and only HGS from 6 to 12 months (2.5 kg [1.8 to 3.1]; $p<0.001$). DEMMI scores did not significantly improve over time. At 3 months, percentage of normative values reached in 1MSTST differed significantly ($p<0.001$) across care pathways, with largest impairments in Med- and SNF-rehab groups. At 12 months these differences were no longer significant, reaching, overall, 90.5% on 6MWD, 75.4% on 1MSTST, and 106.9% on HGS.

Interpretation Overall, physical function improved after hospitalization for COVID-19, with largest improvement within 6 months post-discharge. Patients with rehabilitation after hospital discharge improved in more than one component of physical function, whereas patients without rehabilitation improved solely in muscle strength. Patients who received rehabilitation, and particularly patients with Med- and SNF-rehab, had more severe impairment in physical function at 3 months, but reached equal levels at 12 months compared to patients without follow-up treatment. Our findings indicate the importance of rehabilitation.

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Introduction

The clinical spectrum of coronavirus disease-2019 (COVID-19) ranges from asymptomatic infection to critical illness requiring admission to an intensive care unit (ICU). Although COVID-19 primarily affects the respiratory system, many organs can be affected and a wide range of post-acute sequelae may occur, including impaired physical function.[1-5] Post COVID-19 condition, as defined by the World Health Organization, occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and are not explained by an alternative diagnosis.[6] These symptoms may be new onset or persist from acute illness and may fluctuate or relapse over time. Based on self-reported measures, 49% to 92% of patients hospitalized for COVID-19 experienced one or more persistent symptoms at 12 months follow-up.[2,7-9] Regarding physical symptoms, we previously reported that 63% of COVID-19 patients experienced deconditioning (exertional dyspnea), 41% muscle weakness, and 43% balance problems 12 months after hospital discharge.[9]

Objective and longitudinal data on long-term physical recovery after hospitalization for COVID-19 are scarce. Prior studies mostly focused on cardiorespiratory fitness, reporting 80-110% of predicted levels at 12 months after hospitalization.[2,10-12] However, other components of physical function such as muscle strength and mobility are also important constructs in the evaluation of physical recovery. For example, among non-COVID-19 patients, after admission for acute respiratory distress syndrome, patients still experienced muscle wasting and weakness 12 months after discharge from ICU.[13] Thus, an objective assessment of different components of physical function is needed to obtain in-depth information on long-term physical recovery after COVID-19.

The sudden pandemic forced quick development of care pathways for COVID-19 patients, pathways initially based on inadequate knowledge of patient aftercare needs. Fortunately, as we now know, most hospitalized patients are sufficiently independent at hospital discharge and able to return home with or without support of community-based rehabilitation.[14] However, some patients are referred to medical rehabilitation, often severely affected younger patients with a high premorbid functional level, or to a skilled nursing facility in case of vulnerable patients with a low premorbid functional level.[15,16] Trajectories of physical recovery in patients related to different care pathways have not been assessed to date. This knowledge is important to gain insight into whether care pathways have to be optimized to provide the right physical care for different needs.

The primary study aim was to assess trajectories of physical recovery and levels of physical function reached within the different care pathways. We objectively assessed physical function, comprising cardiorespiratory fitness, muscle strength, and mobility, at 3, 6, and 12 months after hospital discharge. The secondary study aim was to assess differences in physical function across care pathways at follow-up visits. We hypothesized that patients who require more intensive rehabilitation have more impaired physical function at 3 months after hospital discharge and that these differences in physical function reduce over time.

Methods

Study design and population

This study is part of an ongoing two-year prospective multicenter cohort study, "COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system" (CO-FLOW), in the Rotterdam−Rijnmond−Delft region of The Netherlands.[17] The study was performed in 10 centers, including 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities), all located in this region. Patients with COVID-19 who were discharged from one of the participating hospitals were invited to participate in study visits at the outpatient clinic of hospitals if they met the following criteria: 1) COVID-19 diagnosis based on positive reverse transcription polymerase chain reaction, or based on multidisciplinary team decision concerning symptoms and chest computed tomography scan or positive serology; 2) aged 18 years or older; 3) within 6 months, but preferably within 3 months, after hospital discharge; 4) patient or relative has sufficient knowledge of the Dutch or English language.[17] Incapacitated patients were not included, patients were considered non-capable if they were cognitively impaired (e.g. dementia) and therefore unable to understand instructions to perform study measurements. Patients received study information from their pulmonary physician during regular follow-up, or by invitation letter, and for patients with inpatient rehabilitation this was done by the rehabilitation physician or elderly care physician. Recruitment of study participants occurred independent of the patient's recovery status; this was largely based on availability of research personnel to recruit patients and to perform study visits. If patients consented they were contacted by the researchers to schedule the study visit. All 650 participants in the CO-FLOW study provided written informed consent before the start of the measurements.[17] This study was approved by the Medical Ethics Committee of Erasmus MC (MEC-2020-0487) and registered in The Netherlands Trial Register (no. NL8710). More detailed information about the CO-FLOW study protocol is published elsewhere.[17] Here we present a pre-planned interim analysis on physical outcomes of patients who attended at least one follow-up visit at 3, 6, or 12 months after hospital discharge.

Study procedure

Study visits were scheduled around 3, 6, and 12 months after hospital discharge and when possible alongside the clinical follow-up for COVID-19 in the participating hospitals (**Supplementary Figure S1**). Patients who were discharged from clinical follow-up were invited to visit Erasmus MC for the remaining study visits; we arranged a home visit for patients who were unwilling or unable to visit Erasmus MC.[17] During study visits, patients performed non-invasive clinical tests of physical function. Leisure time physical activity level (inactive, light, regular, or hard) before COVID-19 infection was measured with the Saltin−Grimby Physical Activity Level Scale questionnaire.[18] Demographic characteristics, such as migration background, education level, and employment status, and rehabilitative care after hospital discharge were collected with a face-face interview, electronic patients records, and the iMTA Medical Cost Questionnaire.[19] Regarding rehabilitation, during the face-to-face interview patients were asked whether they had received rehabilitative care for COVID-19 illness and, if so, the type of treatment, care setting, and the duration of inpatient rehabilitation. All study visits were conducted by a small team of junior researchers, assistants, and medical students,

who all received training from experienced senior researchers. Clinical characteristics during hospital admission, such as treatment, ICU admission, and length of hospital stay, were retrospectively collected from electronic patient records in the participating hospitals. All collected data were stored in the Castor Electronic Data Capture system (Castor EDC, Amsterdam, the Netherlands).

Care pathways

Patients who are sufficiently independent at hospital discharge are discharged home without rehabilitation or with support of community-based rehabilitation or outpatient medical rehabilitation. Patients unable to be discharged home and who require more intensive rehabilitative care are referred to inpatient medical rehabilitation center or to a skilled nursing facility.[20] We followed patients in four care pathways comprising different post-acute care settings: 1) no rehabilitation (No-rehab), 2) community-based rehabilitation (Com-rehab), 3) in- and/or outpatient medical rehabilitation (Med-rehab), and 4) inpatient rehabilitation in a skilled nursing facility (SNF-rehab). We followed patients in the four different care pathways and categorized them based on the most specialized aftercare they had received after hospitalization for COVID-19, with Med- and SNF-rehab being the most specialized. None of the participants received both Med- and SNF-rehab. The Dutch care pathways, including rehabilitation triage, for hospitalized COVID-19 patients are presented in **Figure 1** and programs across the different rehabilitation services are reported below.[15,16]

No-rehab: Patients are sufficiently recovered and do not require rehabilitation.
Com-rehab: Outpatient treatment to support recovery to premorbid functional levels. This often comprises monodisciplinary treatment once or twice a week, such as physical therapy or occupational therapy, of varying duration ranging from weeks to months.
Med-rehab: Intensive in- or outpatient multidisciplinary treatment to reduce functional deficits and to support recovery to premorbid function levels, aiming to return home in the case of inpatient rehabilitation. The type and duration of treatment is based on patient-centered functional goal setting and varies across patients. The program is guided by an interdisciplinary team of a rehabilitation physician, nurse, physiotherapist, occupational therapist, psychologist, speech- and language therapist, movement therapist, social worker, and dietician, depending on the patients care needs. Treatment during inpatient rehabilitation is often provided 4-5 times per day for approximately 4-6 weeks. The duration of outpatient treatment is usually 8-12 weeks. After inpatient rehabilitation, patient may continue outpatient med-rehab or community-based rehabilitation.
SNF-rehab: Moderately intensive inpatient multidisciplinary treatment to reduce functional deficits and dependency and to support recovery to premorbid function levels, aiming to return home. The type and duration of treatment is based on patient-centered functional goal setting and varies across patients. The program is guided by an interdisciplinary team of an elderly care physician, nurse, physiotherapist, occupational therapist, psychologist, speech- and language therapist, movement therapist, social worker, and dietician, depending in the patients care needs. During inpatient rehabilitation, treatment is provided for a maximum of 5 times a week for 4-8 weeks. After inpatient rehabilitation, patient may continue outpatient SNF-rehab or community-based rehabilitation.

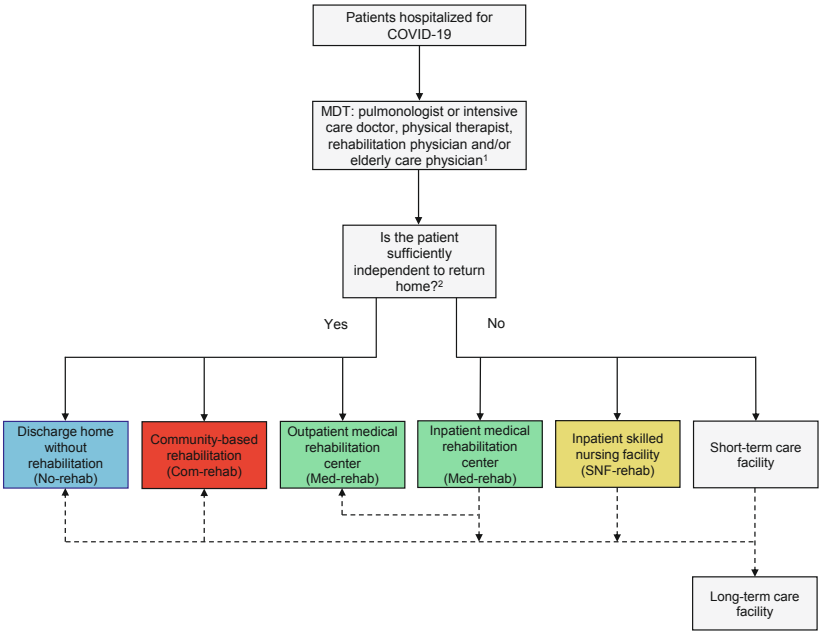

Figure 1. Dutch care pathways for hospitalized COVID-19 patients.
MDT: multidisciplinary team. [1]Assessment of functional impairments (physical, cognitive, and/or psychological), medical status, care needs, comorbidity, and premorbid functional level.[15] [2]Rehabilitation as defined by the World Health Organization aims to help a child, adult or older person to be as independent as possible in everyday activities and enables participation in education, work, recreation, and meaningful life roles such as taking care of family.[20] Geriatric rehabilitation focuses primarily on frail elderly with co-morbidities. Medical rehabilitation is aimed at high-intensity treatment, mostly of a younger population.

Physical outcome measures

Cardiorespiratory fitness was measured with the submaximal 6 min walk test (6MWT) and one-minute sit-to-stand test (1MSTST), which both involve functional performance. For practical reasons the 6MWT was not assessed in patients who were visited at home. During these tests the participants were allowed to rest or stop if needed. During the 6MWT, participants were instructed to walk as far and as fast as possible back and forth along a 30- or 20 m corridor, depending on the test location, with verbal encouragement provided after approximately every minute.[21] Oxygen saturation during the 6MWT was recorded using a fingertip pulse oximeter. Exercise-induced desaturation was indicated by a decrease of ≥4% upon 6MWT.[22] Outcome of the 6MWT was the distance walked in meters (6MWD), which was also normalized to percentage of normative values and to performance below the lower limit of normal (LLN) according to sex-, age-, height-, and weight-stratified equations described by Enright and Sherrill.[23]

As a secondary measure of cardiorespiratory fitness, all participants performed the 1MSTST.[24] Participants started in a seated position (standard chair, 46 cm) and were instructed to perform as many repetitions of sit-to-stand as possible in one minute without using arm support. Outcome

of the 1MSTST was the number of sit-to-stand (STS) repetitions, and these counts were also normalized to percentage of normative values according to sex- and age-stratified reference values as described by Strassmann and colleagues.[25] We included the 1MSTST to facilitate measurement of cardiorespiratory fitness in participants who are unable to perform the 6MWT and for the participants we studied at home. Outcomes on the 1MSTST are strongly correlated with those on the 6MWT in patients with limitations due to pulmonary disease.[26,27]

Muscle strength was assessed by measurement of maximum isometric handgrip strength (HGS) in kg, using the Jamar hydraulic handheld dynamometer. HGS is considered as an indicator of overall muscle strength.[28] Participants were tested in a sitting position with their feet flat on the floor, shoulder in an adducted position and elbow at 90 degrees. They performed three attempts per hand with approximately 30 sec of rest in between. Arm support was provided to those who were unable to hold the dynamometer without support. We used the maximum HGS measured over six attempts (3 per arm) as outcome measure, and HGS was also expressed as percentage of normative values according to sex- and age-stratified reference values, and as performance below the cutoff for weak HGS, defined as <27 kg in men and <16 kg in women.[29,30]

Mobility was measured with the de Morton Mobility Index (DEMMI) test, originally developed to measure mobility in elderly hospitalized patients and also validated in an ICU population.[31,32] The DEMMI test consists of 15 items administered from easiest as follows: tasks in bed (3 items), tasks in a chair (3 items), static balance (4 items), walking (2 items), and dynamic balance (2 items). The raw sum score ranges from 0 to 19 and is then converted into an interval score ranging from 0 to 100, where higher scores represent better mobility.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), Shapiro–Wilk tests indicated that all continuous variables were not normally distributed, and categorical variables as a number and percentage. To assess differences in demographic and clinical characteristics during hospital admission across care pathways (No-, Com-, Med-, and SNF-rehab) we performed a $\chi 2$ test or Kruskal–Wallis test, as appropriate, and a Bonferroni correction was applied for multiple testing (significance level set at $p<0.001$). For the primary aim, we used generalized estimating equations (GEE) with repeated measurements to explore the trajectories of physical outcomes (6MWT, 1MSTST, HGS, and DEMMI) over time in the total cohort and within care pathways in separated analyses. The GEE approach considers within-subject correlations and uses all available measurements despite incomplete data. All GEE analyses were performed using an unstructured correlation matrix. For the assessment of physical recovery in the total cohort we entered measurement time (3, 6, and 12 months) as fixed factor in each GEE analysis. For the assessment of physical recovery within care pathways we entered care pathway as fixed factor, the interaction of time and care pathway, and adjusted for demographic (age, sex, and employment status) and clinical (having one or more comorbidities, obesity, delirium, thrombotic event, admission to intensive care unit, and the length of hospital stay) characteristics during hospital admission in each GEE analysis. Missing data in categorical covariates were analyzed in the category no or unknown (no or unknown versus yes). For the

covariate obesity we first imputed missing body mass index (BMI) values with the median BMI value within care pathways, as appropriate, and values were then dichotomized (obese if BMI≥30 kg/m^2). Likewise, we used GEE analysis to assess the trajectories of the percentages of normative values reached in 6MWT, 1MSTST, and HGS over time; no appropriate normative values for DEMMI are available for our sample. These GEE models were adjusted for the same covariates as previously mentioned, excluding age and sex and in case of the 6MWT also obesity (normative values are already adjusted for these characteristics). We used least significant difference post hoc tests for pairwise comparisons between follow-up visits in the total cohort and within care pathways. We also performed similar GEE analyses to asses trajectories of physical outcomes and percentage of normative values reached in physical tests within care pathways without adjustment for covariates, see **Supplementary Figures S2** and **S3**. For the secondary aim, we performed a cross-sectional data analysis to assess whether the percentage of normative values reached in 6MWT, 1MSTST, and HGS differed across care pathways at each time point. These outcomes were obtained from post hoc tests using the previously described GEE analyses adjusted for covariates. The GEE results are presented as the estimated mean and standard error (SE) as well as estimated mean difference between time points and their 95% confidence interval (95% CI). The source data of physical outcomes are presented in **Supplementary Table S2** for the total cohort and in **Supplementary Table S3** stratified according to care pathway. The level of statistical significance was set $p<0.05$ unless stated otherwise. All statistical analyses were performed with IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA).

Role of the funding source

Funders of the study had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results

Study population

Between July 1, 2020, and Sept 9, 2021, 650 patients who were hospitalized for COVID-19 were prospectively enrolled in the CO-FLOW study (**Figure 2**). All patients were discharged from hospital between March 24, 2020 and June 17, 2021. The total number of patients hospitalized for COVID-19 during the recruitment period in the region was 4569 of whom 1199 (26%) died during hospitalization.[33] The number of patients that had been invited is largely unknown due to logistical reasons. From the 3370 survivors, 650 patients (19% of all survivors) were included in this study. As of this interim analysis at Dec 3, 2021, 582 patients attended ≥1 study visit and were included in this analysis. The proportion of patients with ≥1 comorbidities was slightly lower and the length of hospital stay shorter in patients who were included in this analysis compared to those who were not (**Supplementary Table S1**).

In total, 114 (19.6%) patients did not participate in follow-up treatment (No-rehab), 315 (54.1%) received Com-rehab, 80 (13.7%) received Med-rehab, and 73 (12.5%) received SNF-rehab. The

majority of Com-rehab patients (291/315, 92.4%) received physiotherapy. In Med-rehab, 67 patients (83.8%) received inpatient rehabilitation for a median stay of 32.0 (IQR 25.0-42.0) days, of whom 10 (14.9%) patients continued outpatient Med-rehab after discharge; 13 (16.2%) patients received only outpatient treatment. All 73 (100%) patients in SNF-rehab received inpatient rehabilitation, for a median stay of 29.5 (IQR 18.5-39.0) days; 3 (4.2%) patients continued outpatient SNF-rehab after discharge.

Table 1 presents the demographic and clinical characteristics during hospital admission in the total cohort and stratified according to care pathway. Among all 582 patients, the median age was 60.0 (53.0-67.0), 31.1% were female, and the median length of hospital stay was 12.0 (IQR 6.0-27.0) days. Significant differences existed among patients across the different care pathways. Compared to the other care pathways, the SNF-rehab group was significantly older (67.0 [60.5-73.0] years), the No-rehab group had fewer comorbidities (67.3% had ≥1 comorbidities), and the Med-rehab group was characterized by a high proportion of patients with obesity (58.8%). Patients in both the Med- and SNF-rehab groups were characterized by worse clinical characteristics; the majority of these patients were admitted to an ICU and they required a significantly longer hospital stay than patients in the No- and Com-rehab groups.

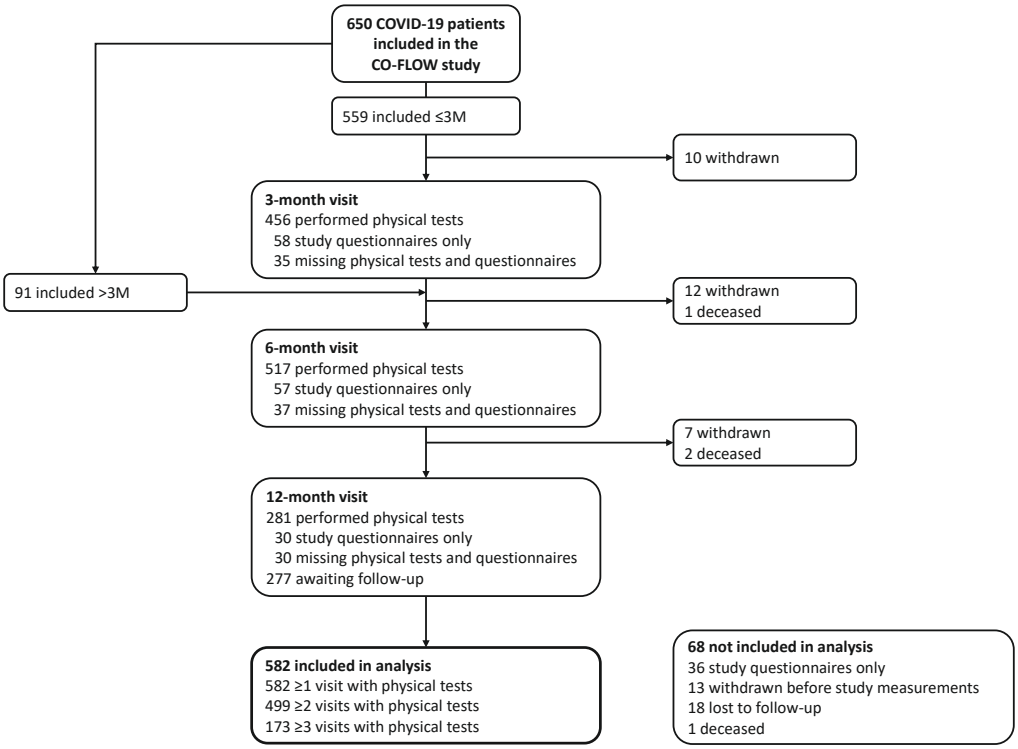

Figure 2. Flowchart of CO-FLOW study participants included in the analysis.
In total 582 patients attended at least one follow-up visit with physical tests and were included in this analysis. ≤3M refers to participants enrolled prior to or at 3 months after hospital discharge; >3M refers to participants enrolled after 3 months but within 6 months after hospital discharge.

Table 1. Demographic and clinical characteristics during hospital admission for COVID-19 in the total cohort and stratified according to care pathway.

	n[a]	All (N=582)	No-rehab (n=114)	Com-rehab (n=315)	Med-rehab (n=80)	SNF-rehab (n=73)	p value[e]
Demographic characteristics							
Median (IQR) age, years	-	60.0 (53.0-67.0)	59.0 (51.0-68.0)	60.0 (53.0-67.0)	57.0 (53.0-62.8)	67.0 (60.5-73.0)	<0.001*
Sex	-						0.018
Female		181 (31.1)	30 (26.3)	115 (36.5)	17 (21.3)	19 (26.0)	
Male		401 (68.9)	84 (73.7)	200 (63.5)	63 (78.8)	54 (74.0)	
Median (IQR) BMI, kg/m^2	69	29.3 (25.7-32.1)	27.9 (24.7-31.0)	28.1 (25.8-32.0)	30.0 (27.5-33.8)	27.7 (25.6-33.2)	<0.001*
Comorbidities	-						
≥1		473 (81.3)	76 (67.3)	266 (84.4)	66 (82.5)	65 (89.0)	<0.001*
Obesity (BMI≥30 kg/m^2)		224 (38.5)	31 (27.2)	119 (37.8)	47 (58.8)	27 (37.0)	<0.001*
Diabetes		117 (20.1)	20 (17.5)	65 (20.6)	12 (15.0)	20 (27.4)	0.24
Cardiovascular disease and/or hypertension		225 (38.7)	32 (28.1)	125 (39.7)	29 (36.3)	39 (53.4)	0.006
Pulmonary disease		145 (24.9)	17 (14.9)	88 (27.9)	20 (25.0)	20 (27.4)	0.05
Renal disease		52 (8.9)	9 (7.9)	32 (10.2)	4 (5.0)	7 (9.6)	0.51
Gastrointestinal disease		30 (5.2)	6 (5.3)	16 (5.1)	7 (8.8)	1 (1.4)	0.24
Neurological disease		60 (10.3)	8 (7.0)	30 (9.5)	8 (10.0)	14 (19.2)	0.05
Malignancy		65 (11.2)	9 (7.9)	38 (12.1)	8 (10.0)	10 (13.7)	0.56
Autoimmune disease		61 (10.5)	11 (9.6)	32 (10.2)	7 (8.8)	11 (15.1)	0.57
Mental disorder		29 (5.0)	3 (2.6)	16 (5.1)	6 (7.5)	4 (5.5)	0.49

Table 1. Continued.

	n[a]	All (N=582)	No-rehab (n=114)	Com-rehab (n=315)	Med-rehab (n=80)	SNF-rehab (n=73)	p value[e]
Migration background	3						0.49[b]
European		415 (71.7)	76 (67.9)	234 (74.3)	54 (68.4)	51 (69.9)	
Dutch Caribbean		80 (13.8)	18 (16.1)	38 (12.1)	12 (15.2)	12 (16.4)	
Asian		36 (6.2)	6 (5.4)	15 (4.8)	8 (10.1)	7 (9.6)	
Turkish		25 (4.3)	7 (6.3)	13 (4.1)	3 (3.8)	2 (2.7)	
(North) African		23 (4.0)	5 (4.5)	15 (4.8)	2 (2.5)	1 (1.4)	
Education level	7						0.34
Low		201 (35.0)	40 (35.7)	107 (34.1)	23 (29.9)	31 (43.1)	
Middle		202 (35.1)	38 (33.9)	108 (34.4)	31(40.3)	25 (34.7)	
High		172 (29.9)	34 (30.4)	99 (31.5)	23 (29.9)	16 (22.2)	
Smoking status	4						0.12[b]
Never		254 (43.9)	53 (47.3)	140 (44.4)	38 (48.7)	23 (31.5)	
Former		313 (54.2)	56 (50.0)	168 (53.3)	39 (50.0)	50 (68.5)	
Current		11 (1.9)	3 (2.7)	7 (2.2)	1 (1.3)	0 (0.0)	
Physical activity level[c]	5						0.20
Inactive		76 (13.2)	15 (13.4)	40 (12.7)	7 (9.1)	14 (19.2)	
Light		305 (52.9)	56 (50.0)	164 (52.1)	44 (57.1)	41 (56.2)	
Regular		159 (27.6)	30 (26.8)	93 (29.5)	21 (27.3)	15 (20.5)	
Hard		37 (6.4)	11 (9.8)	18 (5.7)	5 (6.5)	3 (4.1)	
Employed	6	344 (59.7)	67 (59.8)	181 (57.8)	68 (88.3)	28 (37.8)	<0.001*

Table 1. Continued.

	n[a]	All (N=582)	No-rehab (n=114)	Com-rehab (n=315)	Med-rehab (n=80)	SNF-rehab (n=73)	p value[e]
Clinical characteristics							
PCR-confirmed COVID-19 infection	-	572 (98.3)	108 (94.7)	313 (99.4)	79 (98.8)	72 (98.6)	
Other confirmed COVID-19 infection[d]	-	10 (1.7)	6 (5.3)	2 (0.6)	1 (1.3)	1 (1.4)	
Thrombotic event	13	89 (15.6)	8 (7.1)	34 (11.0)	27 (34.6)	20 (28.6)	<0.001*
Delirium	17	144 (25.5)	17 (14.9)	39 (12.7)	50 (66.7)	38 (55.1)	<0.001*
Oxygen supplementation	-	561 (96.4)	106 (93.0)	304 (96.5)	80 (100.0)	71 (97.3)	na
HFNC	37	177 (32.5)	19 (17.9)	81 (27.5)	37 (52.1)	40 (54.8)	<0.001*
ICU admission	-	237 (40.7)	19 (16.7)	85 (27.0)	76 (95.0)	57 (78.1)	<0.001*
IMV	-	205 (35.2)	12 (10.5)	65 (20.6)	73 (91.3)	55 (75.3)	<0.001*
Median (IQR) duration of IMV, days	8	14.0 (8.0-26.5)	8.5 (6.0-17.8)	8.0 (6.0-13.8)	23.5 (14.3-33.8)	15.0 (10.0-32.0)	<0.001*
Tracheostomy	11	73 (12.8)	3 (2.7)	12 (3.8)	36 (46.8)	22 (31.9)	<0.001*
Median (IQR) LOS ICU, days	4	16 (9.0-30.0)	8.0 (4.0-14.0)	9.0 (6.3-15.0)	28.0 (18.0-39.0)	20.0 (13.0-39.0)	<0.001*
COVID-19 directed treatment	31						0.23[b]
None		132 (24.0)	32 (29.1)	62 (20.3)	19 (27.9)	19 (28.4)	
Steroids		388 (70.4)	71 (64.5)	228 (74.5)	41 (60.3)	48 (71.6)	
Antivirals		80 (14.5)	24 (21.8)	50 (16.3)	5 (7.4)	1 (1.5)	
Anti-inflammatory		66 (12.0)	3 (2.7)	33 (10.9)	13 (19.1)	17 (25.4)	
Hydroxy)chloroquine		16 (2.9)	5 (4.5)	5 (1.6)	6 (8.8)	0 (0.0)	
Convalescent plasma		8 (1.5)	2 (1.8)	4 (1.3)	0 (0.0)	2 (3.0)	
Median (IQR) LOS hospital, days	1	12 (6.0-27.0)	7.0 (4.0-10.5)	9.0 (5.0-16.0)	43.0 (30.5-54.8)	29.0 (21.5-45.0)	<0.001*

Table 1. Continued.

	n[a]	All (N=582)	No-rehab (n=114)	Com-rehab (n=315)	Med-rehab (n=80)	SNF-rehab (n=73)	p value[e]
Time interval from discharge to follow-up visit, days							
Median (IQR) 3 months	-	93.0 (88.0-101.0)	92.0 (88.0-101.3)	94.0 (88.0-102.0)	93.0 (88.0-100.0)	92.0 (88.0-101.3)	0.99
Median (IQR) 6 months	-	184.0 (180.0-192.0)	183.0 (180.0-191.0)	184.0 (180.0-192.0)	186.0 (178.8-195.3)	182.0 (179.0-193.0)	0.88
Median (IQR) 12 months	-	366.0 (362.0-372.0)	365.0 (360.0-372.0)	366.0 (361.3-372.0)	365.5 (361.8-371.3)	365.5 (363.0-381.3)	0.32

Data are presented as n (%) unless stated otherwise. Care pathways comprise patients with No-rehab: no rehabilitation, Com-rehab: community-based rehabilitation, Med-rehab: in- and outpatient medical rehabilitation, and SNF-rehab: inpatient rehabilitation in a skilled nursing facility after hospitalization for COVID-19. IQR= interquartile range; BMI= body mass index; PCR= polymerase chain reaction; HFNC=high flow nasal cannula; ICU=intensive care unit; IMV=invasive mechanical ventilation; LOS=length of stay; na=not applicable.

[a]*In case of missing data the number of missing data are presented.*

[b]*Due to small group sizes we assessed differences in migration background as European vs non-European, in smoking status as never vs ever, and in COVID-19 directed treatment as none vs any treatment.*

[c]*Leisure time physical activity level was measured with the Saltin-Grimby Physical Activity Level Scale questionnaire.*[18]

[d]*COVID-19 diagnosis based on multidisciplinary team decision concerning symptoms and chest computed tomography scan or positive serology.*

[e]*Obtained using a $\chi 2$ test or Kruskal-Wallis test, as appropriate. Statistically significant p value after Bonferroni correction ($p<0.001$) is denoted by *.*

Table 2. Physical function in COVID-19 patients at 3, 6, and 12 months after hospital discharge.

	3 months	6 months	12 months	Mean difference 3–6 months (95% CI), p value	Mean difference 6–12 months (95% CI), p value	Mean difference 3–12 months (95% CI), p value
Cardiorespiratory fitness						
6MWT						
6MWD, m	476.0 (5.3)	490.9 (5.3)	495.2 (5.6)	14.9 (7.4 to 22.4), <0.001	4.3 (-3.4 to 12.1), 0.3	19.2 (10.4 to 28.0), <0.001
6MWD, %pred[a]	87.8 (1.0)	89.8 (0.9)	90.5 (1.0)	2.0 (0.4 to 3.6), 0.01	0.7 (-0.8 to 2.3), 0.4	2.8 (0.9 to 4.6), 0.004
1MSTST						
STS repetitions, n	24.9 (0.5)	27.1 (0.5)	27.7 (0.6)	2.2 (1.5 to 2.8), <0.001	0.6 (-0.2 to 1.5), 0.2	2.8 (1.8 to 3.8), <0.001
STS repetitions, %pred[b]	67.1 (1.2)	72.9 (1.2)	75.4 (1.5)	5.8 (4.0 to 7.6), <0.001	2.5 (0.07 to 5.0), 0.04	8.3 (5.6 to 121.1), <0.001
Muscle strength						
HGS						
Maximum, kg	35.5 (0.6)	39.0 (0.6)	41.4 (0.6)	3.5 (2.9 to 4.0), <0.001	2.5 (1.8 to 3.1), <0.001	5.9 (5.1 to 6.7), <0.001
Maximum, %pred[c]	91.1 (1.0)	100.2 (1.0)	106.9 (1.2)	9.1 (7.7 to 10.5), <0.001	6.6 (4.9 to 8.4), <0.001	15.7 (13.7 to 17.7), <0.001
Mobility						
DEMMI						
Total score	88.0 (0.6)	88.7 (0.6)	89.4 (0.7)	0.7 (-0.4 to 1.7), 0.2	0.7 (-0.5 to 1.9), 0.3	1.4 (0.05 to 2.7), 0.04

Data are presented as estimated mean (standard error) unless stated otherwise, obtained from generalized estimating equations analysis. The number of patients included in the analysis for 6MWT: 537, 1MSTST: 567, HGS: 577, and DEMMI: 573. 95% CI=95% confidence interval; 6MWT=6 min walk test; 6MWD=6 min walk distance; %pred=percentage of normative value; 1MSTST=1 min sit-to-stand test; STS=sit-to-stand; HGS=handgrip strength; DEMMI=de Morton Mobility Index.

[a] *Calculated using reference equations described by Enright and Sherill.*[23]

[b] *Reference values described by Strassman and colleagues.*[25]

[c] *Reference values described by Dodds and colleagues.*[29]

Overall trajectories of physical function

Table 2 shows the GEE outcomes of physical tests at follow-up visits in the total cohort.

Cardiorespiratory fitness: A total of 58, 87, and 54 patients did not perform the 6MWT at 3, 6, and 12 months, respectively, due to logistical reasons such as home visits or patients were physically unable to perform the 6MWT. At 3 months the estimated mean 6MWD was 476.0 m (SE 5.3) and 87.8% (1.0) of norm; the number of STS repetitions was 24.9 (0.5) and 67.1% (1.2) of norm. Both 6MWD and STS repetitions improved significantly from 3 to 6 months, but not thereafter (**Table 2**). The proportion of patients with a 6MWD result below the LLN was 21.4% (81/379) at 3 months, 16.5% (73/442) at 6 months, and 16.8% (40/238) at 12 months (**Supplementary Table S2**). At 12 months, patients performed 90.5% (1.0) of normative 6MWD and 75.4% (1.5) of normative STS repetitions.

Muscle strength: At 3 months the estimated mean HGS was 35.5 (SE 0.6) kg and 91.1% (1.0) of norm. HGS improved significantly from 3 to 6 months as well as from 6 to 12 months (**Table 2**). The proportion of patients with weak HGS decreased from 11.5% (51/442) at 3 months to 6.3% (32/512) at 6 months and to 5.7% (16/280) at 12 months (**Supplementary Table S2**). Patients performed 106.9% (1.2) of normative HGS at 12 months.

Mobility: At 3 months the estimated mean DEMMI score was 88.0 (SE 0.6) points. DEMMI scores did not significantly improve over time (**Table 2**).

Trajectories of physical function within care pathways

The trajectories of physical function and percentage of normative values reached within care pathways are graphically presented in **Figures 3** and **4**, the outcomes of GEE analyses are presented per physical test in **Supplementary Tables S4-S7**.

Cardiorespiratory fitness: The 6MWD improved significantly in Com- and Med-rehab from 3 to 6 months but not thereafter; no improvement was found within No- and SNF-rehab (**Figure 3A**). Likewise, the number of STS repetitions improved in both Com- and Med-rehab as well as in SNF-rehab from 3 to 6 months, but not thereafter (**Figure 3B**). Similar trends were found in the trajectories of the percentage of normative values over time within care pathways (**Figures 4A** and **4B**).

Muscle strength: HGS improved significantly in all care pathways from 3 to 6 months as well as from 6 to 12 months (**Figure 3C**). More than 100% of normative HGS was reached within all care pathways at 12 months follow-up (**Figure 4C**). Similar trends were found in the trajectories of the percentage of normative HGS over time within care pathways (**Figure 4C**).

Mobility: DEMMI scores improved significantly in Med-rehab from 3 to 6 months but not thereafter; no significant improvement was found within other care pathways (**Figure 3D**).

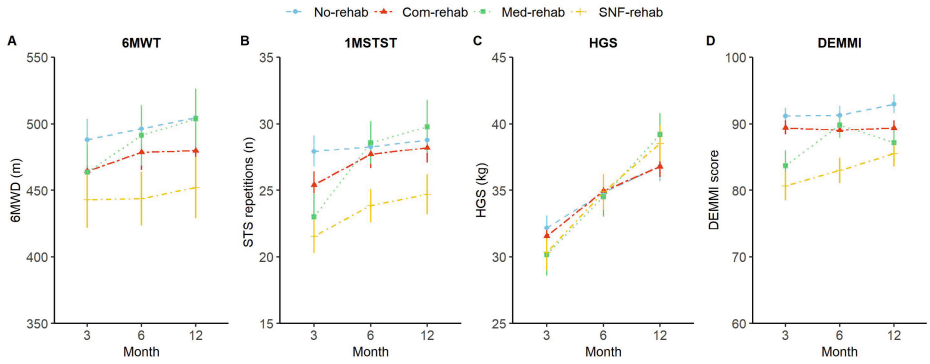

Figure 3. Trajectories of outcomes in 6MWT, 1MSTST, HGS, and DEMMI over time within care pathways assessed at 3, 6, and 12 months after hospital discharge.

Care pathways comprise patients with No-rehab: no rehabilitation, Com-rehab: community-based rehabilitation, Med-rehab: in- and outpatient medical rehabilitation, and SNF-rehab: inpatient rehabilitation in a skilled nursing facility after hospitalization for COVID-19. Trajectories of physical outcomes over time were assessed with generalized estimating equations analysis, adjusted for demographic and clinical characteristics during hospital admission including age, sex, having one or more comorbidities, obesity, employment status, delirium, thrombotic event, admission to intensive care unit, and the length of hospital stay. Data are presented as estimated mean with standard error. In 6MWT: significant improvement in Com-rehab (p=0.01) and Med-rehab (p=0.047) from 3 to 6 months but not thereafter; no significant improvement over time within other care pathways. In 1MSTST: significant improvement in Com-rehab (p<0.001), Med-rehab (p<0.001), and SNF-rehab (p=0.002) from 3 to 6 months but not thereafter; no significant improvement over time within No-rehab. In HGS: significant improvement within all care pathways from 3 to 6 months and from 6 to 12 months (all p<0.001 except for No-rehab from 6 to 12 months [p=0.002]). In DEMMI: significant improvement in Med-rehab (p=0.001) from 3 to 6 months but not thereafter; no significant improvement over time within other care pathways. 6MWT=6 min walk test; 6MWD=6 min walk distance; 1MSTST=1 min sit-to-stand test; STS=sit-to-stand; HGS=handgrip strength; DEMMI=de Morton Mobility Index.

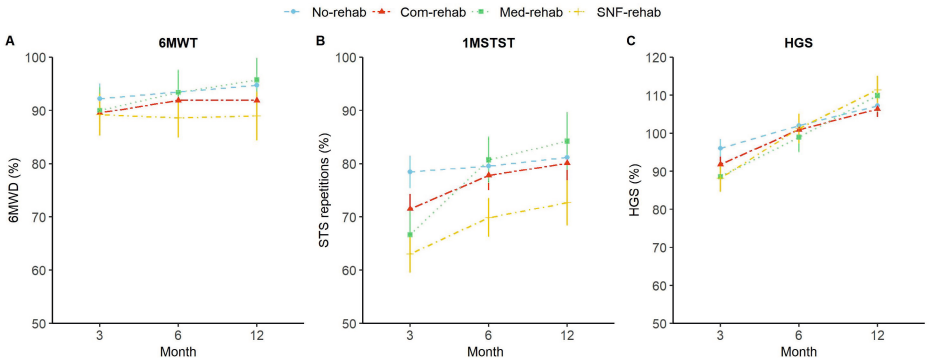

Figure 4. Trajectories of the percentage of normative values reached in 6MWT, 1MSTST, and HGS over time within care pathways assessed at 3, 6, and 12 months after hospital discharge.
Care pathways comprise patients with No-rehab: no rehabilitation, Com-rehab: community-based rehabilitation, Med-rehab: in- and outpatient medical rehabilitation, and SNF-rehab: inpatient rehabilitation in a skilled nursing facility after hospitalization for COVID-19. The percentages of normative values reached in physical tests were assessed with generalized estimating equations analysis, adjusted for demographic and clinical characteristics during hospital admission including having one or more comorbidities, obesity (excluded in 6MWT analysis), employment status, delirium, thrombotic event, admission to intensive care unit, and the length of hospital stay. Data are presented as estimated mean with standard error. In 6MWT: significant improvement in Com-rehab (p=0.03) from 3 to 6 months but not thereafter; no significant improvement within other care pathways. In 1MSTST: significant improvement in Com-rehab (p<0.001), Med-rehab (p<0.001), and SNF-rehab (p=0.001) from 3 to 6 months but not thereafter; no significant improvement over time within No-rehab. In HGS: significant improvement within all care pathways from 3 to 6 months and from 6 to 12 months (all p<0.001 except for No-rehab 6 to 12 months [p=0.002]). Normative values in 6MWT are calculated using reference equations described by Enright and Sherill,[23] in 1MSTST using reference values described by Strassman and colleagues,[25] and in HGS using reference values described by Dodds and colleagues.[29] 6MWT=6 min walk test; 6MWD=6 min walk distance; 1MSTST=1 min sit-to-stand test; STS=sit-to-stand; HGS=handgrip strength.

Comparison of physical function across care pathways

Cardiorespiratory fitness: The percentage of norm reached in the number of STS repetitions differed significantly between care pathways at follow-up, but not in 6MWD. At 3 months, Com-rehab (estimated mean difference -6.9% [95% CI -12.9 to -1.0]; p=0.02), Med-rehab (-11.8% [-21.9 to -1.8]; p=0.02), and SNF-rehab (-15.4% [-23.7 to -7.2]; p<0.001) had a significantly lower percentage of STS repetitions than No-rehab, as well as for SNF-rehab compared to Com-rehab (-8.5% [-15.6 to -1.4]; p=0.02); outcomes did not differ significantly between other care pathways. At 6 months SNF-rehab had a significantly lower percentage of normative STS repetitions than No-rehab (-9.7% [-18.0 to -1.3]; p=0.02), Com-rehab (-7.9% [-15.3 to -0.6]; p=0.04), and Med-rehab (-10.9% [-19.3 to -2.4]; p=0.01); outcomes did not differ significantly between other care pathways. At 12 months these differences across care pathways were no longer significant in STS repetitions.

Muscle strength: The percentage of normative HGS did not significantly differ between care pathways at follow-up visits. However, outcomes of the GEE analysis without adjustment for covariates showed lower percentages of normative HGS in Med- and SNF-rehab than in No- and Com-rehab (**Supplementary Figure S3**).

Discussion

This study provides objective measurements of long-term physical recovery after hospitalization for COVID-19 among patients who followed different care pathways. The study showed that cardiorespiratory fitness improved from 3 to 6 months solely in patients with rehabilitative care after hospital discharge, mobility improved only in Med-rehab from 3 to 6 months, whereas muscle strength improved within all care pathways from 3 to 6 months as well as from 6 to 12 months. The study also showed that the patients who received rehabilitation, and particularly patients with Med- or SNF-rehab, started off worse but reached at 12 months levels of physical function equal to those of less affected patients, indicating the importance of rehabilitation. At 12 months, overall, patients reached 91% of normative 6MWD, 75% of normative STS repetitions, and 107% of normative HGS.

Earlier studies on long-term physical recovery after hospitalization for COVID-19 are limited. Wu et al. reported improvement in 6MWD not only from 3 to 6 months, as in our study, but also from 6 to 12 months after hospital discharge.[12] However, in contrast to our cohort, patients with comorbidities and invasive mechanical ventilation were not included, whereas the overall length of hospital stay for COVID-19 was longer. Also, it is unclear if patients received rehabilitative care after hospital discharge and, if so, in what context. Other studies found no improvement in 6MWD over 12 months follow-up, which could be due to small sample sizes,[10,11] or between 6 and 12 months.[2] Recovery in HGS was assessed only in a cohort of patients admitted to ICU for COVID-19, indicating improved HGS over 12 months follow-up.[11] At 12 months, their patients achieved lower HGS (37 kg) compared to our patients (41 kg), but the study included only critically ill patients whereas our cohort comprised patients from both wards and ICUs.

Physical recovery occurred particularly in patients with rehabilitative care after hospital discharge, showing clinically meaningful outcomes in cardiorespiratory fitness. Bohannon and Crouch suggested that changes between 14.0 and 30.5 m in 6MWD can be considered clinically important (minimal clinically important difference, MCID).[34] Both Med- and SNF-rehab groups exceeded 14.0 m in 6MWD from 3 to 6 months. In 1MSTST, only patients with Med-rehab exceeded the MCID of 3 repetitions.[27] Although we found that the improvement in HGS was statistically significant within all care pathways, these changes may not be considered as clinically meaningful (MCID 5.0-6.5 kg).[35] Noteworthy, the literature does not identify a clear MCID for HGS and more studies are needed. Furthermore, it should be realized that the first study measurements were performed 3 months after hospital discharge and physical recovery within the first 3 months after hospital discharge was not assessed. Our findings imply both statistical significance and clinical meaningful outcomes in cardiorespiratory fitness, in particular in Med-rehab, and underline the importance of rehabilitation.

Our results seem to show that rehabilitation triage was successful, with more intensive rehabilitation provided to most impaired patients after hospitalization for COVID-19. Triage is the process of evaluating patients in relation to clinical, social, and affection pre-requisites to enhance the effectiveness of participation in a therapeutic program.[36] Resources for rehabilitation are limited and the triage process enables the best use of these resources. The fact that the most severely impaired

patients were referred to Med-rehab and that these patients showed both statistically significant and clinically meaningful improvements, seems to underscore an effective triage and rehabilitation process. However, our observational cohort design does not allow definite inferences.

At 12 months, overall, patients showed good recovery in cardiorespiratory fitness and muscle strength. These results are noteworthy given the high proportions of patients with comorbidities and severe illness. Still, 17% of patients had a 6MWD result below the LLN at 12 months. It is important to note that the normative values we used for 6MWD are from a healthy population without comorbidities. Therefore, it is not realistic to expect that all patients would reach 100% of norm. However, overall, our patients reached more than 100% of normative HGS and only 6% had impaired HGS at 12 months. The large proportion of patients that received rehabilitative care (80%) may have played a role in this recovery.

Among all patients, only 75% of norm was reached in 1MSTST at 12 months. This is relatively low compared to the achievements on 6MWT and HGS. Although we used the 1MSTST as a secondary outcome measure for cardiorespiratory fitness, the number of 1MSTST repetitions is also related to functional lower muscle strength.[37] The difference in normative values reached in 6MWT and 1MSTST at 12 months may indicate that there is still some impairment in functional lower muscle strength rather than in cardiorespiratory fitness. This hypothesis is supported by a recent study by Lorent and colleagues, reporting a lower proportion of patients with impaired 6MWD (16/222, 8%) than patients with impaired quadriceps strength (31/222, 32%) at 12 months after hospitalization for COVID-19.[38] However, because the reference values that we have used for the different physical outcomes were obtained from different study samples, as well as that different reference values for 6MWT were used by Lorent and colleagues,[38] the findings should be interpreted with caution.

In the last decade there has been growing attention for the functional long-term impairments among survivors of ICU admission, captured under the term post-intensive care syndrome (PICS).[39] Our patients that had been admitted to the ICU more frequently required more intensive rehabilitation (Med- and SNF-rehab). Not surprisingly, these patients had more impaired physical function at 3 months, but at 12 months these differences caught up. However, at 12 months, impaired 6MWD and HGS remained present in patients across all care pathways. We believe that this underlines that PICS is not unique to intensive care survivors, but long-term functional impairments are part of a continuum of critical illness. Functional impairment in patients that were not admitted to the ICU should be taken as seriously, and all patients should qualify for appropriate rehabilitative care.

This cohort study has several strengths, including the longitudinal and multicenter study design and the objective measurement of varied components of physical function. Also, we included patients who were admitted to either ward or ICU for COVID-19 in The Netherlands. A limitation is that we could not compare our outcomes with pre-morbid levels; therefore, we used normative values of the general population. Unfortunately, normative values on physical tests during the COVID-19 pandemic, including the possible influence of lockdown and restrictive measures, are not available. Furthermore, normative values for the different outcomes are obtained from different reference

groups and the normative values for the 6MWT are from 1998, urgently needing revision. However, these normative values have also been used in other COVID-19 studies.[2,3,10] The 650 participants in the CO-FLOW study were recruited from all patients who survived hospitalization and who visited the outpatient clinic for regular COVID-19 follow-up by pulmonary physicians in the participating hospitals. These numbers depended on the local logistics in each hospital, transfers to other regions, and temporary COVID-19 lock-down regulations, in which clinical follow-up was postponed or only performed by phone. Therefore, these numbers are largely unknown, which is a limitation of this study. However, recruitment of study participants occurred independently of the patients recovery status and was largely based on availability of research personnel. Our study contains an overrepresentation of patients (41%) who had been admitted to ICU compared to all hospitalized patients (16%) for COVID-19 in the Netherlands.[40] Our academic center served as a regional referral center for ICU patients, and many study participants were included from this center. Regarding care pathways, these pathways represent the national strategy of aftercare that was established in the Netherlands and represent hospitalized patients with different disease severity who require different rehabilitation facilities.

In conclusion, this study provides an objective evaluation on physical recovery after hospitalization for COVID-19, following patients across different care pathways. Overall, physical function improved after hospitalization for COVID-19, with largest improvement within 6 months post-discharge. Patients with rehabilitation after hospital discharge improved in more than one component of physical function, whereas patients without rehabilitation improved solely in muscle strength. Patients who received rehabilitation, and particularly patients with Med- or SNF-rehab, had more severe impairment in physical function at 3 months after hospital discharge but reached equal levels at 12 months compared to less affected patients. Future research should look further into refining triage to allocate rehabilitation resources in the best way, finding the most effective rehabilitation programs, and establishing determinants of poor physical recovery.

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Chapter 6

Long-term health outcomes of COVID-19 in ICU- and non-ICU-treated patients up to 2 years after hospitalization: a longitudinal cohort study (CO-FLOW)

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Abstract

Background Many patients hospitalized for COVID-19 experience long-term health problems, but comprehensive longitudinal data up to 2 years remain limited. We aimed to (1) assess 2-year trajectories of health outcomes, including comparison between intensive care unit (ICU) treated and non-ICU-treated patients, and (2) identify risk factors for prominent health problems post-hospitalization for COVID-19.

Methods The CO-FLOW multicenter prospective cohort study followed adults hospitalized for COVID-19 at 3, 6, 12, and 24 months post-discharge. Measurements included patient-reported outcomes (a.o., recovery, symptoms, fatigue, mental health, sleep quality, return to work, health-related quality of life [HRQoL]), and objective cognitive and physical tests. Additionally, routine follow-up data were collected.

Results 650 patients (median age 60.0 [IQR 53.0-67.0] years; 449/650 [69%] male) surviving hospitalization for COVID-19 were included, of whom 273/650 (42%) received ICU treatment. Overall, outcomes improved over time. Nonetheless, 73% (322/443) of patients had not completely recovered from COVID-19, with memory problems (274/443; 55%), concentration problems (259/443; 52%), and dyspnea (251/493; 51%) among most frequently reported symptoms at 2 years. Moreover, 61% (259/427) had poor sleep quality, 51% (222/433) fatigue, 23% (102/438) cognitive failures, and 30% (65/216) did not fully return to work. Objective outcome measures showed generally good physical recovery. Most outcomes were comparable between ICU- and non-ICU-treated patients at 2 years. However, ICU-treated patients tended to show slower recovery in neurocognitive symptoms, mental health outcomes, and resuming work than non-ICU-treated patients, while showing more improvements in physical outcomes. Particularly, female sex and/or pre-existing pulmonary disease were major risk factors for poorer outcomes.

Conclusions 73% (322/443) of patients had not completely recovered from COVID-19 by 2 years. Despite good physical recovery, long-term neurocognitive complaints, dyspnea, fatigue, and impaired sleep quality persisted. ICU-treated patients showed slower recovery in neurocognitive and mental health outcomes and resumption of work. Tailoring long-term COVID-19 aftercare to individual residual needs is essential. Follow-up is required to monitor further recovery.

Trial registration NL8710, registration date 12-06-2020.

Introduction

More than 3 years after the onset of the COVID-19 pandemic, over 771 million people worldwide have been infected with SARS-CoV-2.[1] Although a large proportion of infections has a mild disease course, hospitalization including intensive care unit (ICU) admission for respiratory failure may be required. Many patients do not fully recover to their pre-COVID-19 health status after hospitalization,[2] experiencing a wide range of persistent health problems with fatigue and neurocognitive problems among the most frequently reported.[3,4] Furthermore, incomplete recovery after COVID-19 infection is associated with reduced health-related quality of life (HRQoL).[4,5] Patients with COVID-19 who suffer persistent health problems place a considerable strain on healthcare services and medical costs, on top of the personal and societal impacts.[6]

Although several studies report health problems after COVID-19 up to one year after hospitalization,[3,4,7,8] data beyond one year remain limited. Two large cohort studies from Wuhan, China, showed that while the proportion of patients with persisting symptoms decreased over time, the majority still experienced symptoms 2 years after hospitalization for COVID-19.[4,9] Also population-based studies involving non-hospitalized individuals showed persisting symptoms up to 2 years, with more severely affected individuals having an increased risk of symptom manifestations.[10,11] After ICU treatment, patients often experience persistent symptoms, including physical, cognitive, and mental problems, generally referred to as the Post-Intensive Care Syndrome (PICS).[12] In the Wuhan studies, only 4% (51/1192)[4] and 1.9% (36/1864)[9] of the patients required ICU treatment for COVID-19, limiting inferences about different aftercare needs for ICU- and non-ICU-treated patients. One European study found that 84% of their patients experienced symptoms affecting daily life 2 years after hospitalization for COVID-19, with comparable prevalence of symptoms in ICU- and non-ICU-treated patients.[13] While this finding is in line with several short-term studies,[14,15] others have reported more sequelae in ICU-treated patients compared with non-ICU-treated patients.[5,16,17] Overall, a more comprehensive and multidimensional longitudinal evaluation of long-term health outcomes beyond one year and identification of patients at risk for poor outcomes after hospitalization for COVID-19 are pivotal for refining aftercare strategies. Moreover, an evaluation on potential disparities in long-term health outcomes between ICU- and non-ICU-treated patients with COVID-19 is required. Our study is particularly well-suited for comparing ICU-treated and non-ICU-treated patients, as our study contains a higher proportion of ICU patients compared to the average proportion of ICU admissions across all Dutch hospitals.[18]

Our primary aim of this study was to assess trajectories of a comprehensive range of health outcomes, both patient-reported and objectively measured, in patients with COVID-19 up to 2 years after hospital discharge, including a comparison between ICU- and non-ICU-treated patients. The secondary aim was to identify risk factors for self-reported recovery status and prominent long-term health problems in these patients: fatigue, cognitive failures, sleep quality, and health-related quality of life.

Methods

Study design and participants

We performed a 2-year prospective multicenter cohort study, COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system (CO-FLOW), that follows up patients discharged from hospitals in the Rotterdam-Rijnmond-Delft region in the Netherlands. This study was performed in 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities). This study included patients between July 2020 and October 2021 who had been hospitalized for COVID-19 (diagnosis by laboratory or clinical findings), aged ≥18 years, had sufficient knowledge of the Dutch or English language, and were within 6 months post-discharge. Incapacitated patients (e.g., dementia) were not included. Eligible patients were informed about the CO-FLOW study at hospital discharge and were recruited during routine follow-up at the outpatient clinic of one of the participating centers or during their inpatient stay in a rehabilitation center. In the Netherlands, it is standard practice to offer post-discharge follow-up to patients with COVID-19 at the outpatient clinic of the discharging hospital, with the first visit generally scheduled 6-12 weeks post-discharge. Recruitment of study participants occurred independently of the patient's recovery status and primarily depended on availability of research personnel. The CO-FLOW study protocol has been described in detail elsewhere.[19] The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study (MEC-2020-0487). This study has been prospectively registered in the International Clinical Trial Registry Platform (NL8710). Participants provided written informed consent before the start of study measurements. We reported this observational study according to STROBE guidelines.

Procedures

Study visits were performed at 3, 6, 12, and 24 months after hospital discharge at the outpatient clinic of one of the participating hospitals. For patients unable to visit the hospital for study visits, a research assistant performed study visits at home. During study visits, physical and cognitive tests and recovery and symptom checklist were administered. In addition, a survey of validated patient-reported outcome measures (PROMs) was sent via e-mail or postal mail. Baseline characteristics and routine follow-up data regarding pulmonary and radiological sequelae were retrospectively collected from medical records at the participating facilities and during the first study visit. We collected patients' age, sex, body mass index (BMI), migration background, education level, employment status, smoking status, pre-COVID-19 leisure time physical activity, assessed with the Saltin–Grimby Physical Activity Level Scale questionnaire,[20] and comorbidities at hospital admission. In-hospital characteristics included COVID-19 wave, the first assessment upon admission of laboratory values and chest X-ray abnormalities, type of treatment for COVID-19, thrombosis, delirium, maximum level and type of oxygen support, ICU treatment, length of stay (LOS) in ICU, and LOS in hospital. Additionally, we collected information on patient discharge destination after hospitalization. Routine follow-up at hospitals generally took place around 6 weeks to 3 months post-discharge and were generally continued around 6, 12, and 24 months if residual pulmonary abnormalities persisted. All collected data were stored in the Castor Electronic Data Capture system (Castor EDC, Amsterdam, the Netherlands).

Study outcome measurements

Recovery and symptoms

Self-reported recovery status from COVID-19, as compared to pre-COVID-19 health status, was assessed with the Core Outcome Measure for self-reported recovery from COVID-19 and dichotomized into completely recovered and not completely recovered (mostly recovered, somewhat recovered, half recovered, and not recovered at all).[21] New symptoms since COVID-19 were assessed using a symptom questionnaire (Corona Symptom Checklist, 26 symptoms) to assess the presence of new or worsened symptoms following SARS-CoV-2 infection. At the 24-month visit, patients were asked to also rate the severity (mild, moderate, severe, or very severe) of these symptoms.

PROMs

Fatigue was assessed with the Fatigue Assessment Scale (scores 0-50, cutoff ≥22);[22] dyspnea with the Modified Medical Research Council Dyspnea Scale;[21,23,24] anxiety and depression with the Hospital Anxiety and Depression Scale, subscales Anxiety and Depression (subscale scores 0-21, cutoff ≥11);[25] posttraumatic stress disorder (PTSD) with the Impact of Event Scale-Revised (scores 0-88, cutoff ≥33);[26,27] cognitive failures with the Cognitive Failures Questionnaire (CFQ, scores 0-100, cutoff >43);[28,29] sleep quality with the Pittsburgh Sleep Quality Index (scores 0-21, cutoff ≥5);[30] independency in activities of daily life with the Barthel Index (scores 0-20);[31] physical fitness with the International Fitness Scale (scored as very poor, poor, average, good, or very good);[32] physical activity with the International Physical Activity Questionnaire (expressed in MET-minutes/week);[33] participation in daily life activities with the Utrecht Scale for Evaluation of Rehabilitation-Participation on three scales: frequency, restrictions, and satisfaction (subscale scores 0-100);[34] employment status with the iMTA Productivity Cost Questionnaire (categorized into no, partial, or full return to work) for patients with a paid job before SARS-CoV-2 infection;[35] and health-related quality of life with the 5-level EuroQoL-5D (EQ-5D-5L) questionnaire and the 36-item Short Form Health Survey (SF-36). The EQ-5D-5L consists of the 5-level EQ-5D index value (0 indicates death and 1 perfect health; negative scores indicate a health status worse than death) and a visual analogue scale (EQ-VAS, scores 0-100).[36] The SF-36 consists of 8 domains (scores 0-100) and a physical and mental component summary score.[37]

Objective study measurements

Cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) (score range 0-30, cutoff <26)[38] at the patient's first study visit, and, only if score <26, repeated at subsequent visits. Physical function was evaluated for aerobic capacity with the 6 min walk test (6MWT) assessing the 6 min walk distance (6MWD)[39] and the 1 min sit-to-stand test (1MSTST) assessing the number of sit-to-stand repetitions.[40] Muscle strength was assessed by measurement of maximum isometric handgrip strength (HGS) in kg over three attempts per hand.[41] Mobility was assessed with the De Morton Mobility Index (DEMMI) test (scores 0-100).[42,43] Outcomes of the 6MWT,[44] 1MSTST,[45] and HGS[46] were normalized to the percentage of normative values using reference values, as well as to performance below the lower limit of normal (LLN) for the 6MWT.

Routine follow-up data

Pulmonary function tests (PFT) consisted of spirometry measuring forced vital capacity (FVC) and forced expiratory volume in 1s (FEV_1) in liters, and diffusion capacity of the lungs for carbon monoxide adjusted for hemoglobin (DLCOc) in $mmol \cdot min^{-1} \cdot kPa^{-1}$, according to the standards of the American Thoracic Society and European Respiratory Society.[47] PFT parameters are also expressed as a percentage of predicted FVC, FEV_1, and DLCOc values, using references values from the Global Lung Function Initiative Network.[48,49] A value below the LLN (z-score <-1.64) was defined as abnormal. Radiographic evaluation consisted of chest radiography or thin-section non-contrast chest-CT scan, which was interpreted by experienced radiologists using a standardized assessment. Chest radiographs were classified as normal, moderate, or severe abnormalities. CT scans were scored for the presence of abnormalities including ground-glass opacities (none, moderate, or severe), bronchiectasis or bronchiolectasis (none, moderate, or severe), consolidations, reticulation/fibrosis, and subpleural lines and bands.

Statistical analysis

Data are presented as mean with standard deviation (SD) and/or median with interquartile range (IQR) or as number with percentage. Group comparisons (ICU vs. non-ICU) were performed for continuous variables with the Mann-Whitney U test and for categorical variables with the Chi-squared test. For cognitive function, scores ≥26 were carried forward in future study visits. For the primary aim, we used Generalized Estimating Equations (GEE) with repeated measurements to explore the trajectories of health outcomes over time in the total cohort and comparing ICU and non-ICU groups. The GEE is a semi-parametric approach which considers within- and between-subject correlations and uses all available measurements despite incomplete data. We entered follow-up time (3, 6, 12, and 24 months) as a fixed factor in the GEE analysis for the total cohort. Additionally, we entered group (ICU vs. non-ICU) as a fixed factor and the interaction of follow-up time with group in the GEE for the subgroup analyses. The GEE outcomes of the 2-year trajectories for physical (percentage of normative values) and mental health outcomes are displayed graphically; for mental health variables the GEE analysis was adjusted for age and sex. For the secondary aim, we used GEE analyses to assess risk factors for recovery status, fatigue, cognitive failures, sleep quality, and HRQoL over the 2-year follow-up period. We selected covariables (i.e., characteristics at hospital admission) a priori and entered them as fixed factors in each GEE analysis, including time (follow-up visits), age, sex (male or female), obesity (obese if BMI≥30 kg/m^2, yes/no), cardiovascular disease (yes/no), pulmonary disease (yes/no), diabetes (yes/no), migration background (European or non-European), education (low, middle, or high), employment status (employed, unemployed, or retired), smoking status (current/former or never), steroid or anti-inflammatory treatment (yes/no), ICU admission (yes/no), and the LOS in hospital (days). Each GEE analysis was performed using an unstructured correlation matrix, without data imputation. A P value below 0.05 was considered statistically significant, unless stated otherwise. We used a Bonferroni-corrected α threshold to correct for multiple comparisons in recovery and symptoms ($\alpha=0.00185$), validated PROMs ($\alpha=0.00417$), objective study measurements ($\alpha=0.01$), and routine follow-up data ($\alpha=0.00556$). All statistical analyses were performed with IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA).

Results

We included 650 patients after hospitalization for COVID-19 (**Figure 1**), all discharged between March 24, 2020, and June 17, 2021; 273 (42%) patients received ICU treatment. Study visits were performed between July 1, 2020, and June 7, 2023. **Table 1** shows the baseline characteristics at hospital admission. For the total cohort, the median age was 60.0 (53.0-67.0) years and 449 (69%) were male. Compared to the non-ICU group, the ICU group comprised more males (205 [75%] vs. 244 [65%], p=0.005) and non-Europeans (95 [36%] vs. 86 [23%], p<0.001), and more frequently had obesity (145 [53%] vs. 121 [32%], p<0.001). Most patients in the ICU group (235 [86%]) required invasive mechanical ventilation for a median duration of 15.0 (8.5-28.0) days and patients had longer overall median LOS in hospital than the non-ICU group (31.0 [19.0-47.0] vs. 6.0 [4.0-10.5] days, p<0.001). Moreover, ICU-treated patients were more frequently discharged to inpatient rehabilitation, whereas non-ICU treated patients were mostly discharged home after hospitalization.

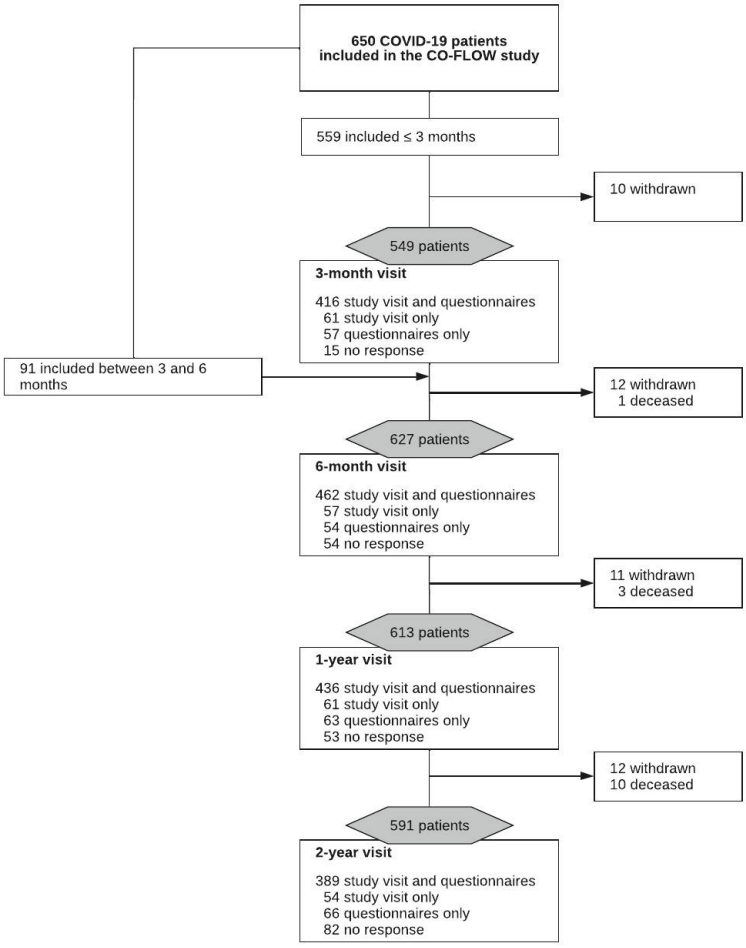

Figure 1. Flowchart of CO-FLOW study visits.

Table 1. Baseline characteristics of study participants.

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Patient characteristics					
Age, years Mean Median		59.7 (11.4) 60.0 (53.0-67.0)	60.6 (11.4) 61.0 (53.0-68.0)	58.6 (11.5) 60.0 (53.0-67.0)	0.19
Sex, male		449 (69%)	244 (65%)	205 (75%)	**0.005**
BMI, kg/m^2 Mean Median	589	29.4 (5.4) 28.4 (25.7-32.2)	28.5 (5.1) 27.6 (25.3-31.0)	30.5 (5.5) 29.7 (26.3-33.3)	**<0.001**
Migration Background	630				**<0.001**
European		449 (71%)	280 (77%)	169 (64%)	
Dutch Caribbean		89 (14%)	42 (11%)	47 (18%)	
Asian		39 (6%)	19 (5%)	20 (7%)	
Turkish		27 (5%)	13 (4%)	15 (6%)	
(North) African		25 (4%)	12 (3%)	13 (5%)	
Education[b]	625				0.40
Low		222 (35%)	130 (36%)	92 (35.5%)	
Middle		218 (35%)	121 (33%)	97 (37.5%)	
High		185 (30%)	115 (31%)	70 (27%)	
Employment	627				0.28
Unemployed		100 (16%)	60 (16%)	40 (15%)	
Employed		372 (59%)	208 (57%)	164 (63%)	
Retired		155 (25%)	98 (27%)	57 (22%)	
Smoking status	631				0.53
Never		280 (44%)	159 (43%)	121 (46%)	
Former		339 (54%)	199 (54%)	140 (53%)	
Current		12 (2%)	9 (3%)	3 (1%)	
Physical activity level[c]	624				0.07
Inactive		86 (14%)	61 (17%)	25 (10%)	
Light		332 (53%)	186 (51%)	146 (56%)	
Moderate		168 (27%)	94 (26%)	74 (29%)	
Vigorous		38 (6%)	24 (7%)	14 (5%)	
Comorbidities					
≥1		543 (83%)	303 (82%)	231 (85%)	0.21
Obesity (BMI≥30 kg/m^2)		266 (41%)	121 (32%)	145 (53%)	**<0.001**
Diabetes		130 (20%)	78 (21%)	52 (19%)	0.61

Table 1. Continued.

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Cardiovascular disease/ hypertension		257 (40%)	146 (39%)	111 (41%)	0.62
Pulmonary disease		162 (25%)	101 (27%)	61 (22%)	0.20
Renal disease		59 (9%)	38 (10%)	21 (8%)	0.30
Gastrointestinal disease		31 (5%)	20 (5%)	11 (4%)	0.45
Neuromuscular disease		68 (11%)	42 (11%)	26 (10%)	0.51
Malignancy		69 (11%)	40 (11%)	29 (11%)	1.00
Autoimmune/ inflammatory disease		68 (11%)	48 (13%)	20 (7%)	**0.03**
Mental disorder		32 (5%)	21 (6%)	11 (4%)	0.37
Vaccinated before admission	641				NA
Yes		5 (1%)	3 (1%)	2 (1%)	
No		636 (99%)	368 (99%)	268 (99%)	
In-hospital characteristics					
COVID-19 wave[d]					**<0.001**
First		180 (28%)	72 (19%)	108 (40%)	
Second		339 (52%)	224 (59%)	115 (42%)	
Third		131 (20%)	81 (22%)	50 (18%)	
Laboratory values					
Creatinine, umol/L	618	83.0 (69.8-101.3)	81.0 (68.0-95.3)	87.0 (72.0-109.8)	**<0.001**
(CKD-EPI) eGFR, ml/min	603	82.0 (66.0-90.0)	83.5 (68.0-90.0)	80.0 (62.5-90.0)	0.07
CRP, mg/L	614	89.0 (48.0-154.3)	74.0 (41.0-121.0)	127.0 (67.0-193.0)	**<0.001**
Ferritin, ug/L	376	833.5 (453.3-1592.3)	665.0 (368.0-1221.0)	1170.0 (585.0-2010.5)	**<0.001**
ALAT, U/L	598	37.0 (25.0-56.0)	35.5 (24.0-53.0)	40.0 (27.8-62.0)	**0.02**
Hemoglobin, mmol/L	616	8.6 (7.9-9.2)	8.6 (7.9-9.2)	8.5 (7.8-9.2)	0.33
MCV, fl	604	88.0 (85.0-91.0)	88.0 (85.0-91.0)	88.0 (85.0-91.0)	0.60
Thrombocytes, 10^9/L	608	211.0 (160.0-276.0)	210.0 (161.0-273.3)	213.0 (160.0-284.0)	0.44
Lymphocytes absolute count, 10^9/L	432	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.9 (0.6-1.1)	0.09
D-dimer, mg/L	313	1.1 (0.6-35.2)	1.2 (0.7-708.3)	1.0 (0.6-3.7)	**0.003**
NT-pro-BNP, pmol/ml	118	18.0 (8.0-53.0)	18.0 (7.0-76.0)	21.0 (8.0-45.0)	0.78
IL-6, pmol/ml	47	53.0 (26.0-173.0)	28.5 (24.5-45.0)	88.0 (28.0-213.5)	**0.03**

Table 1. Continued.

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Chest x-ray abnormalities	619				**<0.001**
Normal		67 (11%)	55 (15%)	12 (5%)	
Moderate		135 (22%)	98 (27%)	37 (15%)	
Severe		417 (67%)	213 (58%)	204 (81%)	
COVID-19 directed treatment					0.36
None		148 (23%)	81 (22%)	67 (25%)	
(Hydroxy)chloroquine		12 (2%)	3 (1%)	9 (3%)	
Steroids		456 (70%)	275 (73%)	181 (66%)	
Antivirals		97 (15%)	76 (20%)	21 (8%)	
Anti-inflammatory		76 (12%)	11 (3%)	65 (24%)	
Convalescent plasma		8 (1%)	6 (1%)	2 (1%)	
Thrombosis	648	102 (16%)	19 (5%)	83 (31%)	**<0.001**
Delirium	648	165 (26%)	14 (4%)	151 (56%)	**<0.001**
Requiring oxygen supplementation		627 (97%)	354 (94%)	273 (100%)	**<0.001**
Requiring high flow nasal cannula	648	208 (32%)	57 (15%)	151 (56%)	**<0.001**
ICU admission		273 (42%)	-	273 (42%)	NA
Invasive mechanical ventilation		235 (36%)	-	235 (86%)	NA
Length of intubation, days Mean Median	229	20.1 (15.4) 15.0 (8.5-28.0)	-	20.1 (15.4) 15.0 (8.5-28.0)	NA
Tracheostomy	648	90 (14%)	-	90 (33%)	NA
Length of ICU stay, days Mean Median	271	22.0 (17.5) 16.0 (9.0-31.0)	-	22.0 (17.5) 16.0 (9.0-31.0)	NA
Length of hospital stay, days Mean Median		19.7 (20.2) 12.0 (6.0-28.0)	8.5 (7.4) 6.0 (4.0-10.5)	35.2 (21.9) 31.0 (19.0-47.0)	**<0.001**
Discharge destination					**<0.001**
Home		481 (74%)	354 (94%)	127 (46%)	
Inpatient medical rehabilitation center		80 (12%)	2 (1%)	78 (29%)	
Inpatient skilled nursing facility		89 (14%)	21 (5%)	68 (25%)	

Table 1. Continued.

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Time interval from discharge to follow-up visits, days					
3 months	430	93.0 (88.0-103.0)	93.0 (87.0-101.0)	93.0 (88.0-105.8)	0.14
6 months	517	184.0 (180.0-193.0)	185.0 (180.0-193.0)	183.0 (178.8-193.0)	0.07
1 year	502	366.0 (361.0-373.0)	366.0 (361.0-373.0)	365.5 (362.0-372.0)	0.59
2 years	449	730.0 (725.0-737.5)	731.0 (725.0-739.0)	729.0 (725.3-735.0)	**0.04**

Data are presented as mean (standard deviation), median (interquartile range), or n (%). Patient characteristics are presented for pre-COVID-19 situation, and age and BMI at the time of hospital admission. The following variables were dichotomized for statistical analysis, migration background was categorized as European versus non-European groups combined, smoking status as never versus former/current, and treatment as no treatment versus any received treatment. P values are obtained using Mann-Whitney U test, or Chi-squared test as appropriate; a P value less than 0.05 was considered statistically significant and is indicated in bold. BMI, Body Mass Index; ICU, Intensive Care Unit; NA, Not Applicable.

[a]Adjusted n is presented for variables with a total number of patients less than 650.

[b]Education comprises low (primary or secondary education); middle (high school); high (postsecondary education or university).

[c]Pre-COVID-19 leisure time physical activity level was measured with the Saltin–Grimby Physical Activity Level Scale questionnaire.[20]

[d]We classified patients by discharge date: the first COVID-19 wave (Feb-Jun 2020; original variant dominant), second wave (Jul 2020-Feb 2021; alpha variant dominant), and third wave (Feb-Jun 2021; beta and delta variants dominant).

Recovery status and symptoms

Total cohort

Recovery status, having ≥1 symptom, and proportion of symptoms of impaired fitness, fatigue, dyspnea, muscle weakness, hair loss, sleep disturbances, and joint pain improved significantly over 2 years in the total cohort, whereas proportion of hearing problems worsened (all p<0.00185) (**Table 2** and **Supplementary Table S1**). At 2 years, 73% (322/443) of patients had not completely recovered from COVID-19. Regarding symptoms, 88% (443/503) experienced ≥1 symptoms, most frequently impaired fitness (62%), fatigue (61%), memory problems (55%), concentration problems (52%), and dyspnea (51%). Patients indicated these symptoms as severe or very severe for impaired fitness in 33% (85/254), fatigue in 43% (108/253), memory problems in 36% (82/225), and concentration problems in 37% (79/217) (**Supplementary Table S2**).

ICU- vs. non-ICU-treated patients

On average, the proportion of patients with muscle weakness, tingling/numbness in extremities, and hoarseness was significantly higher in the ICU group than in the non-ICU group (all p<0.001); other symptoms were comparable (**Table 2**). Over time, the ICU group was more likely to experience memory problems (OR 2.1 [95%CI 1.4 to 3.1], p<0.001) and sleep disturbances (2.2 [1.4 to 3.4], p<0.001) compared to the non-ICU group. At 2 years, outcomes did not differ significantly between groups, except a higher proportion of hoarseness in the ICU group (p<0.001).

Table 2. Trajectories of self-reported recovery and the ten most prevalent symptoms in ICU- and non-ICU-treated patients for COVID-19 up to 2 years after hospital discharge.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	6 M	1 Y	2 Y	P value	3 M	6 M	1 Y	2 Y	3 M	6 M	1 Y	2 Y	P value	P value
Recovery status, n	*159*	*300*	*418*	*443*		*90*	*184*	*225*	*260*	*69*	*116*	*193*	*183*		
Not completely recovered	142 (89%)	248 (83%)	316 (77%)	322 (73%)	**<0.001**	78 (87%)	142 (77%)	159 (74%)	180 (69%)	64 (93%)	106 (91%)	157 (81%)	142 (78%)	0.003	0.08
Symptoms, n	*441*	*528*	*532*	*503*		*275*	*311*	*310*	*300*	*166*	*218*	*222*	*203*		
Impaired fitness	362 (83%)	379 (72%)*	346 (65%)*#	311 (62%)*†	**<0.001**	217 (79%)	218 (70%)	196 (63%)	165 (58%)	145 (88%)	161 (74%)	149 (67%)	138 (68%)	0.02	0.17
Fatigue	116/140 (83%)	162/241 (67%)*	237/380 (62%)#	302/493 (61%)	**<0.001**	74/84 (88%)	93/140 (66%)	146/235 (62%)	190/292 (58%)	42/56 (75%)	69/101 (68%)	91/145 (63%)	132/201 (66%)	0.99	0.16
Dyspnea	87/128 (68)%	127/237 (54%)*	210/378 (56%)	251/493 (51%)	**0.001**	61/78 (78%)	74/135 (55%)	133/235 (56%)	139/292 (48%)	26/50 (52%)	53/102 (52%)	77/143 (54%)	112/201 (56%)	0.47	0.005
Muscle weakness	253 (58%)	258 (49%)*	225 (42%)*#	189 (38%)†	**<0.001**	143 (52%)	135 (43%)	116 (38%)	105 (35%)	110 (66%)	123 (57%)	108 (49%)	84 (41%)	**<0.001**	0.23
Memory problems	238 (54%)	302 (57%)	296 (56%)	274 (55%)	0.44	163 (59%)	190 (61%)	177 (57%)	155 (52%)	75 (45%)	112 (52%)	119 (54%)	119 (59%)	0.11	**0.001**
Concentration problems	232 (53%)	273 (52%)	271 (51%)	259 (52%)	0.81	158 (58%)	166 (54%)	159 (51%)	150 (50%)	74 (45%)	107 (49%)	111 (50%)	109 (54%)	0.19	0.03
Sensory overload	50/109 (46%)	100/229 (44%)	145/381 (38%)	196/495 (40%)	0.50	33/61 (54%)	56/129 (43%)	90/236 (38%)	103/294 (35%)	17/48 (35%)	44/100 (44%)	55/145 (38%)	90/201 (46%)	0.65	0.09

Table 2. Continued.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	6 M	1 Y	2 Y	P value	3 M	6 M	1 Y	2 Y	3 M	6 M	1 Y	2 Y	P value	P value
Joint pain	187 (43%)	218 (41%)	217 (41%)	170 (34%)†	**<0.001**	109 (40%)	113 (36%)	110 (36%)	92 (31%)	78 (48%)	105 (48%)	107 (48%)	78 (38%)	0.002	0.75
Balance problems/ dizziness	184 (42%)	228 (44%)	223 (42%)	200 (40%)	0.53	118 (43%)	126 (41%)	123 (40%)	104 (35%)	66 (40%)	102 (47%)	99 (45%)	96 (48%)	0.09	0.09
Sleep disturbances	160 (36%)	182 (35%)	185 (35%)	141 (28%)*	**0.002**	108 (39%)	119 (39%)	101 (33%)	73 (24%)	52 (31%)	63 (29%)	83 (37%)	68 (34%)	0.97	**<0.001**

The data comprise raw test outcomes and are presented as n (%) or as n/N (%) in the case of adjusted total number. Recovery status from COVID-19 was dichotomized into completely recovered and not complete recovered (not recovered at all, somewhat recovered, half recovered, or mostly recovered). The presence of symptoms was assessed with a symptom questionnaire (Corona Symptom Checklist, CSC) on new or worsened symptoms following SARS-CoV-2 infection. The symptoms fatigue, dyspnea, and sensory overload were added to the CSC in a later stage and therefore contain lower total numbers. The trajectories of all the assessed symptoms are shown in ***Supplementary Table S1****. P values are obtained from Generalized Estimating Equations analysis, a P value less than 0.00185 was considered statistically significant and is indicated in bold. In the total cohort,* * *indicates a significant difference as compared to the previous study visit,* # *indicates a significant difference between the 3-month and 1-year study visits, and* † *between the 6-month and 2-year study visits.* † *indicates significant difference between ICU and non-ICU group at 2 years.*

PROMs

Total cohort

Outcomes of fatigue, mental health, sleep quality, physical fitness, participation, return to work, and HRQoL improved significantly (all p<0.00417) over time in the total cohort (**Table 3**). At 2 years, 51% (222/433) of patients experienced fatigue, 10% (43/446) anxiety, 10% (45/446) depression, 7% (31/446) PTSD, 23% (102/446) cognitive failures, 61% (259/427) poor sleep quality, 18% (81/447) poor or very poor physical fitness, and, among patients with a paid job before COVID-19, 30% (65/216) had not fully returned to work. Regarding HRQoL, patients reached a mean EQ-5D index value of 0.80 (0.22) and EQ-VAS of 73.4 (18.2) by 2 years.

ICU- vs. non-ICU-treated patients

On average, the proportion of patients who had not yet fully returned to work was significantly higher in the ICU group than in the non-ICU group (p<0.001); other outcomes were comparable (**Table 3**). Over time, as for mental health, **Figure 2A** presents the group trajectories of PTSD and cognitive failures scores and the proportion of patients with depression and anxiety (**Supplementary Table S4**); after Bonferroni correction, only PTSD recovery was significantly slower in the ICU than in the non-ICU group. Moreover, the ICU group was less likely to fully return to work over time compared to the non-ICU group (OR 0.26 [95%CI 0.13 to 0.51], p<0.001). At 2 years, outcomes did not differ significantly between groups.

Objective study measurements

Total cohort

Cognitive and physical function, except for the DEMMI, outcomes improved significantly over time in the total cohort (**Supplementary Table S5**). At 2 years, 12% (57/464) of patients had cognitive deficits and patients reached 95% of norm in 6MWD, 83% in 1MSTST, and 108% in HGS, and the mean DEMMI score was 89/100.

Table 3. Trajectories of validated PROMs in COVID-19 patients up to 2 years after hospital discharge.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	6 M	1 Y	2 Y	P value	3 M	6 M	1 Y	2 Y	3 M	6 M	1 Y	2 Y	P value	P value
Fatigue, n	*438*	*483*	*478*	*433*		*272*	*289*	*288*	*257*	*166*	*194*	*190*	*176*		
FAS, total score	25.1 (9.4)	24.2 (9.1)*	23.7 (8.9)*#	23.6 (8.9)†	**<0.001**	25.6 (9.7)	24.7 (9.4)	24.0 (8.9)	23.5 (9.0)	24.5 (8.9)	23.5 (8.6)	23.2 (8.9)	23.7 (8.9)	0.45	0.31
Fatigue (FAS ≥22)	258 (59%)	278 (58%)	266 (56%)	222 (51%)†	**0.004**	166 (61%)	170 (59%)	162 (56%)	132 (51%)	92 (55%)	108 (56%)	103 (54%)	90 (51%)	0.64	0.86
mMRC dyspnea scale, n	*433*	*484*	*473*	*466*		*270*	*289*	*285*	*278*	*163*	*195*	*188*	*188*		
mMRC ≥1	175 (40%)	174 (36%)	163 (35%)	187 (40%)	0.08	117 (43%)	110 (38%)	107 (38%)	113 (41%)	58 (36%)	64 (33%)	56 (30%)	74 (40%)	0.15	0.60
Mental health, n	*436*	*486*	*483*	*446*		*274*	*294*	*291*	*263*	*163*	*194*	*194*	*183*		
HADS-A, total score	5.3 (4.3)	4.7 (4.2)*	4.8 (4.5)#	4.6 (4.2)	**<0.001**	5.5 (4.3)	4.9 (4.3)	4.8 (4.3)	4.5 (4.7)	5.0 (4.2)	4.4 (4.0)	4.8 (4.7)	4.7 (4.3)	0.64	0.23
Anxiety (HADS-A ≥11)	56 (13%)	50 (10%)	53 (11%)	43 (10%)	0.27	38 (14%)	31 (11%)	28 (10%)	19 (7%)	18 (11%)	19 (10%)	25 (13%)	24 (13%)	0.49	0.01
HADS-D, total score	5.0 (4.1)	4.5 (4.0)*	4.4 (4.1)#	4.5 (3.9)	**0.004**	5.2 (4.1)	4.7 (4.0)	4.7 (3.8)	4.5 (3.8)	4.5 (4.2)	4.1 (4.0)	4.0 (4.3)	4.6 (4.1)	0.31	0.13
Depression (HADS-D ≥11)	49 (11%)	45 (9%)	50 (10%)	45 (10%)	0.84	34 (13%)	33 (11%)	28 (10%)	23 (9%)	15 (9%)	12 (6%)	22 (12%)	22 (12%)	0.99	0.004

Table 3. Continued.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	**6 M**	**1 Y**	**2 Y**	**P value**	**3 M**	**6 M**	**1 Y**	**2 Y**	**3 M**	**6 M**	**1 Y**	**2 Y**	**P value**	**P value**
IES-R, total score	14.1 (13.9)	12.2 (12.6)*	12.0 (12.5) #	10.9 (12.5)* ǂ	**<0.001**	13.4 (13.2)	11.7 (12.2)	10.7 (11.6)	9.2 (11.5)	15.5 (14.9)	12.9 (13.2)	13.9 (13.6)	13.2 (13.4)	0.005	**0.002**
PTSD (IES-R ≥33)	51 (12%)	41 (9%)	35 (7%)#	31 (7%)	**0.004**	28 (10%)	22 (8 %)	15 (5 %)	12 (5%)	23 (14%)	19 (10%)	20 (10%)	19 (11%)	0.01	0.06
Cognition, n	*433*	*476*	*470*	*438*		*271*	*290*	*282*	*259*	*162*	*186*	*188*	*179*		
CFQ, total score	29.7 (19.2)	29.4 (18.5)	30.7 (18.7)	30.4 (18.3)	0.16	32.0 (19.7)	30.5 (19.0)	31.8 (18.7)	30.4 (18.3)	25.9 (17.9)	27.9 (17.6)	29.1 (18.8)	30.6 (18.4)	0.10	0.007
Cognitive failures (CFQ >43)	95 (22%)	114 (24%)	103 (22%)	102 (23%)	0.31	67 (25%)	74 (26%)	66 (23%)	58 (22%)	28 (17%)	40 (22%)	37 (20%)	44 (25%)	0.30	0.27
Sleep quality, n	*428*	*471*	*462*	*427*		*264*	*284*	*282*	*251*	*164*	*187*	*180*	*176*		
PSQI, total score	7.0 (4.2)	6.8 (4.2)	6.5 (4.1)#	6.5 (4.3)	**0.002**	7.3 (4.3)	6.9 (4.4)	6. (4.0)	6.6 (4.2)	6.5 (3.9)	6.4 (3.8)	6.5 (4.3)	6.3 (4.4)	0.38	0.06
PSQI, Poor sleep quality (PSQI ≥5)	286 (67%)	311 (66%)	275 (60%)#	259 (61%)	**0.001**	179 (68%)	189 (67%)	164 (58%)	157 (63%)	107 (65%)	122 (65%)	111 (62%)	102 (58%)	0.81	0.21
Functioning in ADL, n	*448*	*499*	*491*	*449*		*271*	*302*	*297*	*263*	*177*	*197*	*194*	*186*		
Barthel index, total score	19.5 (1.5)	19.5 (1.3)	19.6 (1.2)	19.6 (1.2)	0.13	19.5 (1.5)	19.6 (1.3)	19.6 (1.2)	19.6 (1.2)	19.4 (1.5)	19.5 (1.4)	19.6 (1.1)	19.5 (1.2)	0.45	0.27

Table 3. Continued.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	**6 M**	**1 Y**	**2 Y**	**P value**	**3 M**	**6 M**	**1 Y**	**2 Y**	**3 M**	**6 M**	**1 Y**	**2 Y**	**P value**	**P value**
Physical function															
Physical fitness, *n*	*452*	*492*	*487*	*447*		*276*	*297*	*294*	*264*	*176*	*195*	*193*	*183*		
Physical fitness, IFIS, very poor/ poor	128 (28%)	85 (17%)*	87 (18%)#	81 (18%)	**<0.001**	70 (25%)	52 (33%)	47 (16%)	50 (19%)	58 (33%)	33 (17%)	39 (20%)	31 (17%)	0.65	0.09
Physical fitness, IFIS, Average/ good/very good	324 (72%)	407 (83%)	401 (82%)	366 (82%)		206 (75%)	245 (83%)	247 (84%)	214 (81%)	118 (67%)	162 (83%)	154 (80%)	152 (83%)		
IPAQ-SF, *n*	*356*	*371*	*350*	*340*		*216*	*224*	*214*	*202*	*140*	*147*	*136*	*138*		
Physical activity, IPAQ-SF, MET min/ wk	4243.4 (6853.9)	4758.8 (7391.9)	4103.9 (6130.2)	3804.2 (5610.0)	0.28	4439.0 (7389.7)	4580.8 (7281.1)	3906.2 (6034.5)	4059.9 (6136.2)	3941 (5946.1)	5030.0 (7574.7)	4414.9 (6287.6)	3429.9 (4732.5)	0.88	0.50
Participation, n	*440*	*485*	*477*	*436*		*269*	*292*	*287*	*259*	*171*	*193*	*190*	*177*		
USER-P, Frequency	28.0 (11.1)	29.3 (11.1)	29.5 (10.8)#	30.3 (10.8)	**<0.001**	27.6 (11.2)	29.8 (11.1)	29.4 (10.4)	30.1 (10.8)	28.7 (11.0)	28.5 (11.2)	29.8 (11.3)	30.6 (10.8)	0.74	0.04

Table 3. Continued.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	**6 M**	**1 Y**	**2 Y**	**P value**	**3 M**	**6 M**	**1 Y**	**2 Y**	**3 M**	**6 M**	**1 Y**	**2 Y**	**P value**	**P value**
USER-P, Restrictions	79.4 (21.0)	85.3 (17.9)	86.1 (18.9) *#	86.6 (18.0) ǂ	**<0.001**	80.9 (20.2)	86.1 (18.3)	86.9 (18.1)	86.9 (18.4)	77.1 (22.1)	84.1 (17.4)	84.9 (19.9)	86.2 (17.4)	0.20	0.16
USER-P, Satisfaction	64.6 (19.5)	68.2 (18.6)*	68.4 (19.1)#	70.0 (18.8)	**<0.001**	63.8 (19.2)	68.3 (19.2)	68.2 (18.3)	69.4 (19.0)	65.8 (19.9)	68.2 (17.7)	68.6 (20.4)	70.7 (18.6)	0.38	0.54
Employment status, n	*345*	*320*	*299*	*216*		*190*	*183*	*176*	*124*	*155*	*137*	*123*	*92*		
IPCQ, not or partially returned to work	244 (71%)	158 (49%)	93 (31%)	65 (30%)	**<0.001**	107 (56%)	64 (35%)	47 (27%)	32 (26%)	137 (88%)	94 (69%)	46 (37%)	33 (36%)	**<0.001**	**<0.001**
iPCQ, fully returned to work	101 (29%)	162 (51%)	206 (69%)	151 (70%)		83 (44%)	119 (65%)	129 (73%)	92 (74%)	18 (12%)	43 (31%)	77 (63%)	59 (64%)		
HRQoL															
EQ-5D-5L, *n*	*442*	*482*	*479*	*437*		*274*	*288*	*289*	*260*	*168*	*194*	*190*	*177*		
Index value	0.75 (0.24)	0.79 (0.21)*	0.80 (0.21)*#	0.80 (0.22)	**<0.001**	0.76 (0.23)	0.80 (0.21)	0.81 (0.20)	0.80 (0.21)	0.72 (0.26)	0.77 (0.22)	0.79 (0.23)	0.79 (0.23)	0.25	0.09
EQ-VAS	68.5 (19.5)	73.5 (17.9)*	74.0 (17.5)#	73.4 (18.2)	**<0.001**	69.1 (18.9)	73.6 (17.9)	74.3 (16.8)	73.4 (18.4)	67.6 (20.6)	73.3 (17.9)	73.6 (18.5)	73.5 (17.9)	0.74	0.35

Table 3. Continued.

	Total					Non-ICU				ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
	3 M	6 M	1 Y	2 Y	P value	3 M	6 M	1 Y	2 Y	3 M	6 M	1 Y	2 Y	P value	P value
SF-36, *n*	*434*	*481*	*476*	*441*		*274*	*292*	*286*	*262*	*161*	*190*	*191*	*179*		
Physical component summary	41.3 (10.5)	43.4 (10.5)*	44.8 (10.4)*#	44.7 (10.6) †	**<0.001**	42.1 (10.5)	44.2 (10.3)	45.4 (10.4)	45.4 (10.9)	40.1 (10.4)	42.1 (10.6)	44.0 (10.5)	43.7 (10.1)	0.10	0.23
Mental component summary	46.8 (11.9)	48.3 (11.3)*	48.6 (11.1)#	49.2 (10.1)	**<0.001**	46.0 (11.7)	47.2 (11.2)	48.5 (10.5)	48.9 (9.5)	48.0 (12.0)	50.0 (11.3)	48.8 (11.9)	49.6 (10.9)	0.21	0.10

*The data comprise raw test outcomes and are presented as mean (standard deviation) or n (%). Physical activity from the IPAQ-SF was expressed as MET-minutes/week using the formula: (3.3*walking minutes*walking) + (4.0*moderate-intensity activity minutes*moderate days) + (8.0*vigorous-intensity activity minutes*vigorous-intensity days). Employment status is presented for patients with a paid job pre-COVID-19. Categorical outcomes on the mMRC dyspnea scale, IFIS, and recovery status, and the domain scores in EQ-5D-5L and SF-36 questionnaires are presented in* ***Supplementary Table S3A-S3B****. P values are obtained from Generalized Estimating Equations analysis, a P value less than 0.00417 was considered statistically significant and is indicated in bold.* * *indicates a significant difference as compared to the previous study visit,* # *indicates a significant difference between the 3-month and 1-year study visits, and* † *between the 6-month and 2-year study visits. PROMs, Patient-Reported Outcome Measures; ICU, Intensive Care Unit; FAS, Fatigue Assessment Scale; mMRC, Modified Medical Research Council dyspnea scale; HADS-A, Hospital Anxiety and Depression Scale-subscale Anxiety; HADS-D, Hospital Anxiety and Depression Scale-subscale Depression; IES-R, Impact of Event Scale-Revised; PTSD, Posttraumatic Stress Disorder; CFQ, Cognitive Failures Questionnaire; PSQI, Pittsburgh Sleep Quality Questionnaire; BI, Barthel Index; IFIS, International Fitness Scale; IPAQ-SF, International Physical Activity Questionnaire-Short Form; MET, Metabolic Equivalent of Task; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; iPCQ, iMTA Productivity Cost Questionnaire; HRQoL, Health-Related Quality of Life; EQ-5D-5L, 5-level EuroQoL-5D questionnaires; EQ-VAS, EQ-Visual Analogue Scale; SF-36, 36-item Short Form Health Survey.*

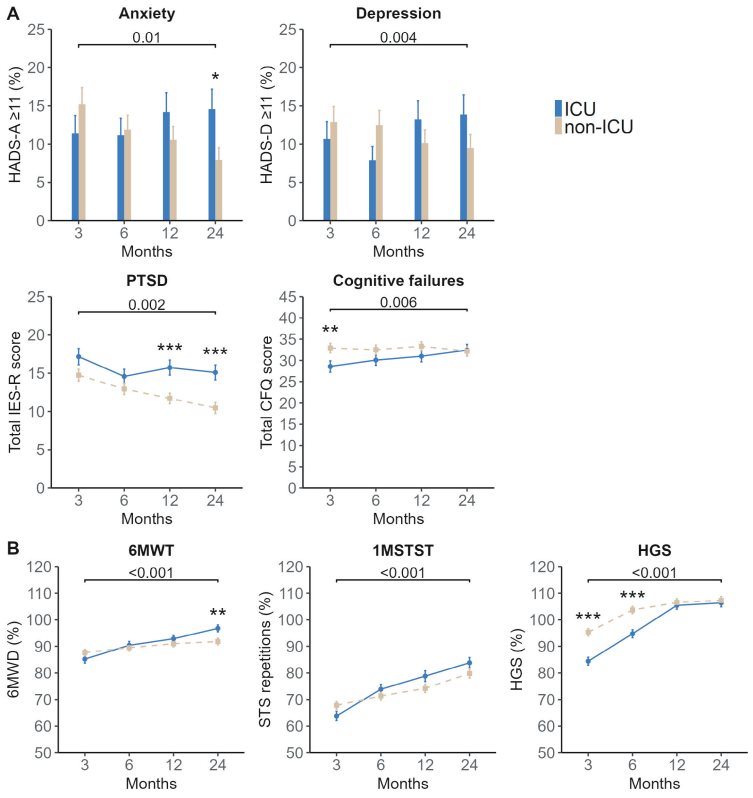

Figure 2. Trajectories of A: mental health and cognition and B: physical function in ICU- and non-ICU-treated patients for COVID-19 up to 2 years after hospital discharge.

Data are presented as estimated proportions or estimated means with standard errors obtained from Generalized Estimating Equations analysis. ***A*** *Estimated proportions (patients with HADS-A ≥11 and HADS-D ≥11) and estimated means (total IES-R score and total CFQ score) are adjusted for age and sex, the fixed value for age was 60 years.* ***B*** *Data are presented as the percentage of normative values reached in 6MWT, 1MSTST, and HGS. Normative values in 6MWT are calculated using sex-, age-, height-, and weight-stratified equations described by Enright and Sherill,[45] in 1MSTST using sex- and age-stratified reference values described by Strassman and colleagues,[46] and in HGS using sex- and age-stratified reference values described by Dodds and colleagues.[47] We compared the 2-year trajectories between the ICU and non-ICU groups and the P value is presented above the horizontal brackets in each panel. A significant group difference at each time point is indicated by *<0.05, **<0.01, and ***<0.001. Within group trajectories are further presented in* ***Supplementary Table S4****. ICU, Intensive Care Unit; HADS-A, Hospital Anxiety and Depression Scale-subscale Anxiety; HADS-D, Hospital Anxiety and Depression Scale-subscale Depression; IES-R, Impact of Event Scale-Revised; CFQ, Cognitive Failures Questionnaire; 6MWT, 6 Min Walk Test; 6MWD, 6 Min Walk Distance; 1MSTST, 1 Min Sit-To-Stand Test; STS, Sit-To-Stand; HGS, Handgrip Strength.*

Objective study measurements

Total cohort

Cognitive and physical function, except for the DEMMI, outcomes improved significantly over time in the total cohort (**Supplementary Table S5**). At 2 years, 12% (57/464) of patients had cognitive

deficits and patients reached 95% of norm in 6MWD, 83% in 1MSTST, and 108% in HGS, and the mean DEMMI score was 89/100.

ICU- vs. non-ICU-treated patients

On average, the ICU group had a significantly higher proportion of patients with desaturation ≥4% during the 6MWT (p<0.001) and a lower mean percentage of norm HGS (p=0.002) than the non-ICU group (**Supplementary Table S5**). Over time, the ICU group showed significantly more improvement in the percentages of norm reached in the 6MWT (estimated mean difference 7.7% [95%CI 4.8 to 10.7], p<0.001), 1MSTST (8.0% [3.7 to 12.3], p<0.001), and HGS (10.0% [6.3 to 13.7], p<0.001) compared to the non-ICU group (**Figure 2B**); trajectories of cognitive function and DEMMI scores were comparable (**Supplementary Table S5**). At 2 years, the ICU group reached significantly higher levels in the percentage of norm 6MWD (estimated mean 96.7% [1.3] vs. 91.4% [1.3], p=0.003) than the non-ICU group, but not in other cognitive and physical outcomes.

Routine follow-up data

The PFT parameters and radiographic abnormalities for the total cohort at each visit are shown in **Supplementary Table S6**. Patients without signs of residual radiological or pulmonary function abnormalities were discharged from regular follow-up (**Supplementary Figure S1**). Fifty-five patients with poor initial pulmonary recovery underwent repeated PFT and radiographic imaging up to 2-year follow-up, showing significant continuous improvement in PFT parameters and radiographic abnormalities, however the latter was not significant after Bonferroni correction (**Supplementary Table S7**).

Risk factors for long-term health problems after COVID-19

Over time (overall p<0.001), the percentage of patients reporting complete recovery from COVID-19 increased; patients with pre-existing pulmonary disease were less likely to recover completely (OR 0.43 [95%CI 0.26 to 0.73], p=0.002) (**Figure 3**). No other factors were associated with complete recovery; recovery status did not differ between ICU- and non-ICU-treated patients. Forest plots presenting risk factors for fatigue, cognitive failures, sleep quality, and HRQoL are shown in **Supplementary Figure S2**. Female sex (beta 3.0 [95%CI 1.4 to 4.6], p<0.001), pre-existing cardiovascular disease (1.9 [0.5 to 3.4], p=0.008), and pulmonary disease (3.7 [2.1 to 5.3], p<0.001) were associated with more fatigue; longer follow-up time (overall p<0.001) and older age (-0.10 [-0.18 to -0.01], p=0.03) with less fatigue (**Supplementary Figure S2A**). Female sex (7.5 [4.1 to 11.0], p<0.001) and pre-existing pulmonary disease (7.6 [4.3 to 10.9], p<0.001) were associated with more cognitive failures, older age (-0.22 [-0.39 to -0.05], p=0.01) and pre-existing obesity (-3.1 [-6.1 to -0.002], p=0.05) with less cognitive failures (**Supplementary Figure S2B**). Female sex (1.8 [1.1 to 2.5], p<0.001), non-European background (1.1 [0.3 to 1.9], p=0.008), and pre-existing pulmonary disease (1.3 [0.6 to 2.0], p<0.001) were associated with poorer sleep quality, longer follow-up time with better sleep quality (overall p=0.01) (**Supplementary Figure S2C**). Female sex (-0.04 [-0.08 to -0.002], p=0.04), non-European background (-0.05 [-0.09 to -0.002], p=0.04), being unemployed (vs. employed, -0.07 [-0.12 to -0.02], p=0.009), pre-existing cardiovascular disease (-0.04 [-0.08 to -0.01], p=0.02), pre-existing pulmonary disease (-0.11 [-0.15 to -0.06], p<0.001), and a longer hospital stay

(-0.001 [-0.002 to <-0.001], p=0.05) were associated with poorer HRQoL, and a longer follow-up time (overall p<0.001) with better HRQoL (**Supplementary Figure S2D**).

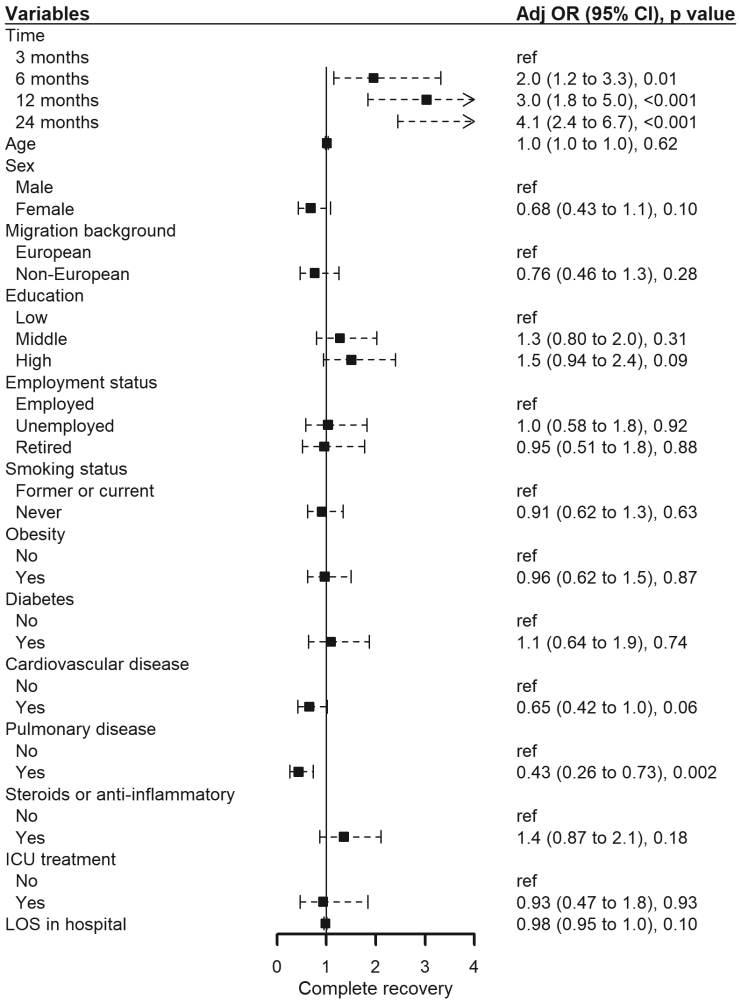

Figure 3. Forest plot presenting risk factors for self-reported recovery status from COVID-19.
Data are obtained using multivariable Generalized Estimating Equations analysis. Recovery status from COVID-19 was assessed with the Core Outcome Measure for Recovery.[22] Recovery was dichotomized into complete recovered and not complete recovered (not recovered at all, somewhat recovered, half recovered, or mostly recovered). Adj OR, Adjusted Odds Ratio; CI, Confidence Interval; ICU, Intensive Care Unit; LOS, Length Of Stay (in days).

Discussion

In this multicenter cohort study we comprehensively evaluated long-term health outcomes in 650 patients hospitalized for COVID-19 up to 2 years post-discharge, including a comparison between ICU- and non-ICU-treated patients. Many health outcomes improved over time. Nonetheless, 73% of the patients had not completely recovered from COVID-19 at 2 years. Despite good physical recovery in most patients, long-term neurocognitive complaints, dyspnea, fatigue, and poor sleep quality persisted in many. ICU-treated patients tended to show slower recovery of neurocognitive symptoms, mental health outcomes, and resumption of work compared to non-ICU-treated patients, while showing more improvements in physical outcomes. Yet, overall, outcomes were comparable between groups at 2-year follow-up. Particularly female sex and pre-existing pulmonary disease were risk factors for poorer health outcomes.

In line with our previous findings,[50] we found that ICU-treated patients showed more improvements in physical tests than non-ICU-treated patients. ICU-treated patients had the poorest post-discharge outcomes, with a higher potential for improvement. Moreover, they generally had good prior performance status, allowing them to survive ICU treatment. Last, most ICU-treated patients received intensive rehabilitation,[50] resulting in reaching (near) normative levels over time, comparable to the total cohort, which may suggest adequate physical rehabilitation.

As for mental health, ICU-treated patients showed slower recovery in PTSD and there was a tendency toward increasing proportions of anxiety and depression over time compared with non-ICU-treated patients, in line with our previous findings[51] and those of another COVID-19 post-ICU cohort describing deteriorating mental health outcomes from 1 to 2 years of follow-up.[52] Thus, ICU-treated patients may require extended monitoring for long-term mental health issues beyond 2 years potentiating timely interventions.

Regarding neurocognitive problems, the proportion of patients with cognitive failures and symptoms of memory or concentration problems was comparable between groups at 2 years, being prevalent in our entire study group. However, cognitive failures tended to increase over time in ICU-treated patients, as did self-reported memory and concentration problems. Moreover, ICU-treated patients had significantly more difficulties resuming work, building on previous findings,[53] potentially related to this higher neurocognitive symptom burden.[54]

Our findings may suggest unmet needs regarding neurocognitive rehabilitation, emphasizing the need for further development of COVID-19 aftercare strategies. Notably, in the Netherlands, COVID-19 care pathways primarily anticipated physical problems, in contrast to mental and cognitive problems. As for future pandemics, proactive strategies using a comprehensive assessment of physical, mental, and cognitive functioning should be considered in aftercare strategies.

ICU treatment was not an independent risk factor for the selected long-term health problems in our study. In contrast, several studies have shown that more severe acute COVID-19 is associated with a

higher risk for health problems beyond 1 year.[4,17] This discrepancy may be attributed to heterogeneity in study populations, methodologies, and measurements. The increased rate of persistent complaints in ICU-treated patients is frequently attributed to the superimposed effects of the PICS. However, similar long-term health problems are also experienced by patients with a mild SARS-CoV-2 infection, who do not require ICU admission or hospitalization.[55] Therefore, it seems less plausible to attribute these long-term health problems to PICS.[56]

The most important determinants for long-term health problems were female sex and pre-existing pulmonary disease. We consistently[4,16] identified female sex as major risk factor, except for self-reported complete recovery. Contrary, the PHOSP-COVID study did find a negative association between female sex and complete recovery 1 year after hospitalization.[2] This difference may resolve beyond 1 year or be due to using a different recovery scale. As for underlying pulmonary disease, some studies showed that particularly patients with asthma are at risk for poorer health outcomes after COVID-19;[16] unfortunately, our data did not allow differentiation of pulmonary diseases to assess this into more depth.

Last, we found non-European migration background to be associated with poorer sleep quality and HRQoL, but not with other health outcomes. A few studies on health problems after COVID-19 suggest that ethnic minorities are disproportionately impacted, but data from European countries are scarce.[57] As we do not unequivocally find a relation between migration background and the assessed health outcomes, it remains unclear whether the found associations were COVID-19 specific, or attributable to pre-existing social and health inequalities, and thus requires further study.

Overall, the vast majority of our patients (88%) reported at least one new or worsened COVID-19-related symptom 2 years post-discharge, compared to 55% to 84% in other reports.[4,13] Consistently, impaired fitness, neurocognitive problems, fatigue, dyspnea, poor sleep quality, and reduced HRQoL were identified as most prominent health problems 2 years after hospitalization for COVID-19.[4,13,58]

Noteworthy, we observed some discrepancies between self-reported symptoms and objectively assessed outcomes, such as between dyspnea and pulmonary function, self-reported muscle weakness and HGS, and self-reported impaired fitness and objectively assessed aerobic capacity. Factors contributing to this disparity include individual interpretations and experiences of symptoms as well as insufficient understanding of the underlying biological etiology of persistent health problems after COVID-19. Self-reported measures might capture a broader range of sensations, whereas objective tests often focus on specific aspects of functioning. Nonetheless, the subjective experience of health problems is essential as it reflects the extent to which they hinder daily functioning and highlights the need for a better understanding of the etiology of the persistent problems.[59]

Strengths of this study include its prospective multicenter design with 2-year follow-up of a large cohort of ICU- and non-ICU-treated patients, the comprehensive evaluation of both PROMs and objective measures, and high response rate (78% [509/650]) up to 2 years. We were able to perform multivariable analyses to identify risk factors for prominent health problems. Study limitations include

the absence of control groups of individuals without COVID-19 and non-hospitalized individuals with COVID-19 and the inability to compare our outcomes with pre-COVID-19 levels, only to the first assessment and reference values. Since most patients were unvaccinated against COVID-19 prior to hospital admission, our findings might be less generalizable to those who had been vaccinated beforehand, as vaccination appears to reduce the risk of long-term health problems.[60] Selection bias might play a role in our study as we included a higher percentage of ICU patients (42%), due to high inclusion rate from an academic hospital, compared to the average ICU admissions across all Dutch hospitals (14%) which limits the representativeness of our cohort and might overestimate poor outcomes. However, this allowed for comparison between ICU- and non-ICU-treated patients on long-term health outcomes. We observed no noticeable disparity on health outcomes at 2 years between these groups; therefore, overestimation of poor outcomes is unlikely to play a major role. In addition, we lack data on the eligible recruitment population due to the surge of patients admitted to the participating centers. However, recruitment of study participants occurred independently of the patient's recovery status and primarily depended on availability of research personnel. Moreover, our participant characteristics align with those of the average Dutch patients hospitalized for COVID-19.[18] Also, as one of the inclusion criteria was sufficient knowledge of the Dutch or English language, ethnic minorities are somewhat underrepresented in our study compared to the demographics of the recruitment area. Nonetheless, the ethnic minority group still comprised 29% of the participants allowing for assessment of differences between ethnicity groups. Furthermore, severity of symptoms was only assessed at the 2-year follow-up, after we concluded that given the high prevalence of persisting symptoms, a more detailed longitudinal assessment would have been beneficial.

In conclusion, most health outcomes improved over the 2 years after hospitalization for COVID-19. Nonetheless, many patients suffer from long-term health problems, with neurocognitive symptoms, dyspnea, fatigue, and poor sleep quality among the most frequent problems at 2 years and a significant proportion of patients still report incomplete recovery. Despite slower recovery in some outcomes, most 2-year health outcomes were comparable between ICU- and non-ICU-treated patients. Generally, while physical rehabilitation seems adequate, there is a need for targeted aftercare strategies addressing a variety of long-term problems and continuous research into effective treatments, including more tailored rehabilitative support and pharmacological treatment options. Moreover, our study underlines the importance of prolonged follow-up to monitor recovery from COVID-19 beyond 2 years. Therefore, we extended our study with yearly follow-up, addressing in particular the main persisting health problems.

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Chapter 7

Trajectories of device-assessed physical activity and sleep in ICU- and non-ICU-treated patients up to 2 years after hospitalization for COVID-19, and their association with HRQoL

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*** Listed in Appendix

Submitted.

Abstract

Background COVID-19 may affect physical and sleep behaviors, but device-assessed data are scarce. We explored 2-year trajectories of device-assessed physical and sleep behaviors post-hospitalization, comparing intensive care unit (ICU) treated patients and non-ICU-treated patients, and their association with health-related quality of life (HRQoL).

Methods Patients wore a wrist-worn accelerometer for 7 days at 3-6, 12, and 24 months post-hospitalization. Physical behavior: physical activity volume, time spent in light (LIPA) and moderate-to-vigorous physical activity (MVPA), and inactivity. Sleep behavior: sleep duration, efficiency, and sleep regularity index (SRI). HRQoL was assessed with the EQ-5D-5L questionnaire. Multivariable GEE models were used to assess trajectories, and associations of physical activity and sleep duration with HRQoL adjusted for baseline characteristics and health outcomes.

Results We recruited 358 patients hospitalized for COVID-19 (mean age 59.7±10.5 years, 246 [69%] males, 137 [38%] ICU-treated). Estimated mean physical activity volume was 23.5 mg/day (SE 0.40), spending 153.5 minutes (2.6) in LIPA, 32.6 minutes (1.4) in MVPA, and 10.8 hours (0.07) inactive at 3-6 months. Sleep duration was 6.9 (0.05) hours/night, efficiency 71.1% (0.40), and SRI 52.7% (0.72). These outcomes did not change significantly over time in the entire cohort, but ICU-treated patients started with less physical activity, showing significantly greater improvements between 3-6 months and 1 year visits than non-ICU-treated patients, estimated mean difference MVPA 6.2 minutes [1.7 to 10.6], p=0.007. Such difference was also found for SRI (3.1% [0.38 to 5.8], p=0.03), but not for sleep duration and efficiency. MVPA was significantly associated with HRQoL ($\beta_{adjusted}$ 0.08 [0.04 to 0.12], p<0.001).

Conclusion Device-assessed physical and sleep behaviors seemed generally sufficient up to 2 years post-hospitalization for COVID-19 and did not change over time. However, ICU-treated patients started with less physical activity, which improved over the first year post-discharge reaching the levels of non-ICU-treated patients, likely reflecting recovery from critical illness. Less time spent in MVPA was associated with poorer HRQoL, even after adjusting for covariables.

Introduction

Many patients hospitalized for COVID-19 experience long-lasting health problems, persisting for months or even years after the acute infection.[1-3] The symptoms are diverse and often co-occurring across the physical, cognitive, and psychological domains, affecting health-related quality of life (HRQoL).[4] Although long-term health effects of COVID-19 can occur regardless of the severity of acute illness, hospitalization and intensive care unit (ICU) admission are associated with a higher risk of long-term health problems.[4,5]

Many diseases affect people's physical activity and sleep; therefore, it can be assumed that patients hospitalized for COVID-19 may also face difficulties in resuming physical and sleep behaviors. However, these behaviors are still poorly understood in this population. Furthermore, studies assessing these behaviors have mainly relied on questionnaires, suggesting reduced physical activity and poor sleep quality after COVID-19.[6,7] At the same time, research shows a weak relationship between self-reported and device-assessed measures of physical activity and sleep.[8] Device-based instruments can more validly monitor physical and sleep behaviors and are less prone to biases.

The few studies using device-based assessments of physical activity and sleep in patients previously hospitalized for COVID-19 were primarily cross-sectional and within the first year after hospital discharge.[9-14] Two studies reported low levels of physical activity and disrupted sleep patterns 2-7 months after hospitalization for COVID-19.[9,10] A longitudinal study reported persistent circadian alterations up to 12 months follow-up, but focused on ICU-treated patients only, with few patients having repeated assessments.[12-14] Given the limited number of studies and lack of long-term longitudinal assessments in a broad cohort, this study assessed 2-year trajectories of physical and sleep behaviors following hospitalization for COVID-19. Furthermore, we previously found that ICU-treated patients for COVID-19 were more physically impaired than non-ICU-treated patients after hospitalization, showing lower levels of objectively assessed physical fitness.[3] Therefore, comparing these groups' trajectories of physical and sleep behaviors could determine whether a similar pattern exists.

Regular physical activity, particularly moderate-to-vigorous physical activity (MVPA), and good sleep are well-established contributors to overall health and well-being.[15-18] Many patients experience persistent health complaints and reduced health-related quality of life (HRQoL) after hospitalization for COVID-19. However, the impact of device-assessed physical activity and sleep on HRQoL after COVID-19 is unknown.

We aimed to assess trajectories of device-assessed physical and sleep behaviors up to 2 years after hospitalization for COVID-19, including comparisons between ICU- and non-ICU-treated patients. Additionally, we explored whether physical activity and sleep duration are associated with HRQoL.

Methods

Study design and participants

The "COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system" (CO-FLOW) study is a two-year multicenter prospective cohort study conducted in the Rotterdam–Rijnmond–Delft region of the Netherlands. The study was performed in 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities). Between July 2020 and October 2021, we included adult patients hospitalized with confirmed COVID-19 with sufficient knowledge of Dutch or English and within 6 months after hospital discharge. Incapacitated patients (e.g., dementia) were not included. More information about the CO-FLOW study design can be found elsewhere.[19] The CO-FLOW study was approved by the Medical Ethics Committee of Erasmus MC (MEC-2020-0487). This study has been prospectively registered in the International Clinical Trial Registry Platform (NL8710). All participants provided written informed consent before the start of study measurements. Here, we present longitudinal device-assessed physical and sleep behaviors in a subsample of the CO-FLOW study participants.

Procedures

Study visits were scheduled around 3, 6, 12, and 24 months after hospital discharge and, when possible, alongside the clinical follow-up for COVID-19 in the participating hospitals. Patients discharged from clinical follow-up were invited to visit the Erasmus Medical Center (MC) for the remaining study visits. We arranged a home visit for patients unwilling or unable to visit the Erasmus MC. From mid-October 2020 onward, a subgroup of the CO-FLOW study participants was invited during their 3- or 6-month visit to wear a wrist-worn accelerometer for the next 7 consecutive days to measure physical and sleep behaviors. Participation was solely based on the availability of devices at the study visit; there were no additional patient in- or exclusion criteria. Patients who wore the device at the 3- or 6-month visit were repeatedly invited to wear one at the 12-month and 24-month visits. Participants received the device with instructions during the study visit or by post if they could not attend the visit. Participants were instructed to wear the device on their dominant wrist[20] immediately upon receiving it, to wear it continuously or as much as possible as non-wear will lead to invalid data. They were told they could perform all kinds of activities as the device was waterproof. The accelerometer assessment period started at 7 PM on the day of study assessments for 7 continuous days of 24 hours. Participants were asked to return the device in a prepaid envelope after the 7 days**.** Baseline demographic and clinical characteristics during hospital admission were retrospectively collected from medical records at the participating facilities and during the study visits, which were stored in the Castor Electronic Data Capture system (Castor EDC, Amsterdam, the Netherlands).

Accelerometer assessments

We used the wrist-worn GENEActiv tri-axial accelerometer (GENEActiv; Activinsights Ltd, Kimbolton, Cambridgeshire, UK). Accelerometer data were sampled at 100Hz, with acceleration expressed relative to gravity (g units, 1 g = 9.81 m/s^2). The raw accelerometer data were extracted using GENEActiv PC software V.3.2 and processed using the R-package GGIR version 3.1-0 in R.[21-23] The auto-calibration method by van Hees et al.[24] was used to correct for the sensor calibration error. We used the Euclidean Norm of raw accelerations Minus One (ENMO), with negative values rounded to zero and ENMO values averaged over 5-second epochs, to quantify movement and express it in milligravity (mg).[25] Sleep episodes were identified using a validated GGIR algorithm guided by the sleep log, and individual nights with not enough valid accelerometer data (cleaning code higher than 1) were excluded.[26] Non-wear among valid days was imputed by the default settings in GGIR, taking the average of all valid data on similar time points on other days. Accelerometer measurements of ≥16 h/day were considered valid. Participants were included in the analysis if their wear times during the waking window and sleep period time window (SPT-window) each corresponded to ≥2/3 (non-wear <33.3%) of the respective windows for at least 3 days or nights, respectively.[27] Complete valid wear resulted in 6 days (waking-to-waking windows) and 7 nights (from sleep onset at night to the following wake up to start the day) per participant.

Physical behavior: The average acceleration in mg was used as a proxy for physical activity volume. Physical behavior included physical activity and inactivity (indicative of sedentary behavior), all obtained for each waking window per day.[28,29] Physical activity was categorized by intensity, including light PA (LIPA; 40-100 mg) and moderate-to-vigorous physical activity (MVPA; acceleration ≥100 mg). LIPA and MVPA were expressed in minutes. MVPA was further accumulated in ≥1-minute bouts, retaining activities lasting at least 1 minute, for which 80% of the activity met the 100 mg threshold criteria. The time spent in inactivity (<40 mg) was expressed in hours.

Sleep behavior: Outcomes were obtained for each SPT-window using a validated automated sleep detection algorithm without using sleep diaries.[30] The total sleep duration was expressed in hours, which was defined by no change in arm angle greater than 5° for ≥5 minutes. Sleep efficiency was defined as the ratio between the total sleep duration and the SPT-window duration, expressed as a percentage. The sleep regularity index (SRI) is the probability of an individual being in the same state (asleep vs. awake) at any two time points 24 hours apart and was expressed in a percentage ranging between 0 (random pattern) and 100 (perfect regularity, identical days).[31]

Patient-reported outcome measures

Health-related quality of life was measured on 5 domains and 5-levels with the EuroQoL (EQ-5D-5L) questionnaire, which includes the EQ-5D index.[32] We multiplied the EQ-5D index with factor 100 in this study, with 0 indicating death and 100 perfect health; negative scores indicate a health status worse than death.

Additionally, we assessed outcomes of fatigue, anxiety, depression, and cognitive failures during follow-up visits. Fatigue was assessed with the Fatigue Assessment Scale (FAS), a total score ranging from 0-50.[33] Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS), with the subscale scores for anxiety and depression ranging from 0-21.[34] Cognitive failures were assessed with the Cognitive Failures Questionnaire (CFQ), a total score ranging from 0-100.[35,36]

Baseline characteristics

Patient demographic and clinical characteristics at the time of hospital admission were collected. These included age, sex, body mass index (BMI, in kg/m^2), migration background, education level, employment status, smoking status, comorbidities, and the in-hospital characteristics treatment for COVID-19, thrombosis, delirium, ICU treatment, and the length of stay in ICU and in the hospital. Pre-COVID-19 leisure time physical activity level (inactive, light, moderate, or vigorous) was assessed using the Saltin−Grimby Physical Activity Level Scale (SGPALS) questionnaire at the first follow-up visit.[37] BMI was also measured at follow-up visits.

Statistical analysis

Participants with at least one valid follow-up measurement of physical or sleep behaviors were included in the analysis. Continuous variables are presented as mean with standard deviation and median with interquartile range (IQR) and categorical variables as number with percentage. Accelerometer outcomes were averaged over the valid measured days during the 7 days, resulting in averaged daily estimates for each participant. The first accelerometry assessment was conducted at either the 3- or 6-month follow-up visit, and we included the questionnaire outcomes corresponding to that visit in the analysis. Group comparisons were performed using the Mann-Whitney U test or Chi-squared test.

We used Generalized Estimating Equations (GEE) analyses with repeated measurements for linear models using an unstructured working correlation matrix to assess trajectories of device-assessed outcomes of physical and sleep behaviors. The GEE is a semi-parametric approach that considers within- and between-subject correlations and uses all available measurements despite incomplete data. For the total cohort analysis, we entered measurement time (3-6, 12, and 24 months) as a fixed factor in the GEE analyses to assess the outcomes of interest over time. To evaluate the effect of ICU treatment for COVID-19 on these outcomes, we additionally entered group (ICU vs. non-ICU) and an interaction term of group with time into the model, adjusted for covariables. These covariables included age and sex (female vs. male) and other patient characteristics that differed significantly between these groups at hospital admission (i.e., migration background [non-European vs. European] and BMI). BMI was incorporated into the analysis as a time-varying variable. We also used linear GEE models to assess relationships between physical activity and sleep with HRQoL (EQ-5D index) over time. We added measurement time and the time-varying variables LIPA, MVPA, and sleep duration into separate univariable models to evaluate their association with HRQoL. Then, we analysed these variables together in a multivariable model to further explore their independent association

with HRQoL while adjusting for covariables. Two models were explored; time, age, and sex were always incorporated in the multivariable models. In model 1, potential confounders included baseline characteristics (migration background, education level, employment, leisure time physical activity level, BMI, the most prevalent [diabetes, cardiovascular disease, and pulmonary disease], ICU admission, and length of hospital stay) at hospital admission, except for BMI (time-varying variable). Variables significantly associated (Spearman's rank correlation) with MVPA at 3-6 months were entered into the multivariable model 1. In model 2, we explored the additional adjustment for time-varying health outcomes, including fatigue (FAS score), cognitive failures (CFQ score), anxiety (HADS-A score), and depression (HADS-D score). Model parameters are presented as adjusted estimated mean with standard error or adjusted estimated mean difference with corresponding 95% confidence interval (CI) and p-value. A p-value <0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA).

Results

Of the 650 CO-FLOW study participants, 375 were invited to wear an accelerometer device at the 3- or 6-month visit, of whom 17 declined. Patients with accelerometer measurements were invited for repeated measurements at the 1- and 2-year visits. In total, 358 patients had valid data available at one or more time points and were included in the final analysis (**Figure 1**). All patients were discharged from the hospital between March 26th, 2020, and June 1st, 2021, of whom 137 (38%) patients received ICU treatment for COVID-19. **Table 1** presents the baseline characteristics of participants at hospital admission. The median age of patients was 60.5 [53.0-67.0] years, and 246/358 (69%) were male. Baseline characteristics did not differ significantly between CO-FLOW participants included in the final analysis (n=358) and those not (n=292, composed of patients who were not invited or who declined the invitation), except that participants in the analysis received more frequently COVID-19 treatment (83% vs. 75%) and were less often admitted to the ICU for COVID-19 (38% vs. 57%) (**Supplementary Table S1**).

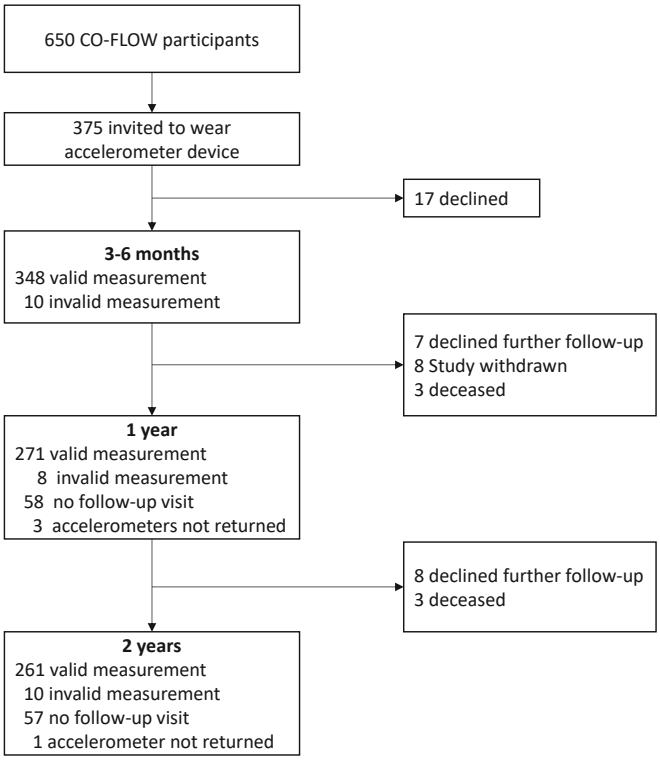

Figure 1. Study flowchart. In total, 358 participants had valid accelerometer data at one or more follow-up visits and were included in this study, including 137 (38%) intensive care unit (ICU) treated patients and 221 (62%) non-ICU-treated patients. Patients declined further accelerometer assessments during follow-up for various reasons, including skin rashes, inability to wear the device at work, and unwillingness to wear it.

Table 1. Baseline characteristics of study participants.

	N[a]	All (n=358)	Non-ICU (n=221)	ICU (n=137)	P value
Patient characteristics					
Age, years		59.7±10.5	60.1±10.2	59.2±11.0	0.99
Mean		60.5 (53.0-67.0)	60.0 (53.0-67.0)	61.0 (54.0-67.0)	
Median					
Sex, male		246 (69%)	144 (65%)	102 (74%)	0.07
BMI, kg/m^2	330	29.2 (5.4)	28.7±5.3	30.1±5.6	**0.01**
Mean		28.2 (25.6-32.1)	27.6 (25.2-31.3)	29.0 (26.3-33.1)	
Median					
Migration Background					**0.03**
European		266 (74%)	173 (78%)	93 (68%)	
Dutch Caribbean		52 (14%)	25 (11%)	27 (20%)	
Asian		17 (5%)	10 (5%)	7 (5%)	

Table 1. Continued.

	N[a]	All (n=358)	Non-ICU (n=221)	ICU (n=137)	P value
Turkish		10 (3%)	5 (2%)	5 (4%)	
(North) African		13 (4%)	8 (4%)	5 (4%)	
Education[b]	356				0.54
Low		116 (33%)	75 (34%)	41 (30%)	
Middle		127 (36%)	74 (33%)	53 (39%)	
High		113 (32%)	72 (33%)	41 (30%)	
Employment	357				0.88
Employed		224 (63%)	137 (62%)	87 (64%)	
Unemployed		54 (15%)	35 (16%)	19 (14%)	
Retired		79 (22%)	49 (22%)	30 (22%)	
Smoking status					0.66
Never		162 (45%)	98 (44%)	64 (47%)	
Former		189 (53%)	117 (53%)	72 (53%)	
Current		7 (2%)	6 (3%)	1 (1%)	
Physical activity level[c]					
Inactive		44 (12%)	33 (15%)	11 (8%)	0.14
Light		187 (52%)	108 (49%)	79 (58%)	
Moderate		105 (29%)	68 (31%)	37 (27%)	
Vigorous		22 (6%)	12 (5%)	10 (7%)	
Comorbidities					
≥1		291 (81%)	179 (81%)	112 (82%)	0.86
Obesity (BMI≥30 kg/m^2)		139 (39%)	74 (33%)	65 (47%)	**0.01**
Diabetes		77 (22%)	48 (22%)	29 (21%)	0.90
Cardiovascular disease or hypertension		148 (41%)	92 (42%)	56 (41%)	0.89
Pulmonary disease		83 (23%)	52 (24%)	31 (23%)	0.85
Renal disease		32 (9%)	20 (9%)	12 (9%)	0.93
Gastrointestinal disease		14 (4%)	7 (3%)	7 (5%)	0.36
Neuromuscular disease		37 (10%)	27 (12%)	10 (7%)	0.14
Malignancy		41 (12%)	28 (13%)	13 (9%)	0.36
Autoimmune/inflammatory disease		41 (12%)	30 (14%)	11 (8%)	0.11
Mental disorder		20 (6%)	12 (5%)	8 (6%)	0.87
In-hospital characteristics					
COVID-19 wave[d]					
First		79 (22%)	24 (11%)	55 (40%)	**<0.001**
Second		188 (53%)	135 (62%)	53 (39%)	

Table 1. Continued.

	N[a]	All (n=358)	Non-ICU (n=221)	ICU (n=137)	P value
Third		91 (25%)	62 (28%)	29 (21%)	
COVID-19 directed treatment					
None		60 (17%)	28 (13%)	32 (23%)	**0.01**
(Hydroxy)chloroquine		6 (2%)	0 (0.0)	6 (4%)	
Steroids		272 (76%)	179 (81%)	93 (68%)	
Antivirals		65 (18%)	53 (24%)	12 (9%)	
Anti-inflammatory		44 (12%)	8 (4%)	36 (26%)	
Convalescent plasma		5 (1%)	4 (2%)	1 (1%)	
Thrombosis	351	63 (18%)	14 (6%)	49 (36%)	**<0.001**
Delirium	349	85 (24%)	7 (3%)	78 (57%)	**<0.001**
Requiring oxygen supplementation		345 (96%)	208 (94%)	137 (100%)	NA
Requiring high flow nasal cannula		113 (32%)	39 (18%)	74 (54%)	**<0.001**
ICU admission		137 (38%)	-	137 (100%)	NA
Invasive mechanical ventilation		122 (34%)	-	122 (89%)	NA
Length of intubation, days	117	19.8±16.1	-	19.8±16.1	NA
Mean		14.0 (8.0-27.0)	-	14.0 (8.0-27.0)	
Median					
Tracheostomy	353	44 (12%)	-	44 (32%)	NA
Length of ICU stay, days	135	22.4±18.6	-	22.4±18.6	NA
Mean		16.0 (9.0-31.0)	-	16.0 (9.0-31.0)	
Median					
Length of hospital stay, days		19.1±20.0	8.7 (6.8)	35.7±22.8	**<0.001**
Mean		11.0 (6.0-27.0)	7.00 (4.0-11.0)	30.0 (19.0-48.0)	
Median					

Data are at the time of hospital admission and are presented as number (%) unless indicated otherwise. The following variables were dichotomized for group comparison in statistical analysis: migration background as European vs. non-European groups, smoking status as never vs. former/current, and treatment as no treatment vs. any received treatment. P values are obtained using the Mann–Whitney U test or Chi-squared test as appropriate; a P value less than 0.05 was considered statistically significant and is indicated in bold. BMI Body Mass Index, ICU Intensive Care Unit, NA not applicable.

[a] *Adjusted n is presented for variables with a total number of patients less than 358.*

[b] *Education comprises low (primary or secondary education); middle (high school); high (postsecondary education or university).*

[c] *Pre-COVID-19 leisure time physical activity level was measured with the Saltin–Grimby Physical Activity Level Scale questionnaire.*[37]

[d] *Patients were classified by discharge date: the first COVID-19 wave (Feb–Jun 2020; original variant dominant), second wave (Jul 2020–Jan 2021; alpha variant dominant), and third wave (Feb–Jun 2021; beta and delta variants dominant).*

Device-assessed physical and sleep behaviors

Total cohort

Figure 2 shows the density plots of device-assessed physical and sleep outcomes in the total cohort at each visit. At 3-6 months, the estimated mean physical activity volume was 23.5 (SE 0.40) mg, spending 153.5 (2.6) minutes in LIPA and 32.6 (1.4) minutes in MVPA per day, while spending 10.8 (0.07) hours inactive. The estimated mean sleep duration was 6.9 (0.05) hours per night with an efficiency of 71.1% (0.40) and an SRI of 52.7 (0.72). Physical and sleep outcomes did not change significantly over time in the total cohort (**Figure 2**).

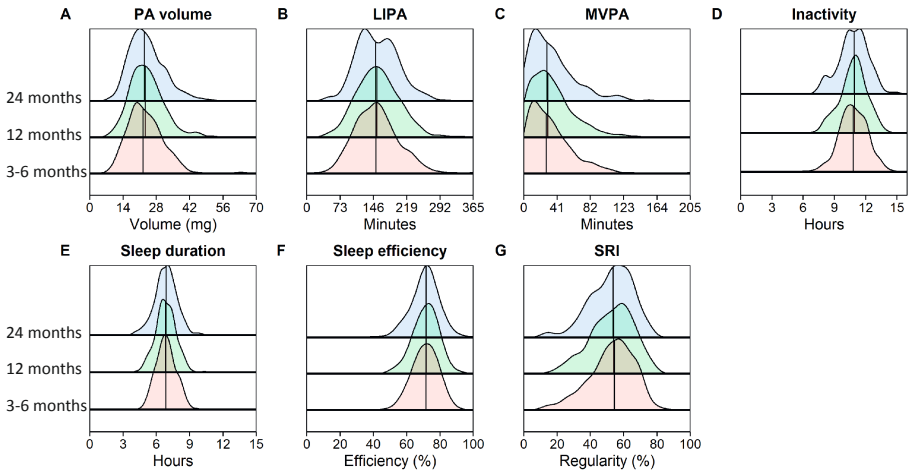

Figure 2. Density plots of device-assessed physical and sleep behaviors after hospitalization for COVID-19.
Data are presented for study visits at 3-6 months (red shaded area), 12 months (green shaded area), and 24 months (blue shaded area) after hospital discharge. In each density plot, the vertical lines represent the median value per visit. Generalized estimating equations analyses were performed to assess the effect of measurement time on each outcome of physical (A-D) and sleep (E-G) behaviors. These outcomes did not change significantly over time (all p>0.05). PA, physical activity; mg, milligravity; LIPA, light physical activity; MVPA, moderate-to-vigorous physical activity; SRI, sleep regularity index.

ICU- versus non-ICU-treated patients

Figure 3 shows the 2-year trajectories of device-assessed physical and sleep outcomes for ICU- and non-ICU-treated patient groups. Overall, outcomes did not differ significantly between groups at the between-group level, except that sleep efficiency was significantly lower in the ICU-treated patients than in non-ICU-treated patients (p=0.03). Over time, the trajectories of physical behavior differed significantly between groups. ICU-treated patients began with poorer physical outcomes, which were significantly different from those in non-ICU-treated patients for PA volume (p=0.02) and time spent in MVPA (p=0.04). They showed significantly greater increase in PA volume (estimated mean difference 2.5 mg [95% CI 1.4 to 3.6], p<0.001), time spent in LIPA (14.4 minutes [5.8 to 23.1], p=0.001) and MVPA (6.2 minutes [1.7 to 10.6], p=0.007), and a greater reduction in inactive time (-0.4 hours [-0.6 to -0.09], p=0.009), from 3-6 months to 1 year as compared to non-ICU-treated patients. For sleep, a similar pattern was found for SRI, with ICU-treated patients starting with

significantly lower SRI at 3-6 months (p=0.03), showing significantly greater increase (3.5% [0.8 to 6.3], p=0.01) than non-ICU-treated patients up to 1 year, but not for sleep duration and efficiency. Trajectories did not differ significantly between groups between the 1- and 2-year visits.

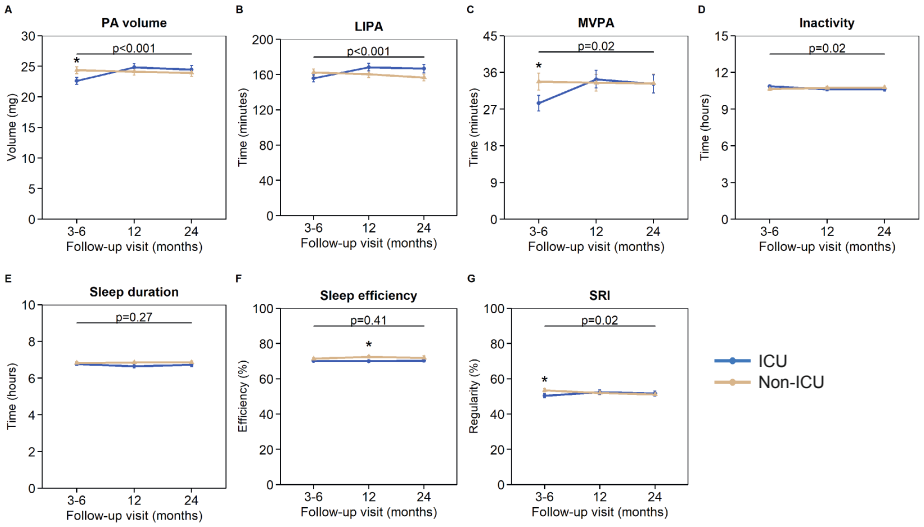

Figure 3. Trajectories of device-assessed physical and sleep behaviors after hospitalization for COVID-19.
*Data are presented as estimated mean with standard error. We used generalized estimating equations analysis to compare trajectories of physical (A-D) and sleep (E-G) variables between ICU- and non-ICU-treated patients, adjusted for age, sex, and migration background at the time of hospital admission and time-varying BMI. P values for comparing trajectories between groups are presented in each plot; * indicates a significant (p<0.05) group difference at the follow-up visit. ICU, intensive care unit; BMI, body mass index. PA: physical activity; mg, milligravity; LIPA, light physical activity; MVPA, moderate-to-vigorous physical activity; SRI, sleep regularity index.*

Association of LIPA, MVPA, and sleep duration with HRQoL

The EQ-5D index improved significantly over time in the total cohort, from an estimated mean of 77.3±1.2 at 3-6 months to 80.6±1.2 at 1 year and 79.5±1.2 at 2 years (p<0.001). In univariable analysis, time spent in MVPA was significantly associated with the EQ-5D index ($\beta_{adjusted}$ 0.17 [95% CI 0.13 to 0.21], p<0.001), whereas LIPA (0.028 [-0.002 to 0.06], p=0.06) and sleep duration (0.32 [-1.3 to 2.0], p=0.71) were not. In multivariable analyses, time spent in MVPA remained independent and significantly associated with the EQ-5D index in model 1 after adjusting for baseline characteristics (0.12 [0.07 to 0.17], p<0.001). In model 2, after further adjusting for health outcomes of fatigue, cognitive failures, anxiety, and depression (**Supplementary Table S2**), this association remained significant (0.08 [0.04 to 0.12], p<0.001) (**Table 2**).

Table 2. Multivariable models for the associations between device-assessed physical activity and sleep duration with HRQoL after hospitalization for COVID-19.

	Model 1 $\beta_{adjusted}$ (95% CI)	**P value**	**Model 2** $\beta_{adjusted}$ (95% CI)	**P value**
Device-assessed variables				
LIPA, minutes	-0.003 (-0.03 to 0.03)	0.98	0.01 (-0.02 to 0.04)	0.46
MVPA, minutes	0.12 (0.07 to 0.17)	**<0.001**	0.08 (0.04 to 0.12)	**<0.001**
Sleep duration, hours	-0.94 (-2.2 to 0.34)	0.15	-0.61 (-1.7 to 0.47)	0.27
Covariables				
Follow-up visit				
3-6 months	*Reference*		*Reference*	
1 year	3.3 (1.7 to 5.0)	**<0.001**	1.9 (0.34 to 3.5)	**0.02**
2 years	2.5 (-0.05 to 4.9)	**0.05**	0.92 (-1.2 to 3.0)	0.39
Age, years	0.04 (-0.2 to 0.3)	0.76	-0.10 (-0.27 to 0.07)	0.25
Sex				
Male	*Reference*		*Reference*	
Female	-5.8 (-10.5 to -1.1)	**0.01**	-1.8 (-5.4 to 1.8)	0.32
BMI	-0.14 (-0.54 to 0.26)	0.49	-0.11 (-0.42 to 0.21)	0.50
Education level				
Low	*Reference*		*Reference*	
Middle	-0.45 (-5.3 to 4.4)	0.86	-0.24 (-3.8 to 3.3)	0.90
High	2.4 (-2.3 to 7.1)	0.32	1.3 (-2.0 to 4.7)	0.45
Employment				
Employed	*Reference*		*Reference*	
Unemployed	-6.1 (-13.1 to 0.95)	0.09	-7.1 (-12.3 to -1.8)	**0.01**
Retired	5.8 (0.6 to 11.0)	**0.03**	2.2 (-1.3 to 5.7)	0.22
Physical activity level[a]				
Inactive/light	*Reference*		*Reference*	
Moderate/vigorous	0.93 (-3.0 to 4.8)	0.64	-0.07 (-3.0 to 2.9)	0.96
Diabetes				
No	*Reference*		*Reference*	
Yes	1.6)-3.7 to 6.9)	0.55	1.9 (-1.9 to 5.8)	0.32
Cardiovascular disease				
No	*Reference*		*Reference*	
Yes	-4.7 (-9.2 to -0.07)	**0.05**	-2.6 (-6.0 to 0.75)	0.13
Pulmonary disease				
No	*Reference*		*Reference*	
Yes	-9.3 (-14.8 to -3.9)	**<0.001**	-3.6 (-7.6 to 0.45)	0.08
Length of stay in hospital, days	-0.07 (-0.18 to 0.03)	0.16	-0.09 (-0.17 to -0.01)	**0.03**

Table 2. Continued.

	Model 1 $\beta_{adjusted}$ (95% CI)	**P value**	**Model 2** $\beta_{adjusted}$ (95% CI)	**P value**
Patient-reported health outcomes				
Fatigue (FAS total score)			-0.93 (-1.1 to -0.72)	**<0.001**
Cognitive failures (CFQ total score)			0.02 (-0.09 to 0.13)	0.73
Anxiety (HADS-A total score)			-0.70 (-1.17 to -0.22)	**0.004**
Depression (HADS-D total score)			-0.75 (-1.2 to -0.29)	**0.001**

Data are presented as adjusted β-coefficient with 95% CI, obtained from generalized estimating equations analysis using linear models for HRQoL (EQ-5D-5L index multiplied with factor 100). In model 1 (n=330), covariables included fixed patient characteristics at time of hospital admission, time-varying BMI, and the length of hospitalization for COVID-19. Model 2 (n=324) included model 1 and further adjustment for time-varying patient-reported health outcome of fatigue, cognitive failures, anxiety, and depression. A P value less than 0.05 was considered statistically significant and is indicated in bold. HRQoL, health-related quality of life; EQ-5D-5L, 5-level EuroQoL-5D questionnaire; LIPA, light physical activity; MVPA, moderate-to-vigorous physical activity; BMI, body mass index; CI, confidence interval; FAS, fatigue assessment scale; CFQ, cognitive failure questionnaire; HADS, hospital anxiety and depression scale with subscale scores for anxiety (A) and depression (D).

[a] *Pre-COVID-19 leisure time physical activity level was measured with the Saltin–Grimby Physical Activity Level Scale questionnaire.*[37]

Discussion

This multicenter prospective cohort study assessed 2-year trajectories of device-assessed physical and sleep behaviors following hospitalization for COVID-19. Overall, these behaviors seemed sufficient in the total cohort throughout follow-up. However, ICU-treated patients had lower physical activity levels at the first visit but improved over the first year post-discharge, reaching the levels of non-ICU-treated patients. While our findings preclude any causal inference, less time spent in moderate-to-vigorous physical activity (MVPA) was associated with poorer HRQoL, even after adjusting for baseline characteristics and concurrent health outcomes of fatigue, cognitive failures, anxiety, and depression.

Few studies have assessed device-based measurements of physical and sleep behaviors in patients hospitalized for COVID-19. In one study, patients spent less time in MVPA and more time inactive at 2-7 months follow-up,[10] while patients in another study were more physically active at 3-6 months follow-up,[11] compared to our findings at 3-6 months follow-up. Recently, Rowlands et al. published age-referenced values for physical activity volume using UK Biobank data.[38] Compared to its 50th percentile for the age of 60 years (28.68 mg in women; 28.09 mg in men), our patients had somewhat lower physical activity volume (approximately 24 mg/day at each visit). However, compared to the WHO recommendations for physical activity, our data (approximately 32 minutes MVPA/day at each visit) suggest that patients show sufficient MVPA at the total group level. Adults are recommended to engage in at least 150-300 minutes of moderate-intensity physical activity or do at least 75-150 minutes of vigorous-intensity physical activity throughout the week for substantial health benefits, while limiting inactive time.[39]

For sleep, one study reporting device-assessed sleep behavior showed a somewhat longer sleep duration, higher sleep efficiency, and comparable SRI compared to our data at similar follow-up time.[9] According to the American National Sleep Foundation, the recommended sleep duration is 7-9 hours/night, while 6-11 hours is considered 'acceptable'; shorter or longer sleep durations are associated with negative health effects.[40] Our patients slept approximately 7 hours/night, suggesting a good sleep duration.

It should be noted that most available evidence for the physical and sleep recommendations comes from studies using self-reported assessments.[39,41] Together, it is challenging to draw definitive conclusions about the level of physical and sleep behaviors observed in our study. Moreover, comparing device-based outcomes between studies is complicated by differences in devices, measurement protocols, placements (e.g., thigh-worn vs. wrist-worn accelerometers), and variations in software and processing methods across studies.[42] Nonetheless, our findings suggest that patients generally maintained sufficient physical activity and sleep during study visits following hospitalization for COVID-19.

ICU-treated patients for COVID-19 showed more improvement in physical activity during the first year post-discharge than non-ICU-treated patients, likely reflecting recovery from critical illness. In line with current findings, our previous study found that ICU-treated patients had poorer objectively assessed physical fitness after hospitalization but improved over time and reached levels comparable to, or even better than, those of non-ICU-treated patients in later follow-ups.[3] ICU survivors are known to be at increased risk for new or worsening physical, cognitive, and mental health problems after discharge, a condition commonly referred to as the post-intensive care syndrome.[43] Most ICU-treated patients in our study had a good pre-COVID-19 health status, and they often were transferred to inpatient rehabilitation centers with intensive therapy,[44] which may have contributed to their favorable physical recovery. At the 1-year follow-up, physical behavior was comparable between ICU- and non-ICU-treated patients.

We found that less time spent in MVPA was associated with poorer HRQoL after hospitalization for COVID-19. Although the effect was modest, MVPA remained independently associated with HRQoL even after adjusting for baseline characteristics and concurrent health problems. Over 50% of our patients experienced fatigue throughout the follow-up period, one of the most common and persistent symptoms after COVID-19, which has been negatively associated with HRQoL.[45] It could have been expected that fatigue or other health problems interfere with or influence the association between MVPA and HRQoL, but the association remained. HRQoL is multifactorial and influenced by a range of factors, and our findings support the important role of physical activity in HRQoL.

However, it is crucial to consider a patient's ability to engage in MVPA after COVID-19. Post-exertional malaise (PEM) is increasingly recognized as a prevalent and debilitating symptom in those experiencing long-term sequelae following COVID-19. It is also a key symptom in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PEM refers to worsening or new-onset symptoms immediately or delayed by hours or days after physical, mental, or cognitive exertion, affecting daily activities

and HRQoL.[46] Some patients may have experienced PEM during the study assessments, which may have limited their time spent in MVPA to avoid worsening their health.[47,48] Unfortunately, we did not assess PEM during the study assessments. Patients with PEM are recommended to follow a personalized physical activity or exercise program, gradually improving their physical abilities while staying within their energy limits.[47,49]

The study's strengths include its prospective multicenter design, objective measures, and longitudinal 2-year follow-up period after hospitalization for COVID-19. It should be noted that while we observed an association between MVPA and HRQoL, our findings preclude any causal inference. Our study lacks a control group of individuals without COVID-19. In addition, we lack data on the total eligible recruitment population across participating hospitals due to the surge of patients admitted to the participating centers. However, the recruitment of study participants occurred independently of the patient's recovery status and primarily depended on the availability of research personnel. Selection bias might play a role in our study as the study is composed of a high proportion (38%) of ICU-treated patients, possibly due to the high inclusion rate from our academic hospital, compared to the average ICU admissions across all Dutch hospitals (14%). However, this allowed for physical activity and sleep comparisons between ICU- and non-ICU-treated patients. Our sample of the CO-FLOW study participants with accelerometer measurements was less frequently treated in the ICU (38%) than those not participating in the current study (42%). This may be explained by the higher frequency of ICU admissions during the first COVID-19 wave in the Netherlands (Feb-Jun 2020) than during later waves. CO-FLOW measurements started in July 2020, whereas the accelerometer assessments began only in mid-October 2020, and we, therefore, missed some patients from the first wave, as they had already completed their 3- and 6-month follow-up visits.

In conclusion, device-assessed physical and sleep behaviors seemed generally sufficient in the cohort up to 2 years after hospitalization for COVID-19 and did not change over time. However, ICU-treated patients started with less physical activity but improved over the first year post-discharge, reaching the levels of non-ICU-treated patients, likely reflecting recovery from critical illness. Our findings indicate that less time spent in moderate-to-vigorous physical activity was associated with poorer HRQoL, even after adjusting for covariables.

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Chapter 8

Acute COVID-19 treatment is not associated with health problems 2 years after hospitalization

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Abstract

Objectives Various mechanisms, such as immune dysregulation, viral reservoir, and auto-immunity, are hypothesized to underlie the pathogenesis of long-term health problems after hospitalization for COVID-19. We aimed to assess the effect of in-hospital COVID-19 treatments on prominent long-term health problems.

Methods In this prospective multicenter cohort study, we enrolled patients (age ≥18 years) who had been hospitalized for COVID-19 in the Netherlands between July 2020 and October 2021. We retrospectively collected data on in-hospital COVID-19 treatments, including steroid, anti-inflammatory, and antiviral treatments. Patients completed questionnaires on self-reported recovery, dyspnea, fatigue, cognitive failures, and health-related quality of life and performed the 6-minute walk test at the 2-year follow-up visit.

Results Five hundred two patients with COVID-19 were included, all were discharged from the hospital between March 2020 and June 2021. The median age at admission was 60.0 (IQR 53.0-68.0) years and 350 (69.7%) patients were male. At hospital admission, 5/405 (1.2%) of the patients had been vaccinated against SARS-CoV-2. Among all 502 patients, the majority (248 [49.4%]) received steroids only, 57 (11.4%) anti-inflammatory treatment, 78 (15.5%) antiviral treatment, and 119 (23.7%) none during hospitalization. Long-term health problems were common in all groups. We found that in-hospital treatments were not significantly associated with health problems at 2 years after hospital discharge, nor after adjusting for confounders.

Conclusion Many patients with COVID-19 suffer from long-term health problems 2 years after hospital discharge. Acute treatment for COVID-19 is not associated with long-term health problems.

Introduction

COVID-19, caused by SARS-CoV-2, has resulted in a worldwide pandemic, requiring hospitalization for respiratory insufficiency in numerous patients. Many of these patients suffer lingering and debilitating health problems that can persist for months or years,[1] commonly referred to as "long COVID" or "post-COVID syndrome". Long COVID comprises a wide range of symptoms, with dyspnea, fatigue, and neurocognitive symptoms among the most frequently reported, may negatively affect health-related quality of life, and more commonly affects patients after severe COVID-19.[1,2]

During the acute phase, patients hospitalized for COVID-19 commonly exhibit hyper-inflammation and so-called "cytokine storm".[3] During the pandemic, treatment insights have continued to develop. Several treatments have been recommended to combat the disturbances caused by SARS-CoV-2, including steroids and targeted immunomodulatory (suppressing the inflammatory cytokine storm) and antiviral (suppressing viral replication) treatments in those requiring supplemental oxygen.[4] The immune dysregulation caused by SARS-CoV-2 can persist into convalescence, and such dysregulation has been associated with long COVID.[5,6] Although currently incompletely understood, various mechanisms, including immune dysregulation, persistence of SARS-CoV-2 in tissues, and auto-immunity, are hypothesized to underlie long COVID pathogenesis.[5] As such, various in-hospital treatments may affect long-term health outcomes after severe COVID-19. In line with this, nirmatrelvir/ritonavir treatment appeared to reduce the risk of long-term health problems in several cohort studies.[7,8] Regarding in-hospital COVID-19 treatment, our previous study showed that steroid-treated patients are less likely to report muscle weakness up to 1-year post-hospitalization.[2] Another study found no association between steroid or antiviral treatment and symptoms 2 years post-hospitalization for COVID-19.[1] However, at this time, data are scarce regarding the effect of in-hospital treatment on long-term health outcomes.

Therefore, we aimed to assess the effect of different in-hospital COVID-19 treatments on long-term health problems at 2 years post-discharge. We hypothesized that patients who received immunomodulatory and/or antiviral treatment for COVID-19 may experience fewer health problems than those with steroids only or no treatment.

Methods

The CO-FLOW study is a multicenter prospective cohort study on long-term health outcomes up to 2 years after discharge in adult patients hospitalized for COVID-19 in the Netherlands. The study was conducted in 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities). Patients eligible for the study were those hospitalized for COVID-19 (confirmed by laboratory or clinical diagnosis), aged 18 years or older, had sufficient knowledge of the Dutch or English language, and within 6 months post-discharge. Incapacitated patients (e.g., dementia) were not included. Patient inclusion took place between July 2020 and October 2021.[9] In this study, we included patients who had completed at least one of our

outcomes of interest at the 2-year follow-up and whose data on in-hospital COVID-19 treatment could be retrieved from medical records in the participating hospitals.

We followed national COVID-19 treatment guidelines across the participating hospitals, in line with international recommendations.[4,10] These guidelines evolved due to the initially unknown COVID-19 pathogenesis and treatment effectiveness. At the beginning of the pandemic, no treatment or treatments currently considered ineffective (e.g., (hydroxy)chloroquine and azitromycine), and, more occasionally, immunomodulatory (anti IL-1 or anti IL-6) or antiviral treatments were given. Soon thereafter, patients requiring supplemental oxygen were treated with steroids. Antivirals (remdesivir or convalescent plasma) were initially considered effective for COVID-19 treatment.[4] However, their clinical effectiveness appeared less than anticipated, leading to their discontinuation after the second COVID-19 wave in the Netherlands. During the late second/early third wave, patients with severe illness (≥6 L oxygen and CRP ≥75 mg/L) received immunomodulatory treatment (targeting IL-6). Given these various regimes over time, we categorized patients into four groups based on their in-hospital COVID-19 treatment: 1] steroids only (dexamethasone, prednisolone, or methylprednisolone), 2] anti-inflammatory (anti-IL-6 or anti-IL-1) with or without steroids or antivirals, 3] antivirals (remdesivir, oseltamivir, lopinavir, ritonavir, or convalescent plasma) with or without steroids, and 4] none of the previously described treatments or (hydroxy)chloroquine only.

The primary outcome was self-reported recovery from COVID-19 as assessed with the COVID-19 Core Outcome Measure for recovery[11] and was dichotomized into completely recovered and not completely recovered (comprising mostly recovered, somewhat recovered, half recovered, and not recovered at all). Secondary outcomes were assessed with validated patient-reported outcome measures for dyspnea (modified medical research council dyspnea scale, grades 0-4, ≥1 indicating dyspnea),[12] fatigue (fatigue assessment scale [FAS], score-range 0-50, cutoff ≥22),[13] cognitive failures (cognitive failures questionnaire [CFQ], score-range 0-100, cutoff >43),[14] and health-related quality of life (HRQoL) (5-level EuroQoL-5D [EQ-5D-5L] index, score-range 0 [indicating death] to 1 [perfect health]).[15] Aerobic capacity was assessed with the 6-minute walk test; the 6-minute walk distance (6MWD) was normalized to a percentage of normative value using reference values.[16,17]

We assessed differences in baseline characteristics among treatment groups with the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. We first performed univariable Generalized Estimating Equations (GEE) analyses using logistic and linear models to assess the effect of in-hospital COVID-19 treatment on health outcomes at the 2-year follow-up. Subsequently, to control for confounders, age, sex, and baseline characteristics differing among treatment groups were entered as independent variables in multivariable analyses.

Results

Out of the 650 CO-FLOW study participants, 510 patients completed at least one of the outcomes of interest at the 2-year follow-up. From 502 of these patients (median age 60.0 [IQR 53.0-68.0]

years; 350 [69.7%] male) data were available on in-hospital treatment and those patients were included in this study. These patients were discharged from the hospital between March 24, 2020, and June 17, 2021. At hospital admission, 5/405 (1.2%) of the patients had been vaccinated against SARS-CoV-2. As for treatment, most patients (248/502 [49.4%]) received steroids only, 57/502 (11.4%) anti-inflammatory, 78/502 (15.5%) antivirals, and 119/502 (23.7%) none during hospitalization. Regarding baseline characteristics, age, sex, body mass index, migration background, and comorbidities did not differ significantly among the treatment groups, while the proportion of ex- or current smokers was higher in the anti-inflammatory group compared to the other groups (**Table 1**). Moreover, the anti-inflammatory group showed worse in-hospital characteristics, including more frequent thrombosis and delirium, intensive care unit (ICU) admission, and longer hospital stay than the other groups (**Table 1**); all are related to the indication of this treatment.

Table 1. Baseline characteristics of patients with COVID-19 at hospital admission.

	None[a] (n=119)	**Steroids only (n=248)**	**Anti-inflammatory[b] (n=57)**	**Antivirals[c] (n=78)**	***P*-value**
Age, years	61.0 (54.0-69.0)	60.0 (54.0-68.0)	62.0 (53.0-68.5)	57.5 (49.8-66.0)	0.18
Sex, male	76 (63.9%)	179 (72.2%)	44 (77.2%)	51 (65.4%)	0.18
BMI, kg/m^2	27.9 (25.3-32.0)	28.4 (25.9-32.3)	28.1 (26.3-31.4)	28.7 (25.7-33.0)	0.64
Migration background					
European	92 (77.3%)	191 (78.0%)	42 (73.7%)	57 (73.1%)	0.78
Non-European	27 (22.7%)	54 (22.0%)	15 (26.3%)	21 (26.9%)	
Smoking status					0.01
Never	58 (48.7%)	103 (41.9%)	15 (26.3%)	41 (52.6%)	
Ex or current	61 (51.3%)	143 (58.1%)	42 (73.7%)	37 (47.4%)	
Comorbidities					
Obesity (BMI≥30 kg/m^2)	50 (42.0%)	95 (38.3%)	26 (45.6%)	28 (35.9%)	0.62
Diabetes	15 (12.6%)	46 (18.5%)	8 (14.0%)	13 (16.7%)	0.51
Cardiovascular disease	39 (32.8%)	94 (37.9%)	27 (47.4%)	30 (38.5%)	0.24
Pulmonary disease	27 (22.7%)	60 (24.2%)	13 (22.8%)	23 (29.5%)	0.72
In-hospital characteristics					
Vaccination against SARS-CoV-2[d]	0 (0.0%)	3 (1.4%)	1 (1.9%)	1 (2.0%)	NA
Thrombosis	22 (18.4%)	36 (14.5%)	20 (35.7%)	4 (5.1%)	<0.001
Delirium	43 (36.1%)	46 (18.5%)	20 (35.7%)	7 (9.0%)	<0.001
COVID-19 treatment					NA[e]
Steroids					
Dexamethason	-	215 (86.7%)	51 (89.5%)	61 (78.2%)	
Predniso(lo)n	-	32 (12.9%)	2 (3.5%)	3 (3.8%)	

Table 1. Continued.

	None[a] (n=119)	Steroids only (n=248)	Anti-inflammatory[b] (n=57)	Antivirals[c] (n=78)	*P*-value
Methylpredisolon	-	19 (7.7%)	9 (15.8%)	1 (1.3%)	
Anti-inflammatory					
Tocilizumab	-	-	55 (96.5%)	-	
Anakinra	-	-	2 (3.5%)	-	
Antivirals					
Remdesivir	-	-	1 (1.8%)	66 (84.6%)	
Oseltamivir	-	-	1 (1.8%)	5 (6.4%)	
Lopinavir/ritonavir	-	-	-	2 (2.6%)	
Convalescent plasma	-	-	1 (1.8%)	7 (9.0%)	
(Hydroxy)chloroquine	5 (4.2%)	1 (0.4%)	-	4 (5.1%)	
None	114 (95.8%)	-	-	-	
Supplemental oxygen	111 (93.3%)	246 (99.2%)	57 (100.0%)	77 (98.7%)	0.002
High flow nasal cannula	23 (19.3%)	76 (30.6%)	40 (70.2%)	16 (20.5%)	<0.001
ICU admission	54 (45.4%)	86 (34.7%)	48 (84.2%)	14 (17.9%)	<0.001
Invasive mechanical ventilation	46 (38.7%)	77 (31.0%)	43 (75.4%)	11 (14.1%)	0.02
Length of ICU stay, days	20.0 (11.8-36.5)	18.0 (9.0-35.0)	12.5 (8.0-21.3)	13.5 (6.3-31.0)	0.16
Length of hospital stay, days	13.0 (6.0-33.0)	10.0 (5.0-23.0)	23.0 (16.0-34.5)	8.0 (5.0-14.3)	<0.001
COVID-19 wave[f]					<0.001
First	98 (82.4%)	27 (10.9%)	6 (10.5%)	9 (11.5%)	
Second	17 (14.3%)	159 (64.1%)	13 (22.8%)	69 (88.5%)	
Third	4 (3.4%)	62 (25.0%)	38 (66.7%)	-	

Data are presented as the median with interquartile range or number with percentage. Patients were categorized into groups based on their COVID-19 treatment during hospitalization. P-values are obtained using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. The variables BMI (n=11 none, n=23 steroids only, and n=13 antivirals groups), migration background (n=3 steroids only group), smoking status (n=2 steroids only group), vaccinated against SARS-CoV-2 at admission (n=26 none, n=39 steroids only, n=4 anti-inflammatory, and n=28 antivirals groups) thrombosis (n=1 anti-inflammatory group), delirium (n=1 anti-inflammatory group), and length of ICU stay (n=2 anti-inflammatory group) contain missing values.

BMI, Body Mass Index; ICU, Intensive Care Unit; NA, Not Applicable.

[a]*Comprises patients without steroid, anti-inflammatory, or antiviral treatments, but who may have received (hydroxy) chloroquine.*

[b]*In addition to anti-inflammatory treatment, patients may have received steroids or antivirals.*

[c]*In addition to antiviral treatment, patients may have received steroids.*

[d]*Patient-reported vaccination against SARS-CoV-2.*

Group differences in COVID-19 treatment were not assessed; patients were categorized into groups based on these treatments.

[f]*We classified patients by discharge date: the first -19 wave (Feb-Jun 2020), second wave (Jul 2020-Feb 2021), and third wave (Feb-Jun 2021).*

At the 2-year follow-up (median 731.0 [726.0-740.0] days post-discharge), 427/463 (92.2%) patients reported receiving at least one vaccination against SARS-CoV-2 during follow-up. In the total cohort, 317/435 (72.9%) patients reported that they were not completely recovered from COVID-19. Many patients experienced dyspnea (184/460 [40.0%]), fatigue (220/427 [51.5%]), or cognitive failures (101/432 [23.4%]). Regarding HRQoL, the mean EQ-5D-5L index was .80 (SD .22). Patients reached 94.5% (SD 19.2) of normative 6MWD at 2 years. In univariable GEE analyses, treatment group was not significantly associated with complete recovery, nor with any of the secondary outcomes (dyspnea, total FAS score, total CFQ score, EQ-5D-5L index, or the percentage of normative 6MWD) at 2 years (**Table 2**). These associations remained non-significant after adjusting for confounders (**Table 2**).

Table 2. Health outcomes at 2 years after hospitalization for COVID-19 per treatment group.

	n	None[a]	Steroids only	Anti-inflammatory[b]	Antivirals[c]	Univariable analysis *P*-value	Multivariable analysis[d] *P*-value
Recovery status (completely recovered)	435	24 (23.5%)	67 (31.8%)	10 (21.3%)	15 (24.2%)	0.16	0.23
Dyspnea (mMRC scale grade≥1)	460	45 (40.9%)	84 (37.8%)	16 (32.7%)	36 (47.4%)	0.37	0.13
Fatigue (total FAS score)	427	23.7 ± 9.1	23.1 ± 8.9	23.8 ± 9.1	25.2 ± 9.0	0.44	0.64
Cognitive failures (total CFQ score)	432	31.6 ± 18.6	30.0 ± 18.8	29.1 ± 16.8	31.2 ± 17.7	0.82	0.49
HRQoL (EQ-5D-5L index)	432	0.78 ± .23	0.80 ± 0.21	0.80 ± 0.19	0.79 ± 0.23	0.85	0.83
6MWT (% of normative 6MWD)[e]	365	96.7 ± 21.8	93.8 ± 17.6	97.9 ± 17.7	91.6 ± 21.2	0.29	0.92

Data are raw test outcomes and are presented as the mean with standard deviation or as a number with percentage. We performed Generalized Estimating Equations (GEE) analysis using logistic (recovery status and dyspnea) and linear (fatigue, cognitive failures, HRQoL, and 6MWT) models to assess the effect of treatment group on health outcomes 2 years after hospitalization for COVID-19. mMRC, Modified Medical Research Council Dyspnea Scale; FAS, Fatigue Assessment Scale; CFQ, Cognitive Failures Questionnaire; HRQoL, Health-Related Quality of Life; EQ-5D-5L, 5-level EuroQoL-5D questionnaires; 6MWT, 6-Minute Walk Test; 6MWD, 6-Minute Walk Distance.

[a] *Comprises patients without steroid, anti-inflammatory, or antiviral treatments, but who may have received (hydroxy) chloroquine.*

[b] *In addition to anti-inflammatory treatment, patients may have received steroids or antivirals.*

[c] *In addition to antiviral treatment, patients may have received steroids.*

[d] *Adjusted for age, sex, smoking status, thrombosis, delirium, high flow nasal cannula, intensive care unit treatment, length of stay in the hospital, and COVID-19 wave.*

[e] *Normative values were calculated according to the method described by Enright and Sherrill.*[16]

Discussion

In this cohort study we found that acute COVID-19 treatment did not associate with self-reported recovery or prominent health problems in patients 2 years after hospital discharge. While treatments, especially immunomodulatory, have proven effective in combating immune dysregulation and improving clinical outcomes during the acute phase,[4] they did not influence long-term outcomes in our cohort, despite the continued immune dysregulation observed in patients with long COVID.[5] Likewise, antiviral treatment during hospitalization was not associated with favorable long-term outcomes. However, the nowadays considered most effective antiviral treatments (e.g., nirmatrelvir/ritonavir) were not given in the acute phase of COVID-19 during this study, which may reduce the risk of long-term health problems.[18]

We found that many patients experience persistent health problems 2 years after hospitalization for COVID-19. Although evidence on the association between acute COVID-19 treatment and long-term outcomes is heterogeneous,[1,18] studies consistently identified other factors like age, female sex, underlying pulmonary diseases, and increased COVID-19 disease severity as risk factors for long COVID,[1,19] consistent with our findings (data not shown).
Currently, there is no effective pharmacological treatment for long COVID. The hypothesized causes of long COVID offer potential treatment options,[5] including restoring immune dysregulation and supporting viral clearance. Moreover, long COVID shares similarities with other post-acute infection syndromes (PAISs), such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).[20] Insights from PAISs may enhance our understanding of the pathophysiologic mechanisms of Long COVID. Despite some studies investigating possible treatment options for long COVID, these findings are pending. These outcomes could represent a significant step in understanding the complexities of long COVID, and may improve long-term health outcomes.

Strengths of our study include its longitudinal and multicenter study design, a large sample size of patients who had been hospitalized for COVID-19, and a high response rate at the 2-year follow-up. Recruitment of study participants occurred independently of the patients' recovery status, mitigating selection bias. Our study is limited by its observational design in which confounding by indication may play a role, despite our adjustment for multiple confounders. Our national guidelines on COVID-19 treatment may differ from guidelines in other countries, possibly limiting international generalizability of our findings. Moreover, we did not collect information on doses and duration of COVID-19 treatments, and sometimes various treatment regimens could not be clearly separated.[4] Nonetheless, we have analyzed different types of in-hospital COVID-19 treatments, which have been internationally recommended,[10] revealing no association with long-term health outcomes.

In summary, we found that many patients who had been hospitalized for COVID-19 suffer from dyspnea, fatigue, cognitive failures, and a decreased HRQoL, while showing good aerobic capacity, 2 years after discharge, irrespective of acute COVID-19 treatment. In light of the public health concerns posed by long COVID, there is an urgent need for a better understanding of the underlying etiology of long COVID and assessment of potential pharmacological treatments.

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Chapter 9

Health outcomes up to 3 years and post-exertional malaise in patients after hospitalization for COVID-19: a multicentre prospective cohort study (CO-FLOW)

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Abstract

Background Many patients experience long-lasting health problems after COVID-19. The study aimed to assess 3-year trajectories of a comprehensive set of patient-reported outcome measures (PROMs) in patients hospitalized for COVID-19, particularly focusing on the 2- to 3-year trajectory. Additionally, we evaluated prevalence of post-exertional malaise (PEM) at 3 years, its risk factors, co-occurring health problems, and the 3-year trajectories of patients with and without PEM.

Methods The CO-FLOW multicentre prospective cohort study followed up adults hospitalized for COVID-19 in 7 hospitals, located in the Netherlands. Study assessments were performed at 3, 6, 12, 24, and 36 months post-discharge, conducted between July 1, 2020, and May 22, 2024. PROMs on recovery, symptoms, fatigue, mental health, cognition, participation, sleep quality, work status, health-related quality of life (HRQoL), and PEM were collected. Generalized estimating equations were used to assess health trajectories and multivariable logistic regression to identify risk factors for PEM.

Findings In total, 299/344 (87%) patients completed the 3-year follow-up and were included in the analysis. Complete recovery rates increased ($p<0.001$), from 12% at 3 months to 24% at 3 years. Symptoms of impaired fitness, fatigue, and muscle weakness (all $p<0.0019$) and PROMs for fatigue score, participation, return to work, and HRQoL (all $p<0.005$) improved significantly over time, while PROMs for cognitive failures worsened ($p<0.001$). Between the 2- and 3-year visits, memory problems (OR 1.4 [1.1 to 1.7], $p<0.001$), and scores of fatigue (MD +1.0 [0.4 to 1.6], $p=0.002$), cognitive failures (MD +2.2 [0.9 to 3.4], $p<0.001$), and SF-36 mental component summary (-2.2 [-3.1 to -1.3], $p<0.001$) significantly worsened. At 3 years, 66% of patients experienced fatigue, 63% impaired fitness, 59% memory problems, and 53% concentration problems. PROMs showed that 62% reported poor sleep quality, 55% fatigue, and 28% cognitive failures. PEM was reported by 105/292 (36%) patients at 3 years; risk factors were female sex (OR 3.4 [95%CI 1.9 to 6.0], $p<0.001$), pre-existing pulmonary disease (3.0 [1.7 to 5.6], $p<0.001$), physical inactivity pre-COVID-19 (2.3 [1.2 to 4.1], $p=0.008$), and ICU treatment for COVID-19 (1.8 [1.02 to 3.0], $p=0.04$). Concurrent fatigue, cognitive failures, and dyspnea were more common in patients with (42%) than without (6%) PEM. Patients with PEM showed poor health outcomes throughout the entire follow-up period, including worsening fatigue and HRQoL during the third year.

Interpretation Many health problems persisted up to 3 years post-discharge, with self-reported fatigue and cognitive problems worsening in the third year. PEM was common, and linked to a more severe phenotype of long COVID. These findings highlight the urgent need to optimize treatment options and investigate underlying pathological mechanisms of COVID-19.

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Introduction

Since December 2019, the World Health Organization has reported over 776 million confirmed cases of SARS-CoV-2,[1] causing COVID-19, with a substantial number of these patients requiring hospitalization. The aftermath of COVID-19 showed that many patients do not recover to pre-COVID-19 health with persistent health problems for months or even years,[2,3] a condition referred to as 'long COVID' or 'Post COVID-19 Condition'.[4,5]

Long COVID is a heterogeneous disease, with patients experiencing a broad range of symptoms. The severity of these symptoms varies among patients, with fluctuations and relapses of symptoms over time being common.[6] The most common symptoms include fatigue and cognitive problems. In addition, there is increasing awareness that post-exertional malaise (PEM) is a prevalent and debilitating symptom of long COVID. PEM is the abnormal worsening of symptoms after minimal physical or cognitive activity occurring immediately or delayed by hours or days after the activity.[7,8] PEM limits daily activities and reduces health-related quality of life (HRQoL).[9] Approximately 55-89% of the patients with long COVID experience PEM.[10-13] Although PEM is recognized as a debilitating feature of long COVID, it has been scarcely evaluated—particularly in patients who had been hospitalized for COVID-19,—leaving significant gaps in understanding its long-term prevalence, risk factors, and prognosis.[14]

Hospitalization for COVID-19 is considered a risk factor for developing long COVID. It is estimated that during the early phase of the pandemic, 50-70% of patients hospitalized for COVID-19 experience long COVID, compared to 7-30% of non-hospitalized patients, after 12 or more weeks post-infection.[15-17] Studies have shown that, although some symptoms gradually decreased over time, many patients reported persistent symptoms up to 2 years after hospitalization.[2,3,18]

Insights into health outcomes up to 3 years after hospitalization for COVID-19 remain scarce. Two studies compared health outcomes between 2 and 3 years after hospitalization, showing persistence of symptoms at 3 years in 40-54% of patients.[19,20] Likewise, a healthcare database study demonstrated substantial residual risk and health burden of long COVID in the third year after hospitalization.[21] Longitudinal and more comprehensive assessments are largely lacking, although such insights are warranted to better understand the long-term health outcomes. Gaining insights into the health outcomes over time can assist policy makers and healthcare providers in refining COVID-19 aftercare strategies and guidelines.

The primary study aim was to assess trajectories of patient-reported health outcomes up to 3 years after hospitalization for COVID-19, with a particular focus on changes between the second and third year. The second aim was to assess the prevalence of PEM at 3 years post-discharge, evaluate co-occurring health problems, explore its risk factors, including demographic and clinical characteristics, and assess the 3-year trajectories of patients with and without PEM.

Methods

Study design and participants

This study is part of the "COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system" (CO-FLOW) study, a prospective multicentre cohort study that follows up patients discharged from hospitals in the Rotterdam-Rijnmond-Delft region in the Netherlands. The CO-FLOW study protocol has been described in detail elsewhere.[22] The study was performed in 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centres (1 medical rehabilitation centre and 2 skilled nursing facilities). The study included patients between July 2020 and October 2021 who had been hospitalized for COVID-19, aged ≥18 years, had sufficient knowledge of the Dutch or English language, and were within 6 months post-discharge. Diagnosis of COVID-19 was based on either positive reverse transcription polymerase chain reaction or a clinical diagnosis (symptoms and chest radiological abnormalities) combined with positive serology for COVID-19. Incapacitated patients (e.g., dementia) were not included. Eligible patients were informed about the CO-FLOW study at hospital discharge and were recruited during routine follow-up at the outpatient clinic of one of the participating centres or during their inpatient stay in a rehabilitation centre. In the Netherlands, it was standard practice to offer post-discharge follow-up at the outpatient clinic of the discharging hospital to patients hospitalized for COVID-19, with the first visit generally scheduled 6-12 weeks post-discharge. Patients attending this visit were invited to participate in the study. Data on the total eligible recruitment population was unknown, but recruitment of study participants occurred independently of the patient's recovery status and primarily depended on availability of research personnel. Study visits were performed at 3, 6, 12, and 24 months after hospital discharge.

The CO-FLOW study was extended to further monitor the trajectories of health outcomes by administering a survey of patient-reported outcome measures (PROMs) at 3 years post-discharge. The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved the CO-FLOW study (MEC-2020-0487) and its extension. The study has been registered in the International Clinical Trial Registry Platform (NL8710). Participants provided written informed consent before the start of study measurements. Those participating in the extended CO-FLOW study provided new written informed consent. In this study, we included patients that filled in the survey at 3 years.

Procedures

Procedures of the CO-FLOW study visits up to 2 years are described in detail elsewhere.[22] In short, study visits comprised a comprehensive assessment of objectively assessed physical and cognitive functioning and a symptom questionnaire. Additionally, a survey was sent via e-mail or postal mail alongside each visit. Baseline characteristics and routine follow-up data regarding pulmonary and radiological outcomes were retrospectively collected from medical records at the participating facilities and during the study visits. At the end of the 2-year follow-up period, study participants received an information letter about continuing follow-up by email or postal mail. Patients involved in the extended study were followed up with a survey at 3 years post-discharge. The follow-up survey included PROMs that assessed health problems persisting at the 2-year visit. Additionally, we

added the DePaul Symptom Questionnaire to assess PEM and the Work Limitations Questionnaire (WLQ) to assess work limitations. All collected data were stored in the Castor Electronic Data Capture system (Castor EDC, Amsterdam, the Netherlands).

Baseline characteristics

Characteristics included patients' age, sex, body mass index (BMI), migration background, education level, employment status, smoking status, and comorbidities at hospital admission. Pre-COVID-19 leisure time physical activity was assessed with the Saltin−Grimby Physical Activity Level Scale questionnaire.[23] In-hospital characteristics included treatment for COVID-19, thrombosis, delirium, type of oxygen support, intensive care unit (ICU) admission, and the length of stay (LOS) in both ICU and hospital. Patients were classified based on their discharge date to reflect the timing of COVID-19 waves: first wave (Feb-Jun 2020), second wave (Jul 2020-Jan 2021), and third wave (Feb-Jun 2021).

Study outcome measurements

Recovery

Self-reported recovery status from COVID-19, as compared to pre-COVID-19 health status, was assessed with the Core Outcome Measure for self-reported recovery from COVID-19 and dichotomized into completely recovered and not completely recovered (mostly recovered, somewhat recovered, half recovered, and not recovered at all).[24] Additionally, patients rated their recovery status from COVID-19 on a numeric scale from 0% to 100% at the 3-year follow-up.

Symptoms

New symptoms or worsened symptoms since the SARS-CoV-2 infection were assessed using a symptom questionnaire (Corona Symptom Checklist, 26 symptoms).[25] At the 2- and 3-year follow-up, patients were asked to also rate the severity (mild, moderate, severe, or very severe) of these symptoms.

Patient-Reported Outcome Measures (PROMs)

PEM was assessed using a modified version of the DePaul Symptom Questionnaire, five symptoms were rated for frequency (0-4) and severity (0-4) on a 5-point Likert scale with higher scores indicating greater severity. PEM was indicated if both were scored ≥2 for one or more symptoms, and a total sum score was calculated by summing the scores for both frequency and severity of each symptom (0-40) as severity measure.[26,27] Fatigue was assessed with the Fatigue Assessment Scale (scores 0-50, cutoff ≥22);[28] dyspnea with the Modified Medical Research Council (mMRC) Dyspnea Scale;[29] anxiety and depression with the Hospital Anxiety and Depression Scale, subscales Anxiety and Depression (subscale scores 0-21, cutoff ≥11);[30] cognitive failures with the Cognitive Failures Questionnaire (CFQ, scores 0-100, cutoff >43);[31,32] sleep quality with the Pittsburgh Sleep Quality Index (scores 0-21, cutoff ≥5);[33] participation in daily life activities with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) on three scales: frequency, restrictions, and satisfaction (subscale scores 0-100);[34] employment status with the iMTA Productivity Cost Questionnaire (categorized into no, partial, or full return to work) for patients with a paid job before SARS-CoV-2 infection;[35] work limitations due to health problems following COVID-19 with the

Work Limitation Questionnaire on four scales: time management, physical, mental-interpersonal, and output demands (scores 0 [limited none of the time] - 100 [limited all the time]);[36-38] health-related quality of life with the 5-level EuroQoL-5D (EQ-5D-5L) questionnaire[39] and the 36-item Short Form Health Survey (SF-36).[40] The EQ-5D-5L consists of the 5-level EQ-5D index (0 [death] - 1 [perfect health]; negative scores indicate a health status worse than death) and a visual analogue scale (EQ-VAS, scores 0-100). The SF-36 consists of 8 domains (scores 0-100) and a physical (PCS) and mental component summary (MCS) score (T-scores with mean 50 and standard deviation 10).[41]

Statistical analysis

Data are presented as mean with standard deviation (SD), median with interquartile range (IQR), or as number with percentage. Normality of data was checked with the Shapiro-Wilk test. Group comparisons for continuous variables were performed with the Mann-Whitney U test and for categorical variables with the Chi-squared test. To assess the trajectories of health outcomes over time, Generalized Estimating Equations (GEE) analyses for repeated measurements were used, with linear models for continuous outcomes and logistic models for dichotomous outcomes. The GEE is a semi-parametric approach which considers within- and between subject correlations and uses all available measurements despite incomplete data. We entered follow-up time (3, 6, 12, 24, and 36 months) as a fixed factor in the GEE analysis for the total cohort. Each GEE analysis was performed using an unstructured correlation matrix.

Multivariable logistic regression analysis with backward elimination of variables was performed to assess risk factors for PEM at 3 years. These variables included demographics and acute COVID-19 characteristics at hospital admission and were selected a priori, including age (years), sex (male or female), migration background (European or non-European), education (low, middle, or high), employment status (employed, unemployed, or retired), smoking status (never or current/former), physical activity level (inactive/light or moderate/vigorous), obesity (obese if BMI≥30 kg/m^2, yes/no), cardiovascular disease (yes/no), pulmonary disease (yes/no), diabetes (yes/no), COVID-19 wave (first, second, or third), steroid or anti-inflammatory treatment (yes/no), ICU admission (yes/no), and the LOS in hospital (days). The prevalence of PEM and co-occurring health problems (fatigue, cognitive failures, and dyspnea) in patients with PEM at 3 years were calculated using the cut-off scores of the questionnaires. Moreover, we compared the 3-year trajectories of total scores of fatigue, cognitive failures, and HRQoL (SF-36 PCS and MCS) between patients with and without PEM at 3 years using GEE analysis, correcting for demographics and acute COVID-19 characteristics at hospital admission that significantly ($p<0.05$) differed between groups. Missing data in the variables included in the multivariable analyses were not imputed (missingness ≤ 1% per variable). A P value <0.05 was considered statistically significant, unless stated otherwise. A Bonferroni-corrected α threshold was applied to correct for multiple comparisons in symptoms ($\alpha=0.0019$) and PROMs ($\alpha=0.00417$). All statistical analyses were performed with IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study participants

Between July 1, 2020, and Sept 9, 2021, the CO-FLOW study prospectively enrolled 650 patients who had been hospitalized for COVID-19. After the 2-year follow-up period, 344/650 (53%) patients consented to participate in the CO-FLOW extension study with yearly follow-up survey, of whom 299/344 (87%) completed the 3-year survey and were included in the final analysis (**Figure 1**). These patients were discharged from the hospital between March 26, 2020 and May 21, 2021. **Table 1** presents the baseline characteristics of participants in- and excluded in the final study analysis. The latter group comprised patients (n=306) who did not participate in the study extension and those (n=45) who participated but lacked data at the 3-year visit. Patients included in the analysis were particularly characterized by older age (62 [55-69] years vs. 59 [50-67] years), a European migration background (87% vs. 57%), a high education level (35% vs. 25%), and a hospital admission during the first COVID-19 wave (33% vs. 23%), and had less frequently diabetes (13% vs. 26%) (all $p \leq 0.007$) compared to those not participating; other characteristics were comparable between groups. Outcomes of recovery, symptoms, and PROMs at the 2-year visit did not differ significantly between patients in- and excluded in the analysis, except for the proportion of patients fully returning to work which was significantly lower in those included in the final analysis (62% vs. 84%, $p<0.001$) (**Supplementary Table S1**).

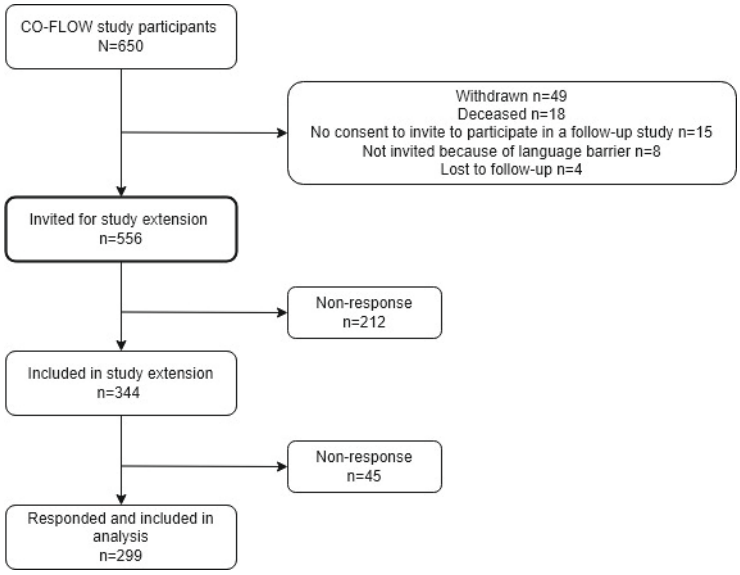

Figure 1. Flowchart of participants included in analysis.

Table 1. Comparison of baseline characteristics at hospital admission between CO-FLOW study participants included and not included in final analysis.

	N[a]	Participants included in analysis	N[a]	Participants not included in analysis	P value
Patient characteristics					
Age, years	299	62 (55-69)	351	59 (50-67)	<0.001
Sex, male	299	210 (70%)	351	239 (68%)	0.56
BMI, kg/m^2	280	29 (26-32)	309	29 (26-33)	0.06
Migration Background	297		333		<0.001
European		258 (87%)		191 (57%)	
Dutch Caribbean		25 (8%)		64 (19%)	
Asian		9 (3%)		30 (9%)	
Turkish		4 (1%)		24 (7%)	
(North) African		1 (1%)		24 (7%)	
Education[b]	296		329		0.007
Low		89 (30%)		133 (40%)	
Middle		104 (35%)		114 (35%)	
High		103 (35%)		82 (25%)	
Employment	296		331		0.06
Unemployed		37 (13%)		63 (19%)	
Employed		179 (61%)		193 (58%)	
Retired		80 (27%)		75 (23%)	

Table 1. Continued.

	N[a]	Participants included in analysis	N[a]	Participants not included in analysis	P value
Smoking status	297		334		0.09
Never		118 (40%)		162 (49%)	
Former		173 (58%)		166 (50%)	
Current		6 (2%)		6 (1%)	
Physical activity level[c]	297		327		0.09
Inactive		30 (10%)		56 (17%)	
Light		164 (55%)		168 (51%)	
Moderate		85 (29%)		83 (25%)	
Vigorous		18 (6%)		20 (6%)	
Comorbidities	299		351		0.08
0		59 (20%)		57 (16%)	
1		88 (29%)		85 (24%)	
≥2		152 (51%)		209 (60%)	
Obesity (BMI≥30 kg/m^2)		111 (37%)		155 (44%)	0.07
Diabetes		39 (13%)		91 (26%)	<0.001
Cardiovascular disease/ hypertension		108 (36%)		149 (43%)	0.10
Pulmonary disease		72 (24%)		90 (26%)	0.65
Renal disease		29 (10%)		30 (9%)	0.61
Gastrointestinal disease		16 (5%)		15 (4%)	0.52
Neuromuscular disease		33 (11%)		35 (10%)	0.66
Malignancy		36 (12%)		33 (9%)	0.28
Autoimmune/inflammatory disease		32 (11%)		36 (10%)	0.85
Mental disorder		12 (4%)		20 (6%)	0.32
In-hospital characteristics					
Vaccinated before admission	299		347		0.13
Yes		295 (99%)		1 (1%)	
No		4 (1%)		346 (99%)	
COVID-19 wave[d]	299		351		0.005
First		100 (33%)		80 (23%)	
Second		138 (46%)		201 (57%)	
Third		61 (20%)		70 (20%)	
Chest x-ray abnormalities	283		336		0.64
Normal		32 (11%)		35 (10%)	
Moderate		57 (20%)		78 (23%)	
Severe		194 (69%)		223 (66%)	

Table 1. Continued.

	N[a]	Participants included in analysis	N[a]	Participants not included in analysis	P value
COVID-19 directed treatment	299		351		
None		67 (22%)		67 (19%)	0.30
(Hydroxy)chloroquine		9 (3%)		3 (1%)	0.04
Steroids		205 (69%)		251 (72%)	0.41
Antivirals		35 (12%)		62 (18%)	0.03
Anti-inflammatory		37 (12%)		39 (11%)	0.62
Convalescent plasma		5 (2%)		3 (1%)	0.35
Thrombosis	298	81 (27%)	350	84 (24%)	0.22
Delirium	298	81 (27%)	350	84 (24%)	0.22
Requiring oxygen supplementation	299	290 (97%)	351	337 (96%)	0.50
Requiring high flow nasal cannula	299	98 (33%)	349	110 (32%)	0.82
ICU admission	299	129 (43%)	351	144 (41%)	0.59
Invasive mechanical ventilation	299	118 (40%)	351	117 (33%)	0.11
Length of intubation, days	113	16 (8-29)	116	13 (9-27)	0.56
Tracheostomy	298	44 (15%)	350	46 (13%)	0.12
Length of ICU stay, days	127	20 (10-33)	144	15 (8-30)	0.04
Length of hospital stay, days	299	14 (6-31)	351	10 (5-26)	0.04
Time interval from discharge to follow-up questionnaires, days					
Three months	232	98 (91-107)	222	95 (88-105)	
Six months	285	189 (182-200)	242	185 (180-194)	
One year	286	371 (364-379)	224	367 (362-378)	
Two years	285	735 (729-746)	180	731 (725-740)	
Three years	297	1100 (1091-1128)	NA	NA	

Data are presented as median (interquartile range) or n (%) at time of hospital admission. The following variables were dichotomized for statistical analysis: migration background was categorized as European versus non-European groups combined, smoking status as never versus former/current, physical activity level as inactive/light versus moderate/vigorous, and treatment as no treatment versus any received treatment. BMI, Body Mass Index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; NA, not applicable.

[a] *Number of patients with available data for each variable.*

[b] *Education comprises low (primary or secondary education); middle (high school); high (postsecondary education or university).*

[c] *Pre-COVID-19 leisure time physical activity level was measured with the Saltin–Grimby Physical Activity Level Scale questionnaire.*[23]

[d] *Patients were classified by discharge date: the first COVID-19 wave (Feb-Jun 2020), second wave (Jul 2020-Jan 2021), and third wave (Feb-Jun 2021).*[42]

Recovery status

Overall, the proportion of patients that felt completely recovered increased over time (p<0.001) (**Supplementary Table S2**). The proportion of patients that felt completely recovered did not differ significantly between the 2- and 3- year visits (mean difference [MD] +0.02 [95%CI -0.03 to 0.06], p=0.48). At 3 years, 72/297 (24%) of the patients felt completely recovered from COVID-19. Patients reported an average a recovery level of 80% (IQR 60-95) compared to their pre-COVID-19 health status.

Symptoms

The prevalence of symptoms of impaired fitness, fatigue, and muscle weakness decreased significantly over total follow-up time (all p<0.0019); a similar trend was found for dyspnea and sleep disturbances but these differences were not significant after Bonferroni correction (**Figure 2**). Between the 2- and 3-year visits, the prevalence of memory problems significantly increased (odds ratio [OR] 1.4 [95%CI 1.1 to 1.7], p<0.001); a similar trend was found for joint pain and sleep disturbances. The prevalence of concentration problems, sensory overload, and balance problems did not significantly change over time.

At 3 years, more than half of the patients experienced fatigue (197/299 [66%]), impaired fitness (188/298 [63%]), memory problems (176/298 [59%]), or concentration problems (158/298 [53%]) (**Supplementary Table S3**). Regarding the severity of these symptoms, impaired fitness was indicated as severe or very severe by 54/184 (28%) patients, fatigue by 71/196 (37%), memory problems by 36/175 (20%), and concentration problems by 41/157 (26%) at 3 years (**Supplementary Table S4A and S4B**).

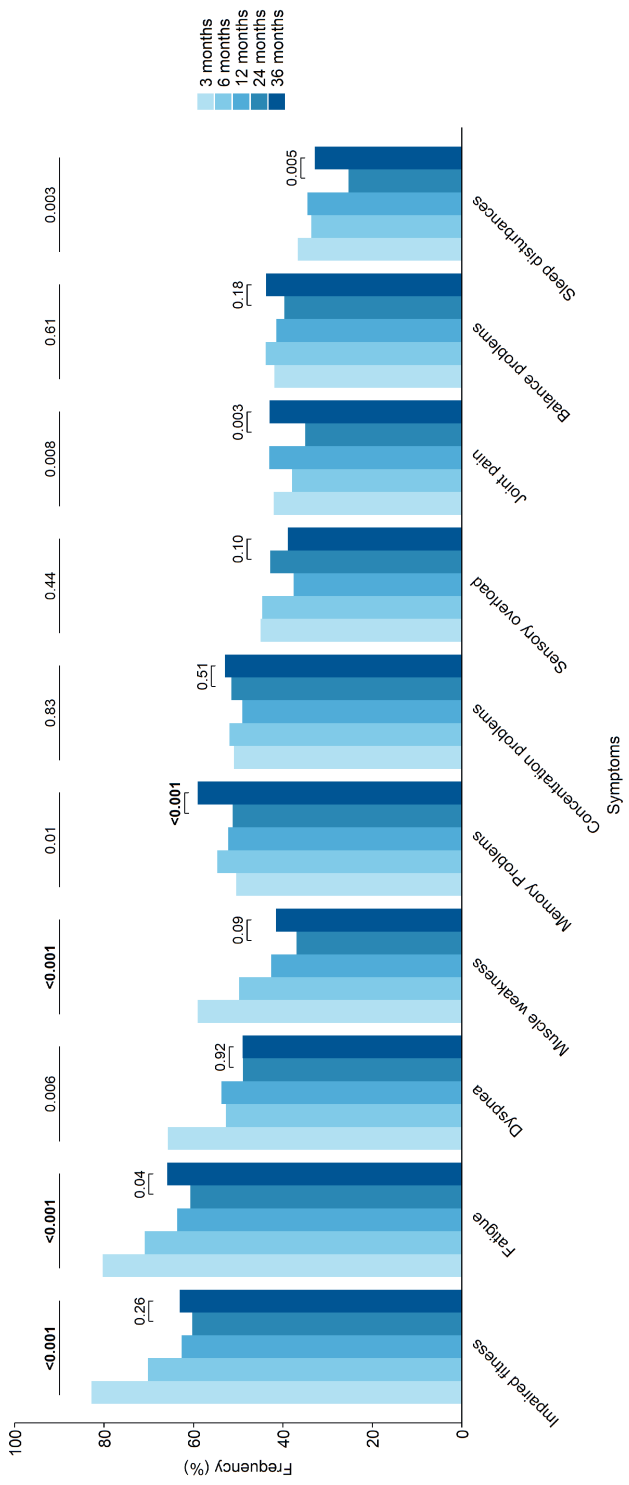

Figure 2. Trajectories of the ten most prevalent symptoms in patients with COVID-19 up to 3 years after hospital discharge. *P values are obtained from Generalized Estimating Equations analysis, and are presented for changes over the overall follow-up period at the top and specifically from 2 to 3 years follow-up above the columns. A P value less than 0.0019 was considered statistically significant and is indicated in bold.*

PROMs

Outcomes for fatigue, participation, return to work, and HRQoL improved significantly over time (all p<0.005); a similar trend was found for mental health outcomes, but these differences did not reach significance after Bonferroni correction (**Figure 3** and **Supplementary table S5**). Cognitive failures significantly worsened over time (p<0.001). Between the 2- and 3-year visits, the fatigue score (MD +1.0 [95%CI 0.4 to 1.6], p=0.002), cognitive failures score (+2.2 [0.9 to 3.4], p<0.001), and SF-36-MCS score (-2.2 [-3.1 to -1.3], p<0.001) significantly worsened; a similar trend was found for the participation satisfaction component score, and employment status. The sleep quality score did not significantly change over time.

At 3 years, 176/286 (62%) patients experienced poor sleep quality, 163/295 (55%) fatigue, 80/283 (28%) cognitive failures, 33/295 (11%) depression, and 25/295 (9%) anxiety (**Supplementary Table S5**). Among patients with a paid job before their SARS-CoV-2 infection, 57/129 (44%) had not fully returned to work. Regarding work limitations due to COVID-19, patients (n=121) were limited for a median of 20.0% (IQR 0.0-45.0) of their time in time management demands, 83.3% (70.3-100.0) in physical demands, 19.4% (2.8-41.7) in mental-interpersonal demands, and 20.0% (0.0-45.0) in output demands. Patients had a median 7.7% loss in productivity compared to reference values of healthy (not limited) employees. Regarding HRQoL, patients reached a median SF-36 physical component score of 47.7 (34.9-54.0) and mental component score of 50.0 (39.5-55.5) at 3 years.

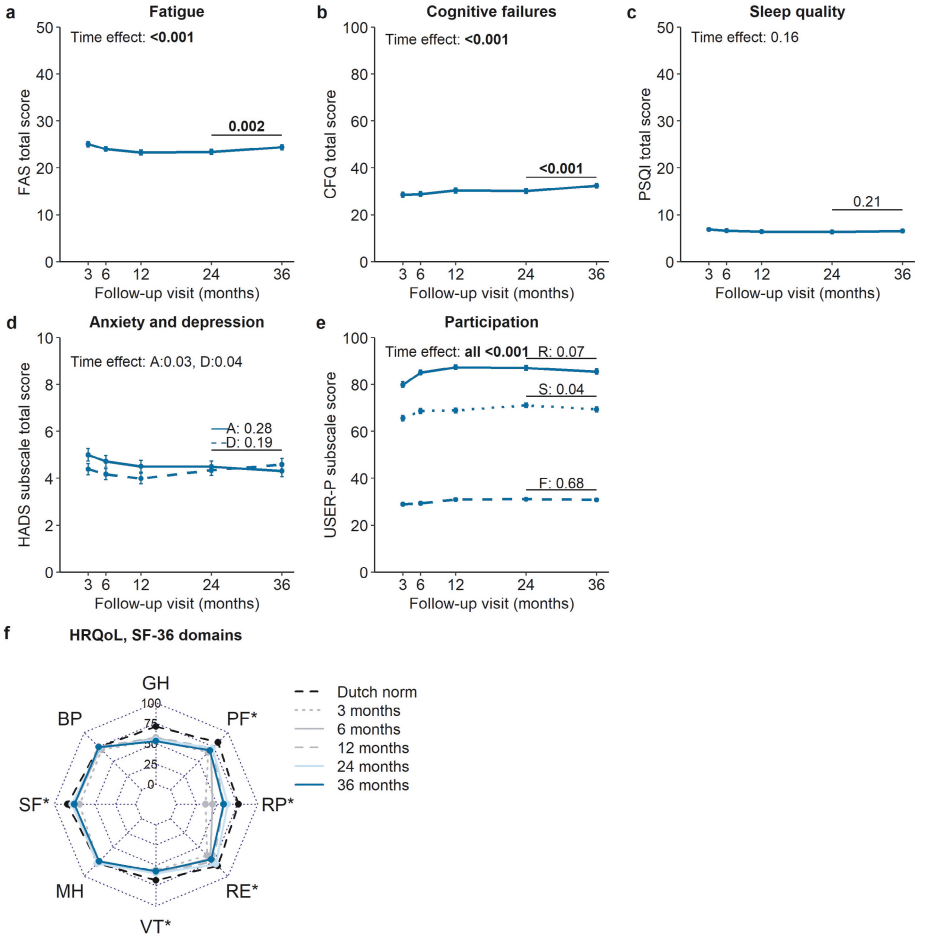

Figure 3. Trajectories of PROMs in patients up to 3 years after hospitalization for COVID-19.
*Data are presented as estimated means with standard errors obtained from Generalized Estimating Equations analysis. The trajectories from 3 to 36 months post-discharge are presented for health outcomes of fatigue (a), cognitive failures (b), sleep quality (c), anxiety [denoted by A] and depression [D] (d), and participation (e). In panel e, USER-P includes the subscales restriction [R], satisfaction [S], and frequency [F]. In the panels a-e, P values are presented for the overall time effect from 3 to 36 months (top left corner) and specifically for the trajectory between the 2- and 3-year visits (above trajectory line). A P value less than 0.00417 was considered statistically significant and is indicated in bold. For HRQoL, data are presented for each SF-36 domain in a spider plot (f), * indicates a P value <0.00417 for the trajectory between the 2- and 3-year visits. FAS, Fatigue Assessment Scale; CFQ, Cognitive Failures Questionnaire; PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; SF-36, 36-item Short Form Health Survey with the domains: GH, General Health; PF, Physical Functioning; RP, Physical Role Impairment; RE, Emotional Role Impairment; VT, Vitality; MH, Mental Health; SF, Social Functioning; BP, Bodily Pain.*

Post-Exertional Malaise (PEM)

A total of 105/292 (36%) patients reported PEM at 3 years. These patients were particularly characterized by a higher proportion of females (48% vs. 19%, p<0.001), having ≥1 comorbidities (89% vs. 76%, p=0.009), and more frequently physical inactive pre-COVID-19 (20% vs. 5%, p<0.001), compared to those without PEM (**Supplementary Table S6**). In the PEM group, the median PEM total score was 18/40 (13-23). Many patients with PEM (92/95 [98%]) experienced co-occurring health problems, with 41/95 (42%) patients experiencing concurrent fatigue, cognitive failures, and dyspnea (**Figure 4a**). Among patients without PEM, 10/179 (6%) also experienced these overlapping health problems. Moreover, patients with PEM reported an average recovery level of 55% compared to 88% among those without PEM at 3 years. The frequency and severity of PEM symptoms are shown in **Supplementary Table S7**.

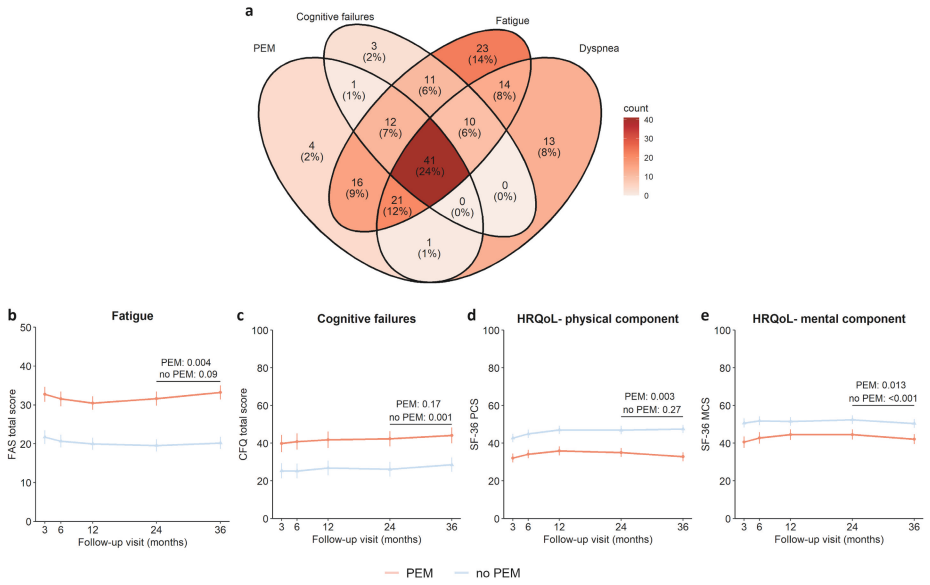

Figure 4. Co-occurring health problems and health outcome trajectories in patients with COVID-19 with and without PEM at 3 years.

Co-occurring health problems in patients with PEM (a) at 3 years after hospital discharge. Group comparisons were performed for the 3-year trajectories of fatigue (b), cognitive failures (c), and HRQoL physical component (d) and mental component summary (e) scores, adjusted for sex, pre-COVID-19 employment, pre-COVID-19 education level, pre-COVID-19 physical activity level, pre-existing comorbidities obesity, pulmonary disease, and cardiovascular disease, and intensive care unit admission during hospitalization. P values are presented for within group differences between the 2- and 3-year visit, obtained from Generalized Estimating Equations analysis. PEM, Post-Exertional Malaise; FAS, Fatigue Assessment Scale; CFQ, Cognitive Failures Questionnaire; HRQoL, Health-Related Quality of Life; SF-36, 36-item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary.

Risk factors for PEM after hospitalization for COVID-19 included female sex (OR 3.4 [95%CI 1.9 to 6.0], p<0.001), pre-existing pulmonary disease (3.0 [1.7 to 5.6], p<0.001), pre-COVID-19 physical inactivity (2.3 [1.2 to 4.1], p=0.008), and ICU treatment for COVID-19 (1.8 [1.02 to 3.0], p=0.04, and a trend was found for younger age (0.97 [0.946 to 1.001], p=0.061).

Figure 4b-e present the 3-year trajectories of fatigue, cognitive failures, and HRQoL in patients with and without PEM. Patients with PEM showed worse outcomes over the entire 3-year follow-up period compared to patients without PEM, with the fatigue score (MD +1.6 [95%CI 0.50 to 2.7], p=0.004), SF-36-PCS (-2.3 [-3.7 to -0.75], p=0.003), and SF-36-MCS (-2.4 [-4.3 to -0.51], p=0.013) scores worsening significantly between the 2- and 3-year visits. In patients without PEM, the cognitive failures score (+2.4 [0.94 to 3.9], p=0.001) and SF-36-MCS (-2.0 [-3.0 to -1.0], p<0.001) worsened significantly in the third year.

Discussion

This multicentre cohort study showed that, despite improvements over time, many health problems persisted up to 3 years after hospitalization for COVID-19. Fatigue and cognitive problems were most frequently reported throughout follow-up, and even worsened between the 2- and 3-year assessments. Furthermore, joint pain, sleep disturbances, resuming work, and HRQoL components, showed a similarly worsening trend. At 3 years, only 24% of our patients reported complete recovery. Importantly, 36% of patients experienced PEM, with most of these patients (98%) experiencing co-occurring health problems. Patients with PEM at 3 years showed poor health outcomes over the entire 3-year follow-up period. Female sex, pre-existing pulmonary diseases, and ICU admission for COVID-19 were identified as risk factors for PEM.

Although fatigue and cognitive failures showed statistically significant worsening between 2 and 3 years of follow-up, the changes in these outcome scores for the total group were relatively small. Taken into account the standard minimal clinically important difference (MCID) of 4 points on the FAS score,[28] 25% of patients reported a clinically important worsening in fatigue scores. As the MCID has not been previously determined for the CFQ, a 10% change (10 points) in CFQ scores was used as the threshold. Between 2 and 3 years, 20% of patients reported a clinically important worsening in cognitive failures scores. On the contrary, 14% of patients had a clinically important improvement in fatigue scores and 10% in cognitive failures scores. Zhang and colleagues also found a worsening of symptoms (fatigue or muscle weakness, joint pain, and hair loss) from 2 to 3 years post-hospitalization for COVID-19, but their sample was less severely ill (4% ICU admission).[20] Yang and colleagues observed no significant changes in symptom rates, while fatigue tended to improve, between 2 and 3 years after hospitalization for COVID-19.[19] The discrepancies in findings across studies may be due to varying study designs, COVID-19 subpopulations, and assessment tools, requiring further cohort studies to confirm previous findings. Nonetheless, the overall picture remains that many problems not only persist over time, but some may even worsen. Additionally, symptoms of long COVID can remit and relapse over time,[6] highlighting the importance of long-term

monitoring beyond 3 years post-hospitalization to better understand disease trajectory and identify factors contributing to long-term recovery. These insights may assist policy makers and healthcare providers in refining COVID-19 aftercare strategies, research agendas, and guidelines.

At 3 years, 36% of our patients experienced PEM, a hallmark feature in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and a key symptom in the recent Long COVID definition.[6] However, PEM is a poorly understood symptom of long COVID. A population-based study of patients after a positive SARS-CoV-2 test reported a prevalence of PEM of 23.2% in females and 17.8% in males up to 18 months post-infection,[43] compared to a prevalence of PEM ranging from 59% to 89% up to 12 months post-infection in patients with long COVID.[10-12] This study demonstrates for the first time that PEM is also a prominent feature in patients after hospitalization for COVID-19.

Our findings show that females, patients with pre-existing pulmonary disease, patients with low pre-COVID-19 physical activity level, and ICU-treated patients for COVID-19 were more likely to experience PEM. These risk factors are also associated with other health problems following COVID-19,[3,44,45] suggesting they contribute to a broader risk for long COVID rather than being linked to just one specific symptom. Notably, 42% of patients with PEM experienced concurrent fatigue, cognitive failures, and dyspnea, while this was only 6% in those without PEM. Moreover, patients with PEM at 3 years showed poorer health outcomes throughout the entire study period. Previous studies on PEM following COVID-19 showed worsening of symptoms following different types of activities,[46] long-term persistence of PEM,[47] and its association with co-occurring health problems[10,11,43,47] and a poorer disease course.[10] Together, these findings support the idea that patients with PEM represent a more severe phenotype of long COVID with potentially unfavourable prognosis. We suggest that the early identification of PEM is crucial to optimize individualized care and improve long-term outcomes.

Long COVID is a complex condition characterized by a wide range of symptoms. Our findings extend and add to findings from previous studies showing persistent symptoms lasting up to 3 years after hospitalization for COVID-19,[19-21] with the prevalence and burden of health outcomes fluctuating over time. Although hospitalization for COVID-19 is a significant risk factor for developing long COVID,[45,48] it can develop after any severity of acute COVID-19 illness. Long COVID is linked to new-onset conditions such as dysautonomia, particularly postural orthostatic tachycardia syndrome (POTS), and ME/CFS. Several hypotheses have been proposed to underlie mechanisms of long COVID. These include viral persistence or latent viral reactivation, immune dysregulation, neuroinflammation, mitochondrial dysfunction, autoimmunity, and microvascular thrombosis, which have also been specifically linked to fatigue and cognitive sequelae.[49-52] Ideally, future studies should include comprehensive assessment of long-term health outcomes, including PEM, dysautonomia, and POTS, and underlying mechanisms of long COVID, to capture its full spectrum.

The strengths of this study include its longitudinal multicentre design with a 3-year follow-up period assessing a comprehensive set of PROMs in a large and clinically well-defined cohort. This approach enabled detailed health assessment at five time points following hospital discharge, providing a thorough evaluation of health trajectories. Recently, PEM has gained recognition as a debilitating

symptom of long COVID,[43] however, studies assessing PEM remain scarce.[14] Our study addresses this gap by being among the first to assess PEM in patients previously hospitalized for COVID-19, providing insights into its prevalence and its role as a defining feature of long COVID. The study also has limitations, including the absence of control groups of individuals without COVID-19 and individuals not hospitalized for COVID-19, and the inability to compare our outcomes with pre-COVID-19 levels. Our findings may not generalize to non-hospitalized patients or those vaccinated before admission, as vaccination has consistently been shown to lower the risk of long-term health problems.[53] This study lacks data on the eligible recruitment population due to the surge of patients admitted to the participating centres. However, recruitment of study participants occurred independently of the patient's recovery status and primarily depended on availability of research personnel. Moreover, our patient characteristics align with those of the average Dutch patients hospitalized for COVID-19.[54] The CO-FLOW study composed of a high percentage of ICU-treated patients (42%) which may contribute to the relatively high percentage of patients with prolonged symptoms compared to other studies on patients hospitalized for COVID-19. Selection bias may have played a role in this long-term follow-up cohort, as 47% (306/650) of patients did not participate in the study extension, potentially leading to an overrepresentation of individuals with long-term health problems. However, although patients included in the 3-year follow-up analysis differed slightly in baseline characteristics from those not included (dropouts and non-responders), health outcomes at 2 years did not differ significantly between the two groups. The study assessment relied on PROMs, which, while providing valuable insight into patients' experience of symptoms and their impact on daily functioning, may introduce bias in estimating health problems due to their inherently subjective nature. To enhance the validity of our findings, validated and widely recognized questionnaires were used to measure health outcomes. The CO-FLOW study comprised both objective and self-reported assessments up to 2 years post-hospitalization; objective assessments indicated generally good physical recovery and minimal cognitive deficits. However, the high symptomatic burden in self-reports was often not reflected in objective measures. To reduce the burden of repeated assessments, a survey was conducted in the extended study at 3 years. Notably, to determine whether changes in health outcomes are reflected in both self-reports and objective measurements, future studies may consider to include a comprehensive evaluation of both self-reported and objective outcomes. Further, PEM was only assessed at the 3-year follow-up, lacking a longitudinal evaluation, and relied on the DePaul Symptom Questionnaire as opposed to the gold standard but burdensome invasive two-day cardiopulmonary exercise testing.

In summary, health problems remained prevalent in patients up to 3 years after hospitalization for COVID-19, with a worsening of self-reported fatigue and cognitive problems during the third year post-discharge. At 3-year follow-up, 36% of patients experienced PEM, with many also experiencing co-occurring health problems, representing a more severe phenotype of long COVID. Our findings highlight the urgent need for research into effective management strategies for long COVID, as well as the importance of ongoing monitoring of disease trajectory to better understand the long-term outcomes of COVID-19.

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Chapter 10

Patients' evaluation of aftercare following hospitalization for COVID-19: satisfaction and unmet needs

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*** Listed in Appendix

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Abstract

Background Patient experiences with COVID-19 aftercare remain largely unknown. We evaluated COVID-19 aftercare from a patient perspective one year after hospitalization, assessing satisfaction and its associated factors, and unmet needs.

Methods The Satisfaction with COVID-19 Aftercare Questionnaire (SCAQ) was developed as part of a multicenter prospective cohort study and administered one year after hospital discharge. The SCAQ assesses (1) patient satisfaction, comprising information provision, rehabilitation, follow-up by hospitals and general practitioners (GPs), the most important aftercare topics, and overall satisfaction, and (2) unmet needs.

Results 487/561 (87%) COVID-19 patients completed the SCAQ, all had been discharged from the hospital between March 2020 and May 2021. Among responders, the median age of patients was 60 (IQR 54–67) years, 338 (69%) were male, and the median length of stay in the hospital was 13 (6–27) days. Patients were least satisfied with information on who could be contacted with questions when health problems arise (59% satisfied or very satisfied). Many patients (75%) received rehabilitation, most frequently community-based (70%). Across the different community-based therapies, ≥60% of patients were satisfied with shared-decision making and ≥70% with the received therapy; a majority (≥79%) indicated a preference for receiving the same therapy again if needed. Regarding follow-up by hospitals, 86% of patients received this follow-up, most frequently visiting a pulmonologist (96%), being generally satisfied with the received aftercare. Aftercare from GPs was received by 39% of patients, with 88% being satisfied with the GP's availability and 79% with referral to appropriate aftercare providers. Patients (>50%) considered information-related items most important in aftercare. Overall, patients rated their satisfaction with aftercare 8/10 (7–9) points. Those who received medical rehabilitation (versus no rehabilitation, adjusted beta 0.61 [95%CI 0.11 to 1.11], p=0.02) or aftercare by a hospital medical specialist (1.1 [0.46 to 1.64], p<0.001) or GP (0.39 [0.053 to 0.72], p=0.023) reported significantly higher satisfaction than those without such aftercare. Unmet needs were reported by 35% of patients, with lack of information (20%) and lack of additional aftercare and/or involvement of their GP (19%) being the most frequently reported.

Conclusion Despite the forced quick development of COVID-19 aftercare, patients were generally satisfied. Follow-up by healthcare professionals and information provision is important to meet patients' aftercare needs.

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, resulted in a challenge for governments and healthcare systems worldwide to provide optimal long-term health care. Millions of people have been infected with SARS-CoV-2, ranging from asymptomatic infection to a life-threatening syndrome.[1] The pandemic forced the quick development of care pathways without adequate knowledge of the patients' long-term care needs.

As we now know, many patients hospitalized for COVID-19 suffer from long-term health effects, comprising physical, cognitive, and mental problems,[1-5] known as long COVID or Post-COVID-19 Condition.[6,7] Previous studies reported that 45%-90% of the patients hospitalized for COVID-19 experience at least one persistent symptom one year after discharge, underlining the importance of follow-up and tailored aftercare.[2,8-10] The large demand for COVID-19 aftercare has required healthcare providers to rearrange their existing services, implementing programs that match the most appropriate level of care for these patients. Post-COVID-19 management has resulted in increased pressure on healthcare services along with higher healthcare costs.[11-13]

Little is known about patients' experiences with aftercare after hospitalization for COVID-19. Understanding the patients' satisfaction with COVID-19 aftercare and unmet needs may help identify potential areas for improvement and may ultimately also improve healthcare services in future pandemics. This study aimed to explore 1) patients' satisfaction with COVID-19 aftercare and its associated factors and 2) unmet needs in patients previously hospitalized for COVID-19. We used the COVID-19 Aftercare Questionnaire (SCAQ), which was specifically designed for this study.

Methods

Study design and participants

We performed a cross-sectional study among patients who had been hospitalized for COVID-19. The study was performed as part of an ongoing two-year prospective multicenter cohort study: COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system (CO-FLOW), conducted in the Rotterdam–Rijnmond–Delft region of the Netherlands. CO-FLOW participants were patients who had been hospitalized for COVID-19 in this region (1 academic hospital and 6 regional hospitals), aged 18 years or older, and with sufficient knowledge of the Dutch or English language. Patients were included between July 2020 and Oct 2021. CO-FLOW visits were performed at 3, 6, 12, and 24 months after hospital discharge and included physical and cognitive tests and an online survey. More information about the CO-FLOW study design can be found elsewhere.[14] The Medical Ethics Committee of Erasmus MC (MEC-2020-0487) approved the CO-FLOW study. All participants provided written informed consent before the start of study measurements. The study is registered on the World Health Organization International Clinical Trial Registry Platform (NL8710). Data were collected and stored using the Castor Electronic Data Capture system (Castor EDC, Amsterdam, the Netherlands).

Study procedures

The SCAQ is an online questionnaire assessed as part of the one-year CO-FLOW study assessments. The questionnaire is only available in Dutch and therefore restricted to participants with sufficient knowledge of the Dutch language. Participants received the SCAQ by email approximately 3–4 weeks before the one-year visit and were invited to complete the questionnaire before the visit; an automatic reminder was sent after seven days. For participants who did not complete the online questionnaire by the time of the visit, the SCAQ was assessed by one of the research team members during the on-site study visit. This was also done for participants who previously received questionnaires per post.

Routine care pathways

Following hospitalization for COVID-19, patients unable to be discharged home and requiring inpatient multidisciplinary rehabilitation were referred to a medical rehabilitation center (Med-rehab) or a skilled nursing facility (SNF-rehab).[15] Patients who were sufficiently independent at discharge were discharged home with or without the support of community-based rehabilitation (Com-rehab), often mono-disciplinary treatment, or referred to outpatient Med-rehab for multidisciplinary rehabilitation. Following Med- or SNF-rehab, patients may have continued rehabilitation in the community.

In the region where this study is conducted, it is standard practice that the discharging hospital offers outpatient follow-up to COVID-19 patients. Some hospitals have designed specific, sometimes multidisciplinary, outpatient clinics for COVID-19 patients, while others embedded the follow-up in regular outpatient clinics. The follow-up program is hospital-specific; the timing of the first follow-up visit varies between 1 and 3 months post-discharge. Pulmonary function tests (spirometry and diffusion capacity), laboratory tests, and radiology (chest radiography and chest CT scans) are generally performed as part of the follow-up. A consultation, face-to-face or a telephone/video consultation due to COVID-19 restrictions, with a hospital medical specialist—most frequently a pulmonologist—is usually scheduled within one week thereafter. Patients with no or limited residual pulmonary abnormalities are discharged from further follow-up in the hospital. Apart from aftercare from hospital medical specialists, general practitioners (GPs) play a pivotal role in coordinating COVID-19 aftercare as many individuals typically reach out to their GP as their first contact when discussing health problems.

Satisfaction with COVID-19 Aftercare Questionnaire (SCAQ)

We developed the SCAQ instrument in co-creation with a subgroup of the CO-FLOW study participants and an implementation specialist. The instrument assesses patient satisfaction and unmet needs regarding COVID-19 aftercare following hospitalization for COVID-19. We performed four online focus group interviews, each consisting of 4–5 participants, to conduct semi-structured interviews on predefined themes related to COVID-19 aftercare, e.g., information provision, rehabilitation, and post-discharge follow-up by hospital and GP. Participants were free to deviate from the predefined themes and interact with each other. The focus groups were audio recorded and transcribed. We included the predefined themes to develop a draft version of the SCAQ and

added the additional themes as indicated by the participants during the focus groups. We conducted a pilot test with 9 participants to assess the questions' clarity, comprehensibility, and feasibility. Textual modifications were made to the SCAQ if necessary.

The final version of the SCAQ assesses 1) patient satisfaction, comprising satisfaction with information provision, rehabilitation, and post-discharge follow-up by hospital and GP, as well as the most important aftercare topics and overall satisfaction, and 2) unmet needs. Patients scored their satisfaction regarding information provision, rehabilitation, and post-discharge follow-up by hospital and GP on a 5-point Likert scale: very dissatisfied, dissatisfied, not satisfied and not dissatisfied, satisfied, or very satisfied. Patients scored their overall satisfaction with COVID-19 aftercare on a 10-point numeric scale. Besides closed questions, patients could enter areas for improvement and other feedback in open-text fields. The number of SCAQ items varied across responders, depending on their specific aftercare received. The time to complete the questionnaire was approximately 10 min. The SCAQ items are presented in more detail in the **Supplementary Methods**.

Information provision

Satisfaction with information provision at hospital discharge or thereafter was assessed in 3 items (e.g., 'How satisfied are you with information about the recovery period?').

Rehabilitation

Satisfaction with rehabilitation was assessed for: A, shared decision-making ('How satisfied are you with discussing your treatment plan with your physician?'); B, the treatment ('How satisfied are you with the treatment you received?'); and C, whether patients would prefer to receive the same type of treatment again if they found themselves in similar circumstances.

For Med- and SNF-rehab, comprising multidisciplinary treatment, satisfaction regarding items A–C was rated for the overall rehabilitation program that is guided by an interdisciplinary team under supervision of a rehabilitation physician or geriatrician. Additionally, items A and B were also rated separately for each therapy during Med-rehab (in- and outpatient) and SNF-rehab (inpatient). For Com-rehab, satisfaction regarding items A–C was rated for each therapy that the patient received (e.g., physical and occupational therapy).

Follow-up by the hospital and GP

Patients were asked whether they had received follow-up by the hospital and, if so, which medical specialist (e.g., pulmonologist, cardiologist, or internist) they had visited. Satisfaction with aftercare from the hospital was assessed in 7 items (e.g., 'How satisfied are you with the timing of the first follow-up visit'). Patients who had not received follow-up by the hospital were asked whether they had received an invitation for a follow-up visit and about their willingness to participate in such follow-up.

Satisfaction with aftercare from the GP was assessed for the GP's availability (e.g., for asking questions) and referral to appropriate aftercare providers.

Most important aftercare topics

Patients scored, with a maximum of 5, the most important aftercare topics (e.g., information about the recovery period and the possibility of getting in touch with peers) from a list of 22 items (**Supplementary Methods**).

Overall satisfaction with COVID-19 aftercare

Patients rated their overall satisfaction with COVID-19 aftercare on a numeric 10-point scale ranging from 'very dissatisfied' (1) to 'very satisfied' (10).

Unmet needs

Potential unmet needs were assessed in information provision, shared decision-making, additional aftercare and/or involvement of the GP, and practical matters (e.g., accessibility of healthcare provider). If one or more of these unmet needs were reported, more specific options (6 to 8 items) followed to further characterize the unmet need (**Supplementary Methods**).

Demographics and clinical characteristics

Demographics and clinical characteristics were collected for descriptive reasons and to assess whether these characteristics were associated with overall satisfaction. We collected patient demographics (age, sex, body mass index [BMI], migration background, education level, living situation, and employment status) and clinical characteristics (comorbidities, timing of hospitalization [COVID-19 wave], oxygen therapy, invasive mechanical ventilation, COVID-19-directed treatment, intensive care unit [ICU] admission, ICU length of stay, and hospital length of stay) at hospital admission from electronic patient records in the participating hospitals and with complementary questionnaires. We classified patients as being hospitalized during the first COVID-19 wave (February to July 2020), the second wave (July 2020 to February 2021), and the third wave (February to June 2021).

Statistical analysis

Continuous variables were not normally distributed and presented as medians with interquartile ranges (IQR); normal distribution of the data was checked with the Shapiro-Wilk test. Categorical variables are presented as numbers with percentages. Some data are presented as both median (IQR) and mean (standard deviation [SD]) to allow for a comprehensive representation of the data distribution. To assess differences in demographics and clinical characteristics between responders and non-responders (patients who did not complete the SCAQ or those lost to follow-up), we used the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. Regarding the most important aftercare topics, patients who selected more than 5 items were excluded from this specific analysis. We performed additional analyses to gain in-depth information on patient satisfaction. For follow-up by the hospital, we assessed the association between groups of satisfaction levels (very dissatisfied or dissatisfied, not satisfied and not dissatisfied, satisfied, or very satisfied) regarding the timing of this follow-up and the number of days between discharge and follow-up using Spearman's rank correlation coefficient. We calculated the timing of follow-up in the hospital as the number of days between hospital discharge and the first follow-up assessment in the hospital. For overall satisfaction, we conducted a multivariable generalized estimating equations (GEE)

analysis to assess determinants for overall satisfaction with COVID-19 aftercare (numeric 10-point scale). For this analysis, age, sex (male vs. female), ethnicity (European vs. non-European), pre-COVID living situation (together with partner or parent vs. alone with or without children), pre-COVID employment status (employed vs. unemployed vs. retired), timing of hospitalization (first vs. second vs. third COVID-19 wave) and aftercare factors including rehabilitation (no rehabilitation vs. Com-rehab vs. Med-rehab vs. SNF-rehab), and follow-up by the hospital (yes vs. no), or by a GP (yes vs. no) were entered as fixed factors in the model. Quotes from open-text fields were not systematically analysed, but manually selected to further illustrate the level of satisfaction with aftercare. A p-value <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA).

Results

Participants

A total of 561 out of 650 CO-FLOW study participants was invited to complete the SCAQ, of whom 487 (87%) responded; 89 patients were not invited due to reasons such as prior withdrawal (n=40), language barrier (n=11), or other reasons (n=38) including inability to attend the one-year follow-up visit (**Figure 1**). **Table 1** presents the demographics and clinical characteristics at hospital admission of the 487 responders, all had been discharged from the hospital between March 2020 and May 2021. The median age of participants was 60 (IQR 54–67) years at admission, 338 (69%) were male, and 385 (79%) had a European background; 202 (42%) patients were treated in the ICU for COVID-19 and the median number of days in the hospital was 13 (6–27). Responders had more frequently a European background and middle to high education level and had less frequently diabetes in comparison to non-responders (n=163) (**Supplementary Table S1**). Patients completed the SCAQ at a median follow-up time of 356 (339–399) days post-discharge. Among responders, 47/487 (10%) patients did not receive any type of aftercare, neither rehabilitation nor follow-up by the hospital or GP.

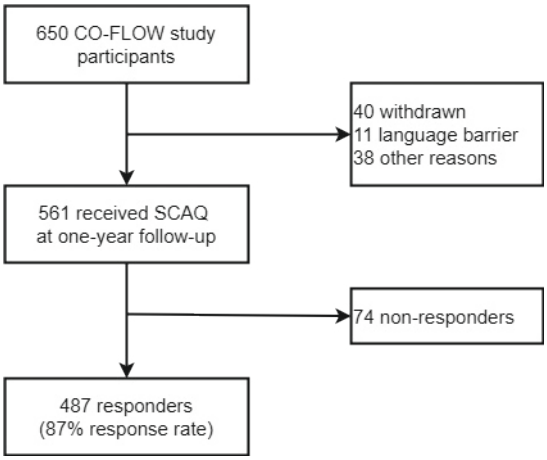

Figure 1. Flowchart of study participants.
SCAQ: Satisfaction with COVID-19 Aftercare Questionnaire.

Table 1. Demographic and clinical characteristics of study participants at hospital admission.

	Study participants (n=487)
Demographic characteristics	
Age (years)	60 (54-67)
Male sex	338 (69)
BMI (kg/m^2)	28 (26-32)
Ethnicity	
European	385 (79)
Dutch Caribbean	59 (12)
Asian	19 (4)
Turkish	13 (3)
(North) African	10 (2)
Education level	
Low	152 (32)
Middle	179 (37)
High	151 (31)
Living situation	
Together, with partner or parent	396 (81)
Alone, with or without children	91 (19)
Employed	294 (61)
Clinical characteristics	
Comorbidities	

Table 1. Continued.

	Study participants (n=487)
≥1 comorbidity	399 (82)
Obesity (BMI≥30 kg/m^2)	194 (40)
Diabetes	82 (17)
Cardiovascular disease or hypertension	182 (37)
Pulmonary disease	121 (25)
Renal disease	44 (9)
Gastrointestinal disease	24 (5)
Neurological disease	51 (10)
Malignancy	57 (12)
Autoimmune disease	57 (12)
Mental disorder	22 (5)
Oxygen therapy	472 (97)
Treatment for COVID-19	
(Hydroxy)chloroquine	13 (3)
Antivirals	71 (15)
Steroids	353 (72)
Anti-inflammatory	57 (12)
Convalescent plasma	8 (2)
ICU admission	202 (41)
Invasive mechanical ventilation	173 (36)
LOS ICU (days)	16 (9-31)
LOS hospital (days)	13 (6-27)
COVID-19 wave	
First	129 (26)
Second	252 (52)
Third	106 (22)

Data are presented as median (interquartile range) or number (%). Variables with missing data are BMI (n=47), ethnicity (n=1), education level (n=5), employed (n=4), treatment for COVID-19 (n=8), LOS ICU (n=2), and LOS hospital (n=1). BMI: body mass index, COVID-19: corona virus disease 2019, ICU: intensive care unit, LOS: length of stay.

SCAQ

Information provision

Most patients were satisfied with the information provided at hospital discharge or thereafter (**Figure 2**). The lowest level of satisfaction (59% satisfied or very satisfied) was found for information on who could be contacted with questions when health problems arise.

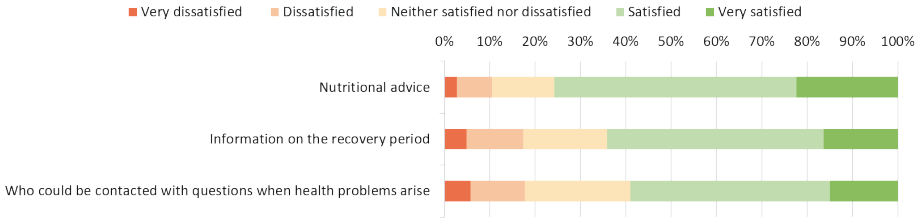

Figure 2. Patients' satisfaction with information provision after hospitalization for COVID-19.
Satisfaction with each item was assessed only for patients to whom it applies (self-indicated). Items were applicable to 362 (74%) of 487 patients on nutritional advice, 432 (89%) on information on the recovery period, and 439 (90%) on information on who could be contacted with questions when health problems arise.

Rehabilitation

Across the three rehabilitation settings Med-, SNF-, and Com-rehab, 342 (70%) patients participated in physical therapy, 124 (26%) in occupational therapy, 107 (22%) in psychological therapy, 71 (15%) in speech and language therapy, 124 (26%) in nutritional therapy, and 100 (21%) in vocational therapy; 123 (25%) patients did not receive rehabilitation. **Table 2** presents the patients' satisfaction with Med-, SNF-, and Com-rehab. Seventy-two (15%) patients received Med-rehab, of whom 89% reported a preference for receiving Med-rehab again if they found themselves in similar circumstances. Out of the 48 (10%) patients in SNF-rehab, 83% reported a preference for receiving SNF-rehab again if they found themselves in similar circumstances. The majority of patients (343/486, 71%) received Com-rehab after hospitalization for COVID-19, most frequently physical therapy (92%); a majority (95%) reported a preference for receiving physical therapy again if they found themselves in similar circumstances. As for vocational therapy, multiple patients reported in the open-text field that they had not (fully) resumed work one year after hospital discharge. These patients emphasized the importance of sharing knowledge about the health effects of COVID-19 with their employer. One patient reported: *'The responsibility lies too much in the hands of the patient. There is little room for shared decision-making. Also, there is little time to discuss progress. There seems to be limited knowledge about COVID-19?'*.

Table 2. Frequency of patients that received rehabilitation after hospitalization for COVID-19.

		(Very) Satisfied with shared decision-making[b]	(Very) Satisfied with treatment[b]	Preference for receiving the same treatment again (yes)[c]
	n (%)[a]	n (%)	n (%)	n (%)
Med-rehab (n=72)				
Rehabilitation physician	72 (100)	58 (82)	63 (89)	63 (89)
Physical therapy	71 (99)	62 (87)	64 (90)	
Occupational therapy	64 (89)	57 (89)	55 (86)	
Psychological therapy	50 (69)	45 (90)	44 (88)	

Table 2. Continued.

	n (%)[a]	(Very) Satisfied with shared decision-making[b] n (%)	(Very) Satisfied with treatment[b] n (%)	Preference for receiving the same treatment again (yes)[c] n (%)
Speech and language therapy	31 (43)	27 (87)	28 (90)	
Nutritional therapy	44 (61)	35 (80)	35 (80)	
Other*	4 (6)			
SNF-rehab (n=48)				
Elderly care physician	48 (100)	29 (60)	42 (88)	40 (83)
Physical therapy	47 (98)	37 (79)	41 (87)	
Occupational therapy	30 (63)	26 (87)	26 (87)	
Psychological therapy	19 (40)	14 (74)	17 (89)	
Speech and language therapy	19 (40)	13 (68)	15 (79)	
Nutritional therapy	30 (63)	27 (93)	28 (97)	
Other*	2 (4)			
Com-rehabd (n=343)				
Physical therapy	316 (92)	277 (88)	276 (87)	299 (95)
Occupational therapy	46 (13)	36 (78)	35 (76)	37 (80)
Psychological therapy	52 (15)	41 (79)	43 (83)	48 (92)
Speech and language therapy	32 (9)	30 (94)	31 (97)	29 (91)
Nutritional therapy	68 (20)	55 (81)	56 (82)	56 (82)
Vocational therapy	100 (29)	77 (76)	71 (70)	80 (79)
Other	3 (1)			

Data were obtained from 486 patients and are presented as n (%), where the percentage indicates the proportion of patients with this therapy among those who participate in this rehabilitation setting. Satisfaction was scaled on a 5-point Likert scale ranging from very satisfied, satisfied, not satisfied and not dissatisfied, dissatisfied, or very dissatisfied. The table presents the frequency of very satisfied or satisfied patients. Med-rehab, in- or outpatient medical rehabilitation; SNF-rehab, inpatient rehabilitation in a skilled nursing facility; Com-rehab, community-based rehabilitation.

[a]*Frequency is calculated based on the number of patients that participated in that specific type of rehabilitation.*

[b]*Frequency based on the number of patients that participated in that specific type of treatment.*

[c]*Med- and SNF-rehab comprise multidisciplinary treatment that is guided by an interdisciplinary team, patients who received Med- or SNF-rehab were therefore asked whether they would like to receive Med- or SNF-rehab again if they found themselves in similar circumstances. Com-rehab often comprise monodisciplinary treatment and patients were therefore asked to indicate for each type of treatment whether they would like to receive the same therapy again if they found themselves in similar circumstances.*

[d]*Com-rehab also comprises patients that may have participated in Med- or SNF-rehab. These patients scored satisfaction with Med- or SNF-rehab and Com-rehab separately.*

[*]*Most frequently a social worker.*

Follow-up by the hospital and GP

In total, 420/487 (86%) patients received follow-up by the hospital, the majority of whom (96%) visited a pulmonologist (**Figure 3A**). In contrast, 67/487 (14%) patients did not undergo this follow-up; in 39% of these patients, follow-up was not initially offered but the patient was willing to participate (**Figure 3B**). Regarding aftercare provided by the hospital medical specialist, the lowest level of satisfaction was found for the possibility of discussing options for aftercare with their medical specialist (76% satisfied or very satisfied, **Figure 3C**). The median follow-up time was 51 (43–66) days (mean 60±28.9 days) after hospital discharge. We found that increased satisfaction with the timing of the first follow-up visit significantly correlated with earlier follow-up in days (r=0.15, p=0.003) (**Supplementary Table S2**).

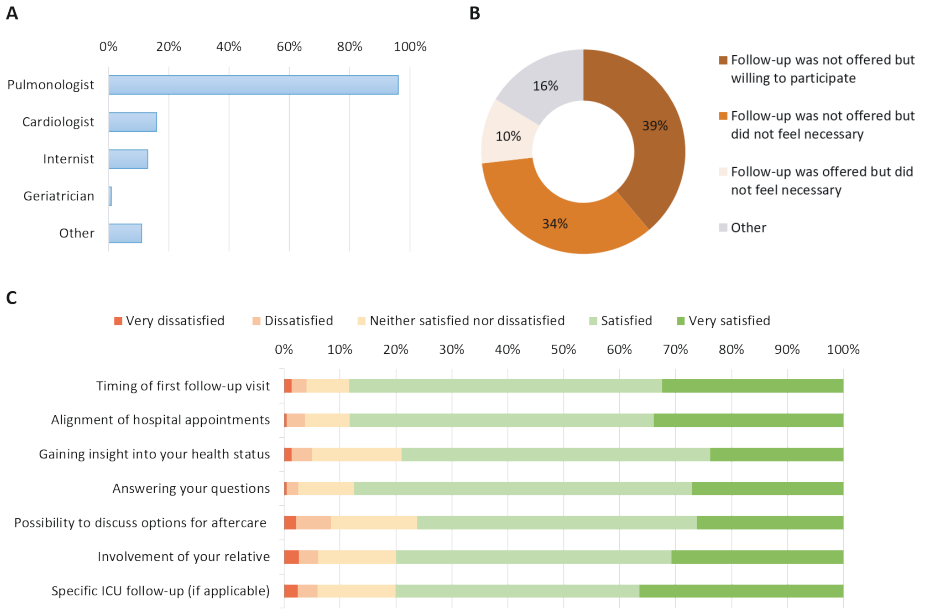

Figure 3. Follow-up by the hospital with **A**: the proportion of 420 COVID-19 patients that visited medical specialists, **B**: reasons for not participating in this follow-up, and **C**: patients' satisfaction with aftercare provided by their medical specialist.
***A**: 420 (86%) patients received follow-up by the hospital, of whom 292 (70%) patients visited one specialist, 77 (18%) two specialists, 33 (8%) three specialists, 14 (3%) four specialists, and 4 (1%) 5 specialists. **B**: Sixty-seven patients did not receive this follow-up; one example for 'other reasons' included 'follow-up via surveys only.' **C**: data are presented for 420 patients who participated in follow-up by the hospital and to whom it applies (self-indicated).*

Regarding GPs, 191/486 (39%) patients received their aftercare, of whom 88% reported being satisfied or very satisfied with their availability and 79% with their referral to appropriate aftercare providers. Several patients expressed gratitude toward the GP in the open-text field; one patient reported: '*The GP called me after my discharge from the hospital. She referred me to physical therapy and providers that have experience in guiding COVID-19 patients. This option was briefly mentioned in the hospital, but the GP discussed this extensively and recommended this type of therapy. For this I am very*

grateful.' However, a minority of patients was not satisfied with the services of the GP and pointed out that they would have liked their (closer) involvement after hospital discharge.

Most important aftercare topics

The most important aftercare topics were information-related, including information about potential problems after hospital discharge (51%), the recovery period (49%), and who could be contacted with questions (29%) (**Supplementary Figure S1**). Moreover, patients considered the involvement of their GP after hospital discharge (28%) and gaining insight into one's own health status and recovery by healthcare providers (24%) among the most important topics.

Overall satisfaction with COVID-19 aftercare

Patients rated their COVID-19 aftercare with a median of 8/10 (7–9) points (mean 7.3±1.9 points). In the multivariable analysis, Med-rehab (vs. no rehabilitation mean difference 0.61 [95%CI 0.11 to 1.11], p=0.02; vs. Com-rehab 0.61 [0.16 to 1.1], p=0.008; vs. SNF-rehab 0.41 [-0.20 to 1.02], p=0.19) or follow-up by the hospital (1.1 [0.46 to 1.64], p<0.001) or GP (0.39 [0.053 to 0.72], p=0.023) predicted higher satisfaction with COVID-19 aftercare than those without this aftercare (**Figure 4**).

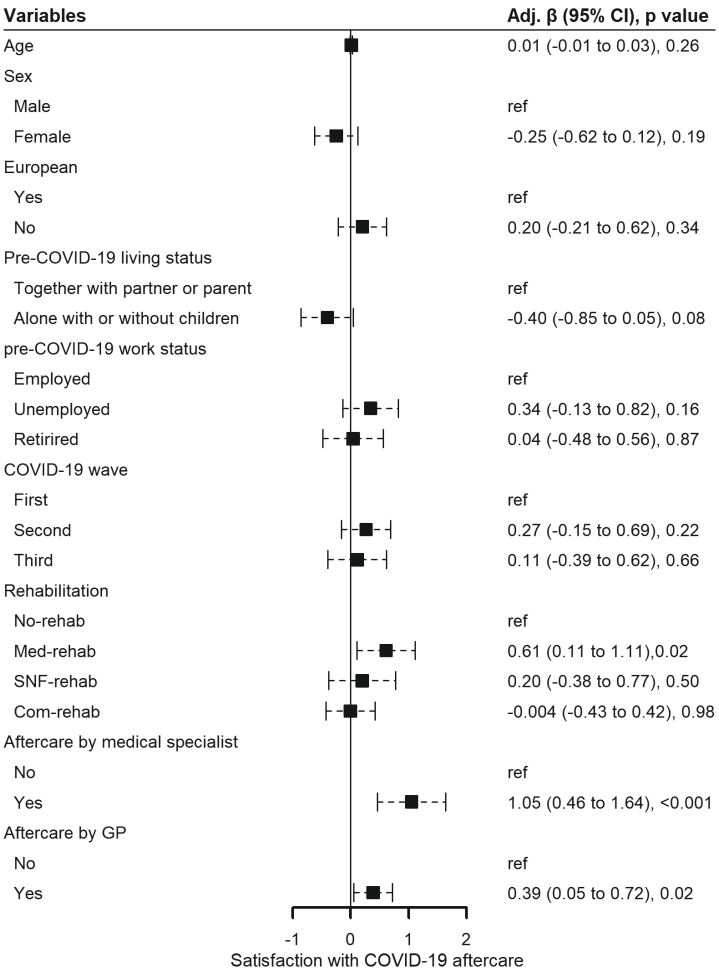

Figure 4. Forest plot showing predictors of the patients' overall satisfaction with COVID-19 aftercare.
The multivariable generalized estimating equations analysis included 482 patients. Satisfaction was assessed on a numeric scale from 0 to 10. For rehabilitation, patients were categorized according to the most specialized aftercare they had received after hospitalization for COVID-19, with Med- and SNF-rehab being the most specialized. Aftercare by a medical specialist indicates post-discharge follow-up provided by the hospital. Adj. β, adjusted beta; CI, confidence interval; No-rehab, patients who did not receive rehabilitation; Com-rehab, community-based rehabilitation; Med-rehab, in- or out-patient medical rehabilitation; SNF-rehab, inpatient rehabilitation in a skilled nursing facility; GP, general practitioner

Unmet needs

Data on unmet needs were available for 485 patients, of whom 170 (35%) reported unmet needs following hospitalization for COVID-19 (**Figure 5**). The most common unmet needs were information provision (20%) and additional aftercare and/or involvement of GP (19%). Specifically, 15% of all patients missed information about the potential problems after hospital discharge, 15%

about the recovery period at home (e.g., how to optimize recovery), and 14% missed (close) involvement of the GP after hospital discharge.

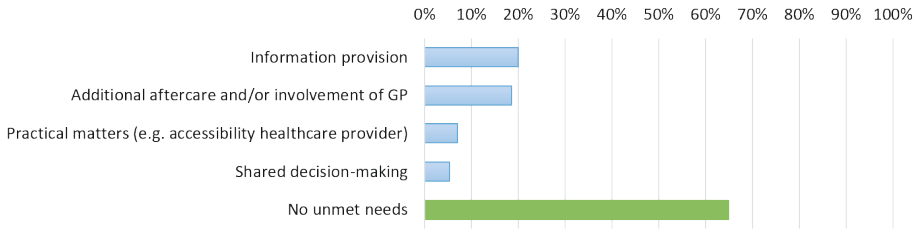

Figure 5. Unmet needs of patients recovering from COVID-19.
Unmet needs are presented for 485 patients.

Discussion

This multicenter cohort study evaluated COVID-19 aftercare from a patient perspective one year after hospital discharge, assessing patient satisfaction and unmet needs. Overall, patients were generally satisfied with their COVID-19 aftercare, rating their overall satisfaction 8 out of 10 points. This while the aftercare was developed quickly and mainly based on expert opinion. Patients who received medical rehabilitation or aftercare from the hospital or GP generally expressed higher overall satisfaction with COVID-19 aftercare than those who did not receive such aftercare. We found that 35% of the COVID-19 patients experienced unmet needs after hospitalization, most frequently the lack of information and the lack of involvement of the GP. These unmet needs were also considered most important in aftercare by the patients, indicating areas for improvement.

It may not be surprising that patients who received more intensive aftercare had a more positive perception of their aftercare than those who did not receive such care. Regarding rehabilitation, patients with medical rehabilitation often had severe COVID-19, which had a significant physical and mental impact, requiring intensive and multidisciplinary rehabilitation to support recovery.[3,4] Our findings indicate that this intensive and multidisciplinary type of rehabilitation is perceived as valuable by the most severely affected patients.

As for follow-up by hospitals, patients can gain insight into their health status, ask questions, and discuss options for aftercare with their medical specialist during this consultation. Our patients were generally satisfied with this aftercare. It is internationally recommended that hospitalized COVID-19 patients are routinely followed up at the discharging hospital.[16-18] Differences have been reported among European countries regarding the timing of the first follow-up visit by hospitals, varying between 1 to 6 months.[19] In our study, the patient's first follow-up visit by the hospital was, on average, 60 days after discharge. Although we found a positive correlation between satisfaction with the timing of the first follow-up and earlier follow-up, the correlation was weak and, therefore, we cannot offer strong recommendations for the timing of follow-up by hospitals.

Regarding GPs, only 39% of COVID-19 patients received aftercare from their GP, with the majority being satisfied with the GP's availability and referral to appropriate aftercare providers. Notably, the lack of involvement of a GP was one of the most frequently reported unmet needs as well as considered among the most important topics in aftercare by patients. GPs have a central role in coordinating COVID-19 aftercare, as patients usually contact their GP as their initial point of contact for health problems.

Our findings thus imply that a follow-up consultation with a healthcare professional is important to meet the COVID-19 patients' aftercare needs. However, we did not explore whether only medical specialists or GPs should provide this aftercare or if other healthcare professionals, such as case managers, could also offer this aftercare. Noteworthy, this type of aftercare is likely valuable not only for COVID-19 patients but also for those with other conditions.

Our findings indicate unmet information needs, while information provision was considered the most important in aftercare. Studies in the Netherlands, Belgium, and the United Kingdom also showed that individuals post-COVID-19 seek information.[20,21] Generally, meeting patients' information needs has been linked to their satisfaction with care and quality of life.[22] Online health platforms and patient support groups have been established across countries to provide COVID-19-related information to the general public, particularly patients and their families. Furthermore, on social media like Facebook, communities were created where COVID-19 patients can connect, share experiences, and offer peer support. Nevertheless, our patients still reported unmet information needs. Notably, we enrolled patients since the onset of the COVID-19 pandemic, a time where aftercare pathways were still in the process of development. Utilizing online health platforms also faces challenges, particularly in reaching diverse populations. For example, older individuals, ethnic minorities, and those from socioeconomically disadvantaged backgrounds are generally less likely to access online health information.[23-28] Nevertheless, these online health platforms and communities serve as valuable sources of information on the developing knowledge of COVID-19, informing many patients, enhancing understanding and reassurance, facilitating self-management, and supporting recovery from COVID-19.[21,29,30] We recommend the early implementation of a centralized online information point, a so-called live resource center, and increasing awareness of this online health platform during future pandemics.

We did not observe an association between patient characteristics such as age, sex, or migration background with patients' satisfaction with COVID-19 aftercare. Noteworthy, our study may have had limitations in assessing the effect of migration background on patient satisfaction as we only included patients with sufficient knowledge of the Dutch language. Moreover, we classified migration backgrounds as European or non-European in the statistical analysis due to the small group sizes of ethnic minorities. A recent study among hospitalized COVID-19 patients in Amsterdam, the Netherlands, showed that ethnic groups, including African Surinamese, South Asian Surinamese, Moroccan, and Turkish origin patients, had a higher risk of long COVID than Dutch origin patients at 12 weeks post-discharge.[31] This suggests that ethnic minorities in the Netherlands may have potentially greater COVID-19 aftercare needs than the general population. Moreover, ethnic

minorities may face challenges in accessing healthcare providers due to language barriers, which may influence their satisfaction with COVID-19 aftercare, which we possibly have missed in our study. Therefore, future research involving larger groups of patients with diverse migration backgrounds is warranted to better address their satisfaction with COVID-19 aftercare needs.

Besides language restrictions, our study is limited by the challenge of generalizing our findings from patients hospitalized for COVID-19 in the Netherlands to other countries. The variation in the course of SARS-CoV-2 variants, infection rates, population characteristics, and healthcare systems across countries resulted in heterogeneous follow-up programs and may hamper international comparisons. Furthermore, our study included patients hospitalized for COVID-19 during the first three COVID-19 waves in the Netherlands; those hospitalized afterward might have different aftercare experiences due to developing aftercare procedures. The median age of our study participants was 60 years; therefore, our findings may be less generalizable to younger age groups. Our study contains an overrepresentation of patients who had been admitted to the ICU compared to other cohort studies on hospitalized COVID-19 patients,[2,32] resulting in a somewhat higher proportion of males in our sample. Our academic center served as a regional referral center for ICU patients, and many study participants were included from this center. However, our patients received various COVID-19 aftercare to support their recovery, providing insights into experiences across different rehabilitation settings. The SCAQ was developed specifically for this explorative study to gain insight into patients' experiences with aftercare following hospitalization for COVID-19 in the Netherlands, as part of the one-year CO-FLOW study visit. Due to time constraints, assessing the validity and reliability of the questionnaire was not feasible. Given the persistent health effects of COVID-19 beyond one year,[2] signifying a potential need for prolonged aftercare, future studies are warranted to evaluate patients' healthcare utilization and satisfaction with aftercare in the longer term. Nonetheless, our study's conclusive findings emphasize the importance of delivering follow-up care and information provision, which hold significance to the broader public as these align with international guidelines.[30] Strengths of the study include its multicentre design and high response rate (87%). The study provides insight into the patients' evaluation of various aspects of COVID-19 aftercare and identifies unmet needs that could facilitate the improvement of care pathways during future pandemics.

In conclusion, we evaluated aftercare following hospitalization for COVID-19 from a patient perspective, leading to two main findings. First, the results emphasized the significance of follow-up after hospitalization to meet COVID-19 patients' aftercare needs. Facilitating a follow-up consultation with a healthcare professional for hospitalized patients during future pandemics is recommended to provide recognition, understanding, and appropriate aftercare to patients. Second, patients hospitalized for COVID-19 experienced unmet information needs. Early implementation of online health platforms across countries, serving as a central information point, could be vital to meeting patients' information needs during future pandemics

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Chapter 11

Immunological profiling in long COVID: overall low grade inflammation and T-lymphocyte senescence and increased monocyte activation correlating with increasing fatigue severity

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Abstract

Background Many patients with SARS-CoV-2 infection develop long COVID with fatigue as one of the most disabling symptoms. We performed clinical and immune profiling of fatigued and non-fatigued long COVID patients and age- and sex-matched healthy controls (HCs).

Methods Long COVID symptoms were assessed using patient-reported outcome measures, including the fatigue assessment scale (FAS, scores ≥22 denote fatigue), and followed up to one year after hospital discharge. We assessed inflammation-related genes in circulating monocytes, serum levels of inflammation-regulating cytokines, and leukocyte and lymphocyte subsets, including major monocyte subsets and senescent T-lymphocytes, at 3-6 months post-discharge.

Results We included 37 fatigued and 36 non-fatigued long COVID patients and 42 HCs. Fatigued long COVID patients represented a more severe clinical profile than non-fatigued patients, with many concurrent symptoms (median 9 [IQR 5.0-10.0] vs 3 [1.0-5.0] symptoms, $p<0.001$), and signs of cognitive failure (41%) and depression (>24%). Immune abnormalities that were found in the entire group of long COVID patients were low grade inflammation (increased inflammatory gene expression in monocytes, increased serum pro-inflammatory cytokines) and signs of T-lymphocyte senescence (increased exhausted $CD8^+$ T_{EMRA}-lymphocytes). Immune profiles did not significantly differ between fatigued and non-fatigued long COVID groups. However, the severity of fatigue (total FAS score) significantly correlated with increases of intermediate and non-classical monocytes, upregulated gene levels of CCL2, CCL7, and SERPINB2 in monocytes, increases in serum Galectin-9, and higher $CD8^+$ T-lymphocyte counts.

Conclusion Long COVID with fatigue is associated with many concurrent and persistent symptoms lasting up to one year after hospitalization. Increased fatigue severity associated with stronger signs of monocyte activation in long COVID patients and potentially point in the direction of monocyte-endothelial interaction. These abnormalities were present against a background of immune abnormalities common to the entire group of long COVID patients.

Introduction

A significant proportion of patients develops long-lasting symptoms after coronavirus disease 2019 (COVID-19). Different terms have been used to describe this condition, such as long COVID, post-acute COVID-19 syndrome, post-acute sequelae of COVID-19, long-haulers, or post COVID-19 condition.[1,2] In the current report, we will use the term long COVID, consistent with most literature and the most commonly used terminology amongst patients. Long COVID represents a broad spectrum of — often disabling — symptoms. Frequently reported symptoms of long COVID are fatigue, impaired fitness, dyspnea, and neuropsychiatric complaints.[3-6] Numerous studies showed the presence of these symptoms beyond 3 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with evidence of persistence even two years after the infection.[7] As patients with long COVID differ substantially regarding symptoms, severity, and recovery profile, attempts have been made to discern different clinical phenotypes of long COVID without reaching consensus to date.[8-10]

Disabling fatigue is one of the most prominent and debilitating symptoms of long COVID. Studies have reported that up to 41% to 60% of patients who had been hospitalized for COVID-19 still suffer from fatigue one year post-discharge, without evident improvement beyond 6 months and negatively impacting quality of life.[5,11-13] Fatigue may coexist with other symptoms; studies showed that fatigue is associated with neuropsychiatric symptoms, such as depression, in patients one year after hospitalization for COVID-19.[14] We have extensively analyzed the underlying immunopathogenic mechanisms of mood disorders in previous studies[15-18] and similar mechanisms might (partially) underlie the prolonged fatigue in long COVID. This problem thus requires in-depth evaluation regarding its pathogenesis, facilitating future interventions.

The prolonged fatigue state after acute COVID-19 shows clinical similarities with other post-infectious fatigue syndromes, such as that after Coxiella burnetii (Q fever) and Epstein-Barr virus (infectious mononucleosis) infection, and also shows similarities with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).[19-21] The latter is characterized by a range of debilitating symptoms, including fatigue, post-exertional malaise (a worsening of symptoms after minimal physical or mental exertion), sleep disturbances, and neurocognitive impairments.[22] Ongoing immune activation, reflected by for instance increased serum cytokine levels and increased circulating $CD8^+$ T-lymphocyte numbers, has been described in both post-infectious fatigue conditions and ME/CFS and is thought to play a role in the pathophysiology of these conditions.[23,24] Given the clinical similarities with post-infectious fatigue syndromes and ME/CFS, a similar immune activation may be involved in long COVID.

To date, several studies have identified persistent inflammatory monocyte and T- and B-lymphocyte abnormalities among patients in the convalescent phase of COVID-19.[25-31] Few studies assessed the association between specific symptoms of long COVID with immunological characteristics. However, a comprehensive and in-depth clinical and immunologic assessment focusing on fatigue, one of the most frequently reported symptom of long COVID, is lacking.

This study aimed to compare clinical and immune profiles of long COVID patients with and without fatigue, as well as with age- and sex-matched healthy individuals. We hypothesized that 1. long COVID patients have a distinct immune profile compared to healthy controls and 2. Long COVID with fatigue would exhibit a more severe and/or different clinical and immune profile than those without fatigue, and would show an immune profile comparable to patients with ME/CFS and mood disorders. We performed an immune assessment between 3-6 months after hospital discharge while clinical symptoms, evaluated with patient-reported outcome measures (PROMs), were longitudinally assessed for up to one-year post-discharge. We determined the expression of various sets of inflammation-related genes in circulating monocytes, serum levels of inflammation-regulating cytokines, and leukocyte and lymphocyte subsets, including major monocyte subsets and senescent T-lymphocytes. These assays were selected because we have previously shown that these assays revealed abnormalities in immune function in patients with various mental and somatic disorders[15-18,32-35] and ME/CFS (unpublished data).

Methods

Study participants and procedure

This cross-sectional study (IMMUNOFATIGUE) was carried out at Erasmus Medical Center (MC) Rotterdam, the Netherlands. The study was performed within a prospective cohort study (CO-FLOW) on long-term outcomes in adult patients who had been hospitalized for COVID-19 in the Netherlands.[36] Patients were eligible to participate in the IMMUNOFATIGUE study if they visited the outpatient clinic at Erasmus MC between 3 and 6 months after hospital discharge for persistent COVID-19 sequelae. In the Netherlands, it is standard practice to offer post-discharge follow-up to COVID-19 patients by the discharging hospital. Study blood samples were taken as part of this follow-up. Demographics and clinical characteristics at hospital admission were retrospectively collected from electronic medical records and via a questionnaire. We reported comorbidity as this was either reported in the medical records or self-reported.

A group of age- and sex-matched healthy controls (HCs) without a history of SARS-CoV-2 infection (self-reported) was recruited among hospital visitors. HCs were asked whether they had been vaccinated against COVID-19 and were screened for fatigue and depression using the Fatigue Assessment Scale (FAS) and Hospital Anxiety and Depression Scale (HADS) questionnaires. HCs who showed indications of chronic depression or fatigue, based on established cut-off scores that are described below, were excluded. All other HCs were included in the study, as they were appropriately age- and sex-matched to the fatigued long COVID group (no further selection necessary). Information on the sample size calculation is provided in the **Supplementary Methods**. All patients and HCs provided written informed consent before the start of study measurements. The Medical Ethics Committee of Erasmus MC approved the study (MEC-2020-1893).

PROMs

PROMs were collected in all patients as part of the CO-FLOW study at 3, 6, and 12 months post-hospital discharge.[36] For the current IMMUNOFATIGUE study, the Beck's Depression Inventory (BDI-21) was added.

Fatigue was assessed with the FAS questionnaire, assessing physical and mental fatigue, which was initially validated in patients with sarcoidosis but also used in other diseases.[37,38] The FAS consists of 10-items rated on a 5-points Likert scale. The total FAS score ranges from 10 to 50, with higher scores indicating increased severity of fatigue. We used a ≥22 cut-off value to indicate substantial fatigue, categorizing patients into fatigued and non-fatigued groups. This value is derived from studies examining sarcoidosis-related fatigue and is also used to indicate fatigue in patients with other conditions, including long COVID.[4,39,40] Patients filled out a symptom questionnaire (Corona Symptom Checklist [CSC], **Supplementary Methods**) to assess the presence of new or worsened symptoms following acute SARS-CoV-2 infection on a binary scale (yes or no). In this study, we included a selection of 12 typical long COVID symptoms. Several symptoms (such as chest pain, sensory overload, and headache) could not be taken into account as they were added to this questionnaire in a later stage and contain incomplete data.[5] Dyspnea was assessed with the Modified Medical Research Council (mMRC) Dyspnea Scale,[41] the questionnaire scales the severity of dyspnea from 0 (no dyspnea) to 4 (severe dyspnea); scores ≥2 were considered representative for the presence of dyspnea symptom. Anxiety and depression were assessed with the HADS and BDI-21. The HADS consists of the subscales anxiety and depression, a subscale score (range 0-21) ≥11 is considered clinically significant.[42] Depressive symptoms were also assessed with the BDI-21, scores (range 0-63) 0-13 denote no/minimal signs of depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression.[43,44] Post-Traumatic Stress Disorder (PTSD) was measured with the Impact of Event Scale-Revised (IES-R),[45] with scores (range 0-88) ≥33 representing clinically significant PTSD. Cognitive failures in everyday life were assessed with the Cognitive Failure Questionnaire, with scores (range 0-100) >43 indicating cognitive failures.[46,47] Health-Related Quality of Life (HR-QoL) was assessed with the 36-item Short Form survey (SF-36).[48] The SF-36 measures general health status and consists of eight domains: physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health perception. Each domain score ranges 0-100, with lower scores indicating more disability.

Blood collection and preparation

Serum and sodium heparinized peripheral blood samples were collected from patients during post-discharge follow-up (March to October 2021) and from HCs between July and November 2021. Peripheral blood mononuclear cells (PBMC) were isolated by low-density gradient centrifugation using Ficoll-density separation shortly after blood draw to avoid erythrophagy-related activation of the monocytes. Isolated PBMC were frozen in 10%-dimetylsulfoxide and stored in liquid nitrogen.

Lymphocyte immunophenotyping

Staining A, the absolute counts of total leukocytes ($CD45^+$), Natural Killer (NK) cells ($CD3^-CD16^+CD56^+$), B-lymphocytes ($CD19^+$), T-lymphocytes ($CD3^+$), $CD4^+$ T-lymphocytes, and $CD8^+$

T-lymphocytes were determined with a clinical laboratory ISO 15189 accredited method. Staining was performed on whole blood using multitest 6-color T-B-NK reagent (BD Biosciences). Flowcytometric analyses were performed using a FACS Canto II instrument (BD Biosciences).

Staining B, the percentages of $CD4^+$ T helper lymphocyte subsets were determined using a 8-color (membrane and intracellular) staining. PBMC were thawed and the recovery and viability of cells were 68% and 97% respectively, as assessed by Trypan blue staining. A total of 1×10^6 of defrosted PBMCs were stimulated for 4 h at 37 °C in RPMI-1640 culture medium with 50 ng/ml phorbol 12-myristrate 13-acetate (PMA; Sigma Aldrich, St. Louis, MO, USA) and 1.0 µg/ml ionomycin (Sigma) in the presence of Golgistop (BD Biosciences). $CD4^+$ T-lymphocyte subsets were identified by their secreting cytokines: T helper (Th)1 ($CD3^+CD4^+IFN\gamma^+$), Th2 ($CD3^+CD4^+IL4^+$), Th17 ($CD3^+CD4^+IL17A^+$). Regulatory T-lymphocytes (T_{reg}) were identified by their transcription factor FOXP3 ($CD3^+CD4^+CD25highFOXP3^+$). The percentages of these $CD4^+$ T-lymphocyte subsets are expressed as percentage of total lymphocytes.

Staining C, a more in-depth analysis of $CD4^+$ and $CD8^+$ T-lymphocyte subsets was performed using a second vial of PBMCs that had been thawed. After thawing, the recovery and viability of cells were 69% and 97% respectively, as assessed by Trypan blue staining. A total of $1{,}5 - 2 \times 10^6$ PBMCs were stained with a cocktail of CD45-V500, CD45RA-BB515, CD3-Alexa Fluor700, CD4-BUV805, CD8-BUV395, CD197-BV421, CD279-RB780 (BD Biosciences), CD28-BV711, CD27-APC and CD57-PE (BioLegend) for 15 minutes at room temperature, washed twice with PBS, pH 7.8 and subsequently stained with viability dye Zombie NIR (BioLegend). 500.000 events in a live/CD45 stopping gate were collected on an Aurora-5 laser instrument. The analysis was performed using FlowJo software. Quadrant gating strategy on CD45RA and CD197 (CCR7) was used to define the $CD4^+$ and $CD8^+$ T-lymphocyte subsets: naïve-like ($CD45RA^+CD197^+$), central memory (T_{CM}, $CD45RA^-CD197^+$), effector memory (T_{EM}, $CD45RA^-CD197^-$) and effector memory RA (T_{EMRA}, $CD45RA^+CD197^-$) (**Supplementary Figure S1**). Within each indicated T-lymphocyte subset, the expressions of CD27 and CD28 as well as CD279 and CD57 were assessed. The percentages of the T-lymphocyte subsets in staining C are presented as percentages of total T-lymphocytes. The monoclonal antibodies used in each staining are in more detail described in **Supplementary table S1**.

Monocyte subsets

Staining D, the percentages of classical monocytes, intermediate monocytes, and non-classical monocytes were determined using a 5-color membrane staining. Thawed PBMC used for staining C (see above) were also used for further monocyte subset analysis. A total of 1×10^6 PBMCs were stained with a cocktail of CD45-PO (Life Technologies), CD64-APC (BD Pharmingen), CD66b-BV421 (BD Horizon), CD14-APC-H7 (BD Biosciences), CD16-PE-Cy7 (Invitrogen) for 30 minutes at RT, lysed with BD Lysing solution (BD Biosciences) for 10 min at RT and washed with PBS pH 7.8. Monocytes were measured using a BD FACS Lyric flowcytometer. The analysis was performed using BD FACSSuite software. Monocytes ($CD45^+CD64^+CD66^-$) were defined as: classical monocytes ($CD14^{++}CD16^-$), intermediate monocytes ($CD14^{++}CD16^+$), and non-classical monocytes ($CD14^+CD16^{++}$).[49] For the monoclonal antibodies used in staining D, see **Supplementary Table S1**.

Monocyte gene expression

We assessed 34 genes of a previously established inflammation-related gene signature found in mood-disorder patients[15,16,18,32,33] and patients with ME/CFS (unpublished data). Expression of inflammation-related genes in monocytes were assessed using procedures that have been described in previous publications.[18] Briefly, $CD14^+$ monocytes were isolated from thawed PBMCs by magnetic cell sorting (Automacs Pro Miltenyi Biotec, Bergisch Gladbach, Germany) and RNA was isolated (Qiagen RNeasy mini kit). The average viability and the purity of monocytes were both 95% as determined by Trypan blue staining and flow cytometry. Subsequently, RNA (0,5 µg) was reverse transcribed (High Capacity cDNA Reverse Transcription Kit; Applied Biosystems, Thermo Fisher Scientific) to obtain cDNA for quantitative-polymerase chain reaction (q-PCR). qPCR was performed using TaqMan Gene expression assays (Applied Biosystems). The expression levels of genes were determined using the comparative cycle (CT) method. All values were normalized to the housekeeping gene ABL1 (ΔCT values). Gene expression values of patients were also expressed relative to the average ΔCT value of HCs (ΔΔCT values). The following genes were evaluated: ABCA1, ABCG1, ADM, BAX, BCL10, BCL2A1, CCL2, CCL20, CCL7, CXCL2, DUSP2, EGR1, EGR2, EMP1, HMOX1, IFI44, IFI44L, IFIT1, IFIT3, IL1A, IL1B, IL1R1, IL6, MAFF, MAPK6, MRC1, MVK, MX1, MXD1, NR1H3, PTX3, SERPINB2, TNF, and TNFAIP3 (**Supplementary Table S2**).

Cytokine and soluble cell surface molecule measurement

The following cytokines and soluble cell surface molecules were measured in serum with a Luminex multiplex bead-based assay (R&D Systems Europe, Abingdon, United Kingdom): brain-derived neurotrophic factor (BDNF), C-C motif chemokine ligand (CCL)2, CCL7, C-X-C motif chemokine ligand (CXCL)9 and CXCL10, cluster of differentiation 163 (CD163), Galectin-9, granulocyte macrophage-colony stimulating factor (GM-CSF), interferon (IFN)-α, IFN-β, IFN-γ, interleukin (IL)-6, IL-7, IL-10, IL-12, P-selectin, T-cell immunoglobulin and mucin domain 1 (TIM-1), and tumor necrosis factor-alpha (TNF-α). IL-6 levels were determined by a high sensitivity ELISA (apDia, Turnhout, Belgium) and serine protease inhibitor B2 (SERPINB2) levels by ELISA (R&D Systems Europe). All assays were performed following the manufacturer's protocol.

Epstein–Barr virus (EBV) and cytomegalovirus (CMV) assessment

Active EBV and CMV were determined in randomly selected patients from the fatigued and non-fatigued long COVID groups to assess whether symptoms could be attributed to viral reactivation, as suggested in the literature.[50] EBV and CMV DNA load was measured using internally controlled quantitative real-time Taqman PCR based on assays performed as published previously.[51,52] For EBV a value over the lower limit of quantification of >100 IU/mL indicated the presence of active virus, and for CMV this was >50 IU/mL.

Statistical analysis

Continuous variables are presented as the median and interquartile range (IQR) and categorical variables as a number and percentage. Differences in demographics and clinical characteristics at hospital admission between groups of fatigued and non-fatigued long COVID patients were assessed using the Mann-Whitney U test for continuous variables and a Fisher's Exact test for dichotomous

categorical variables. The number of clinical symptoms was calculated using 14 typical long COVID symptoms, 12 symptoms from the CSC and the symptoms fatigue (FAS) and dyspnea (mMRC Dyspnea Scale).

For gene expression levels in monocytes, we first identified clusters of mutually correlating genes. Hierarchical cluster analysis of gene expression levels in monocytes was performed using Spearman's rank correlation coefficient matrix. Missing gene values (0.7% of COVID-19 patients and 1.4% of HCs) were imputed with the median of patient or HC value. For single gene expressions we used ΔΔCT values and p-values were calculated with Wilcoxon signed rank test using the Benjamini-Hochberg-method for multiple testing. In the serum analysis, cytokines and soluble cell surface molecules positive in >20% of patients were used in the analysis (**Supplementary Table S3**). A chi-square test was performed to assess differences in the number of patients with and without detectable cytokine and soluble cell surface molecule levels across groups of fatigued and non-fatigued long COVID patients and HCs (**Supplementary Table S3**). Values below the lower limit of detection (LOD) were imputed by half of the lowest value observed of a given cytokine and extreme outliers (TNF-α n=1, IFN-β n=1, IFN-γ n=1, CXCL9 n=2, SERPINB2 n=2) were removed due to potential erratic measurements. We performed a Mann-Whitney U test to compare immune characteristics between the groups of long COVID patients and HCs. To compare immune features of fatigued and non-fatigued long COVID patients and HCs, we performed a Kruskal-Wallis test followed by a post-hoc test using Bonferroni correction for multiple group comparisons. In addition, for cytokines with imputed data, data were also categorized (<LOD vs. ≥LOD) and compared across groups using a chi-square test.

We also analyzed the severity of fatigue (total FAS score) as a continuous outcome in relation to immune characteristics. In preliminary analyses, we considered age, sex, BMI, pre-existing diabetes, the number of days in the hospital, and the number of days between SARS-CoV-2 infection and follow-up as factors potentially associated with fatigue severity. The association between continuous variables and fatigue severity was assessed using Spearman's rank correlation coefficient, while differences in fatigue severity for categorical variables were assessed with the Mann-Whitney U test; none of these variables were significantly associated with the total FAS score and were therefore not included in further analyses as potential confounders. The associations between fatigue severity and immune parameters were assessed using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, USA) and R software version 1.4.2.

Results

Participants

We included 37 long COVID patients who experienced substantial fatigue (total FAS score ≥22) at the time of collecting blood samples, from here on referred to as fatigued long COVID patients. As a contrast group, we included 36 long COVID patients who did not experience substantial fatigue

(total FAS score <22, non-fatigued long COVID), representing patients with mild or no symptoms of fatigue. We included a group of 42 age- and sex-matched HCs; the characteristics of HCs' are shown in **Supplementary Table S4**. FAS items scores in fatigued and non-fatigued long COVID groups and HCs are presented in **Supplementary Table S5**. All patients had been discharged from hospital between October 2020 and May 2021, representing patients with SARS-CoV-2 alpha variant. The median follow-up time (day of blood sampling) since hospital discharge was 107.0 (IQR 92.5-138.5) days.

The patient's demographic and clinical characteristics are shown in **Supplementary Table S6**. Among the fatigued long COVID patients, the median age was 58.0 (55.0-66.0) years, 24 (64.9%) were male, 18 (48.6%) had been treated in the intensive care unit (ICU) for COVID-19, and the length of stay (LOS) in hospital was 17.0 (9.0-26.0) days. In non-fatigued long COVID patients, the median age was 61.0 (52.3-67.0) years, 26 (72.2%) were male, 22 (61.1%) had been treated in the ICU for COVID-19, and the LOS in hospital was 15.0 (10.0-26.8) days. Demographic and clinical characteristics at hospital admission did not differ significantly between fatigued and non-fatigued long COVID patients (**Supplementary Table S6**). The median age of HCs was 62.0 (51.8-68.3) years (p=0.95, comparison with fatigued long COVID group) and 26 (61.9%) were male (p=0.82).

Clinical characteristics

The PROMs in the fatigued and non-fatigued long COVID patients at the time of collecting blood samples are presented in **Table 1**. In the fatigued long COVID group, low energy levels throughout the day and difficulties with concentration were prominent features of the fatigue (**Supplementary Table S5**). Regarding the main symptoms, collectively, all fatigued long COVID patients reported ≥3 symptoms. Other PROMs showed that 40.5% of these patients experienced cognitive failure and signs of depression were found via HADS-D score in 24.3% and via BDI-21 score in 37.2% of the patients. The fatigued long COVID patients experienced significantly more symptoms and reduced HRQoL outcomes as compared to non-fatigued long COVID patients (**Table 1**). In the non-fatigued long COVID group, 21 (65.6%) patients reported ≥3 symptoms and 3 (9.1%) patients experienced cognitive failure, signs of depression were not found.

Table 1. Patient-reported outcome measures in fatigued and non-fatigued long COVID groups.

	Fatigued long COVID (n=37)	Non-fatigued long COVID (n=36)	P value
Number of symptoms[a]	9 (5.0-10.0)	3 (1.0-5.0)	<0.001
≥3 symptoms	37 (100.0)	21 (65.6)	<0.001
FAS			
Total FAS score	31.0 (28.0-36.0)	17.0 (14.0-18.0)	<0.001
Fatigue (≥22)	37 (100.0)	0 (0.0)	<0.001
CSC			
Impaired fitness	37 (100.0)	25 (69.4)	<0.001
Muscle weakness	29 (78.4)	10 (27.8)	<0.001
Concentration problems	27 (73.0)	8 (22.2)	<0.001
Memory problems	27 (73.0)	11 (30.6)	<0.001
Dizziness/balance difficulties	26 (70.3)	8 (22.2)	<0.001
Tingling and/or pain in extremities	20 (54.1)	11 (30.6)	0.059
Joint complaints	19 (51.4)	12 (34.3)	0.16
Sleep disturbances	18 (48.6)	8 (22.2)	0.027
Hair loss	18 (48.6)	10 (27.8)	0.093
Dysgeusia	12 (32.4)	1 (2.8)	0.001
Anosmia	10 (27.0)	5 (13.9)	0.25
Cough	9 (24.3)	4 (11.1)	0.22
mMRC Dyspnea Scale			
Dyspnea[b]	9 (25.7)	2 (6.1)	0.046
Grade 0	12 (34.3)	15 (45.5)	
Grade 1	12 (34.3)	2 (6.1)	
Grade 2	8 (22.9)	2 (6.1)	
Grade 3	1 (2.9)	0 (0.0)	
Grade 4	0 (0.0)	0 (0.0)	
HADS			
Total HADS score	13.0 (9.0-18.0)	4.0 (2.0-6.8)	<0.001
Anxiety (HADS-A ≥11)	5 (13.5)	0 (0.0)	0.054
Depression (HADS-D ≥11)	9 (24.3)	0 (0.0)	0.002
BDI-21			
Total BDI score	10.0 (6.0-15.0)	3.0 (0.5-6.0)	<0.001
None/minimal depression	22 (62.9)	33 (100.0)	<0.001
Mild depression	8 (22.9)	0 (0.0)	0.005
Moderate depression	5 (14.3)	0 (0.0)	0.054
Severe depression	0 (0.0)	0 (0.0)	n.a.

Table 1. Continued.

	Fatigued long COVID (n=37)	Non-fatigued long COVID (n=36)	P value
IES-R			
Total impact score	17.0 (9.5-25.5)	6.0 (3.0-10.0)	<0.001
PTSD (≥33)	5 (13.5)	1 (2.9)	0.20
CFQ			
Total CFQ score	38.0 (26.5-47.5)	15.0 (10.5-26.5)	<0.001
Cognitive failure (>43)	15 (40.5)	3 (9.1)	0.003
SF-36			
Physical functioning	50.0 (40.0-67.5)	85.0 (70.0-95.0)	<0.001
Social functioning	62.5 (43.8-75.0)	100.0 (87.5-100.0)	<0.001
Physical role functioning	0 (0.0-25.0)	100.0 (50.0-100.0)	<0.001
Emotional role functioning	33.3 (0.0-100.0)	100.0 (100.0-100.0)	<0.001
Mental health	64.0 (56.0-72.0)	92.0 (84.0-96.0)	<0.001
Vitality	45.0 (35.0-50.0)	77.5 (70.0-85.0)	<0.001
Bodily pain	57.5 (45.0-72.5)	90.0 (67.5-100.0)	<0.001
General health perception	45.0 (32.5-57.5)	65.0 (55.0-85.0)	<0.001

Data are presented as median (interquartile range) or number (%) for groups of fatigued (total FAS score ≥22) and non-fatigued (total FAS score <22) long COVID patients. Significant group differences between fatigued and non-fatigued long COVID patients were assessed using the Mann-Whitney U test for continuous variables and the Fisher Exact's test for dichotomous categorical variables. In the fatigued long COVID group, missing values for the variables mMRC Dyspnea Scale (n=2) and BDI-21 (n=2) and in the non-fatigued long COVID group for the variables ≥3 symptoms (n=3), joint complaints (n=1), mMRC Dyspnea Scale (n=3), BDI-21 (n=3), IES-R (n=1), and CFQ (n=3). BDI, Beck Depression Inventory; CFQ, Cognitive Failure Questionnaire; CSC. corona symptom checklist; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Event Scale-Revised; mMRC, modified Medical Research Council; SF-36, 36-Item Short Form Health Survey.

[a] *Symptoms (n=14) comprise all symptoms from the CSC, fatigue (total FAS score ≥22), and dyspnea (mMRC dyspnea scale grade ≥2).*

[b] *Dyspnea was indicated by grade ≥2.*

Figure 1 presents the recovery profile of the main symptoms during the first year after hospital discharge. The fatigued patients showed hardly any clinical improvement over time, as 95.0% of the patients reported ≥3 symptoms at one year follow-up. Symptoms were overall less prevalent in non-fatigued patients as compared to the fatigued patients. However, still 55.6% of non-fatigued patients reported ≥3 symptoms at one year follow-up.

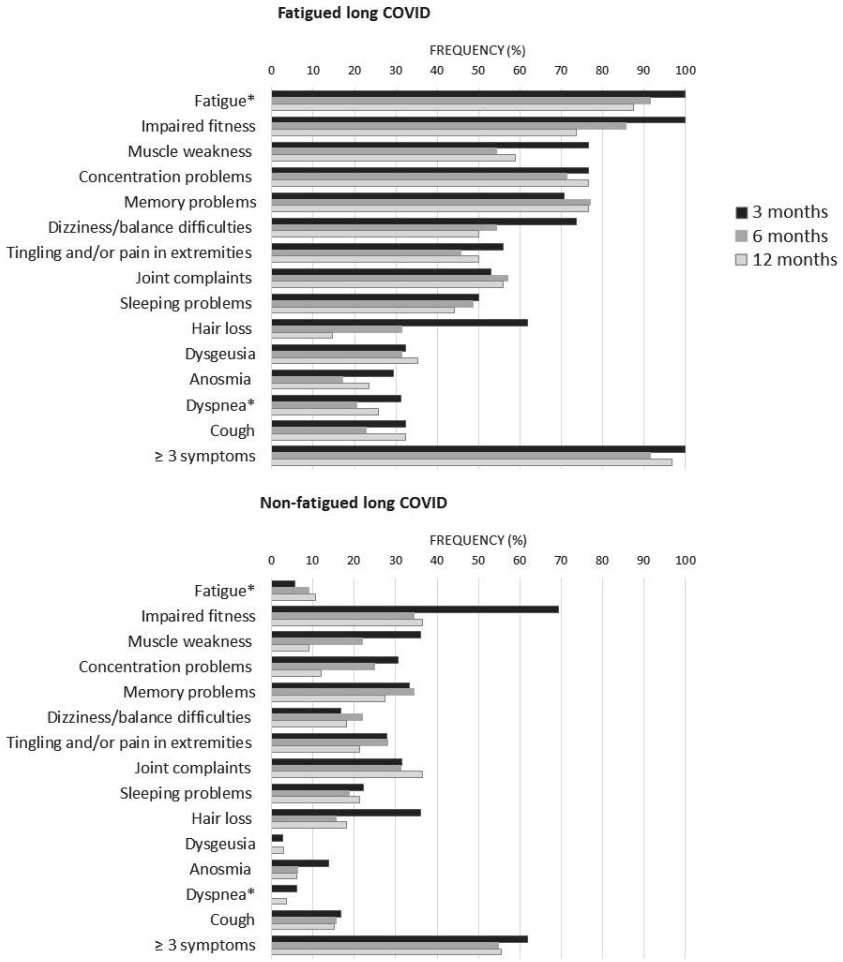

Figure 1. Prevalence of clinical symptoms across fatigued and non-fatigued long COVID patients assessed at 3, 6, and 12 months after hospital discharge.

Symptoms are presented for groups of fatigued (total FAS score ≥22) and non-fatigued (total FAS score <22) long COVID patients at the time of collecting blood samples. In the non-fatigued long COVID group, some patients experienced fatigue at other follow-up visits. Symptoms were obtained from the Corona Symptom Checklist on the presence of new or worsened symptoms following SARS-CoV-2 infection (yes or no).

** The fatigue symptom was obtained from the Fatigue Assessment Scale (FAS) questionnaire, a total FAS score ≥22 denotes fatigue. The dyspnea symptom was obtained from the modified medical research council dyspnea scale, grades ≥2 were used to denote dyspnea.*

Circulating leukocyte and lymphocyte subsets

We performed enumerations of circulating leukocytes, NK cells, B-lymphocytes, T-lymphocytes, and $CD4^+$ and $CD8^+$ T-lymphocytes; **Supplementary Table S7** shows the outcomes per group. Counts of these sets of cells did not show significant differences between fatigued and non-fatigued long COVID groups, only in comparison to healthy controls (HCs). When analyzed as a single group,

the group of long COVID patients showed significantly increased counts of leukocytes and total T-lymphocytes compared to HCs; these increases were due to increases in $CD8^+$ T-lymphocyte counts (**Figure 2A**). Considering fatigue as a graded outcome, we found that increased counts of $CD8^+$ T-lymphocytes significantly correlated with increased fatigue severity (total FAS score, r=0.24, p=0.043) (**Figure 2A**).

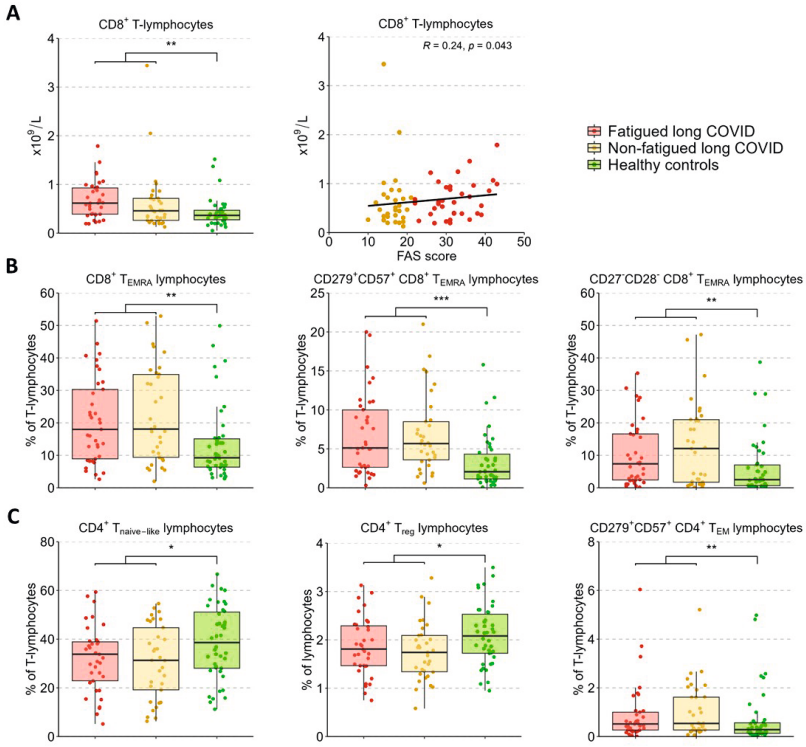

Figure 2. $CD4^+$ T-lymphocyte and $CD8^+$ T-lymphocyte subsets in fatigued and non-fatigued long COVID patients.

*Fatigue was defined as a total score of ≥22 on the Fatigue Assessment Scale (FAS) questionnaire. Data of $CD4^+$ T-lymphocyte and $CD8^+$ T-lymphocyte subsets did not differ significantly between groups of fatigued (n=37) and non-fatigued (n=33) long COVID patients. Significant group differences are presented for the entire group of long COVID patients as compared to healthy controls (n=42) using the Mann-Whitney U test, *p<0.05, **p<0.01, and ***p<0.001.* ***(A)*** *$CD8^+$ T-lymphocyte counts across groups. The correlation between $CD8^+$ T-lymphocyte counts and the fatigue severity (total FAS score) in long COVID patients was assessed using Spearman's rank correlation coefficient.* ***(B)*** *The assessment of $CD8^+$ T-lymphocyte subsets showed an increased percentages of $CD8^+$ T_{EMRA} lymphocytes, particularly $CD8^+$ T_{EMRA}-lymphocyte expressing $CD279^+CD57^+$, and $CD8^+$ T_{EMRA}-lymphocyte expressing $CD27^-CD28^-$, in long COVID patients as compared to healthy controls.* ***(C)*** *The assessment of $CD4^+$ T-lymphocyte subsets showed reduced percentages of $CD4^+$ T_{naive} lymphocytes, regulatory $CD4^+$ T-lymphocytes ($CD4^+CD25highFOXP3^+$), and $CD4^+$ T_{EM} lymphocytes expressing $CD279^+CD57^+$ in long COVID patients as compared to healthy controls.*

In a more in-depth analysis of the $CD4^+$ and $CD8^+$ T-lymphocyte subsets (see **Supplementary Table S8** for the outcomes per group), the percentages of these subsets did not differ significantly between fatigued and non-fatigued long COVID groups. We found a significant increase in the percentage

of CD8$^+$ T_{EMRA}-lymphocytes and the subsets of late stage/exhausted CD279$^+$CD57$^+$ CD8$^+$ T_{EMRA}-lymphocytes and CD27$^-$CD28$^-$ CD8$^+$ T_{EMRA}-lymphocytes in the entire group of long COVID patients compared to HCs (**Figure 2B**). Percentages of naïve CD4$^+$ T-lymphocytes (CD45RA$^+$CCR7$^-$) and CD4$^+$ T_{reg}-lymphocytes (CD25$^+$FOXP3$^+$) were significantly decreased in long COVID patients compared to HCs, while the percentage of exhausted/senescent CD4$^+$ T_{EM}-lymphocytes (CD279$^+$CD57$^+$) were increased (**Figure 2C**). There were no significant correlations found between the percentages of the various CD4$^+$ and CD8$^+$ T-lymphocyte subsets and the fatigue severity in long COVID patients.

Monocyte subsets

Figure 3A presents the percentages of classical (CD14$^+$CD16$^-$), intermediate (CD14^{++}CD16$^+$), and non-classical (CD14$^+$CD16^{++}) monocytes across groups. The percentages of these populations did not differ significantly between fatigued and non-fatigued long COVID groups (**Supplementary Table S9**). The entire group of long COVID patients showed a significantly reduced percentage of classical monocytes and an increased percentage of non-classical monocytes compared to HCs (**Figure 3A**). We found a significant negative correlation between the percentage of classical monocytes and the fatigue severity (r=-0.28, p=0.02), as well as a significant positive correlation between the percentages of intermediate (r=0.28, p=0.02) and non-classical (r=0.31, p=0.009) monocytes and the fatigue severity (**Figure 3B**).

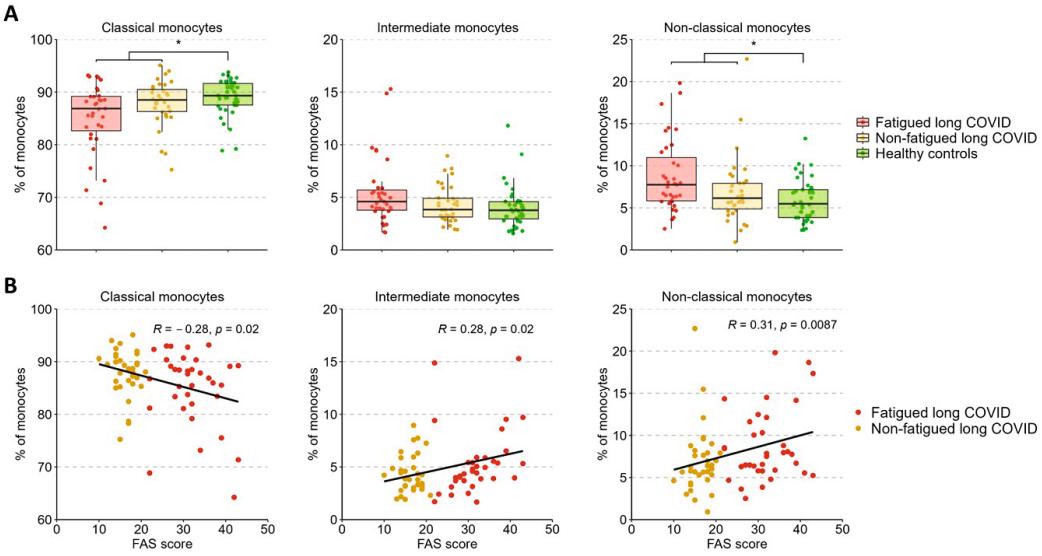

Figure 3. Percentages of classical, intermediate, and non-classical monocytes in fatigued and non-fatigued long COVID patients.

Fatigue was defined as a total score of ≥22 on the Fatigue Assessment Scale (FAS) questionnaire. ***(A)*** *The percentages of classical monocytes (CD14^{++}CD16$^-$), intermediate monocytes (CD14^{++}CD16$^+$), and non-classical monocytes (CD14$^+$CD16^{++}) in groups of fatigued (n=35) and non-fatigued (n=34) long COVID patients and healthy controls (n=40). The percentage of monocyte subsets did not differ significantly between fatigued and non-fatigued long COVID patients. Significant group differences are presented for the entire group of long COVID patients as compared to healthy controls using the Mann-Whitney U test, *p<0.05.* ***(B)*** *The correlation between the percentage of monocyte subsets and the fatigue severity (total FAS score) in long COVID patients was assessed using Spearman's rank correlation coefficient.*

Monocyte gene activation

A gene expression analysis was performed in the total population of $CD14^+$ monocytes. Hierarchical clustering of gene expression levels in monocytes revealed three main gene clusters (**Figure 4A**), similar to the gene clusters found in previous studies in major depressive disorder (MDD), bipolar disorder, and various autoimmune disorders (thyroid autoimmune disease, type 1 diabetes, Sjögren disease and SLE).[16,18,53,54] These clusters represent strong mutually correlating genes within each cluster; only cluster C genes correlated weaker amongst themselves. Gene cluster A was composed of inflammation-regulation genes and genes related to adhesion, chemotaxis, apoptosis, and pyroptotic mechanisms. Cluster B consisted of type 1 IFN driven inflammation-related genes. Cluster C consisted of genes involved in mitochondrial anti-inflammatory action and cholesterol pump genes.

Figure 4B shows the gene expression pattern in monocytes for the fatigued and non-fatigued patients relatively to the expression levels of HCs; differences between fatigued and non-fatigued patients did not reach significance and are therefore not shown. Both long COVID groups were characterized by a significantly overexpression of many cluster A inflammation-regulating genes (e.g. CCL7, CCL20, IL-6) as well as some cluster C genes (BAX, HMOX1) as compared to HCs. The cholesterol pump genes (ABCA1, ABCG1, NR1H3) and the M2 macrophage marker MRC1 were significantly downregulated. Normal expression levels were found for the type 1 IFN induced genes (ISGs) in cluster B. This profile represents a strong pro-inflammatory pyrogenic state of the monocytes.

Upregulated levels of the cluster A inflammatory genes CCL2 ($r=0.29$, $p=0.016$), CCL7 ($r=0.24$, $p=0.048$), and SERPINB2 ($r=0.28$, $p=0.022$) in monocytes were significantly correlated to increased fatigue severity (**Figure 4C**); significant correlations were not found for the other genes.

Serum cytokine and soluble cell surface molecule levels

The level of the various tested inflammation regulating cytokines and soluble cell surface molecules in serum was evaluated to further investigate the inflammatory state of long COVID patients. These levels did not differ significantly between the fatigued and non-fatigued long COVID groups, both groups did show altered levels in comparison to HCs (**Supplementary Table S10**). The entire long COVID group showed significantly increased serum levels of Galectin-9, IL-6, TNF-α, CXCL10, CD163, and CCL2 compared to HCs (**Figure 5A**). Levels of CXCL9, SERPINB2, IFN-β, and IFN-γ were significantly reduced in long COVID patients compared to HCs (**Figure 5A**).

In terms of fatigue severity, a significant positive correlation was found between serum Galectin-9 levels and the fatigue severity ($r=0.24$, $p=0.039$) (**Figure 5B**), a trend toward significance was found for CD163 levels ($r=0.21$, $p=0.078$), but not for the other measured inflammatory mediators.

No signs of EBV and CMV reactivation in long COVID patients

We randomly selected 10 (27.0%) fatigued and 19 (52.8%) non-fatigued long COVID patients to test for the viral load of EBV and CMV. None of the tested patients showed viral loads that exceeded the limit of quantification, and we therefore did not perform further tests on the remaining patients.

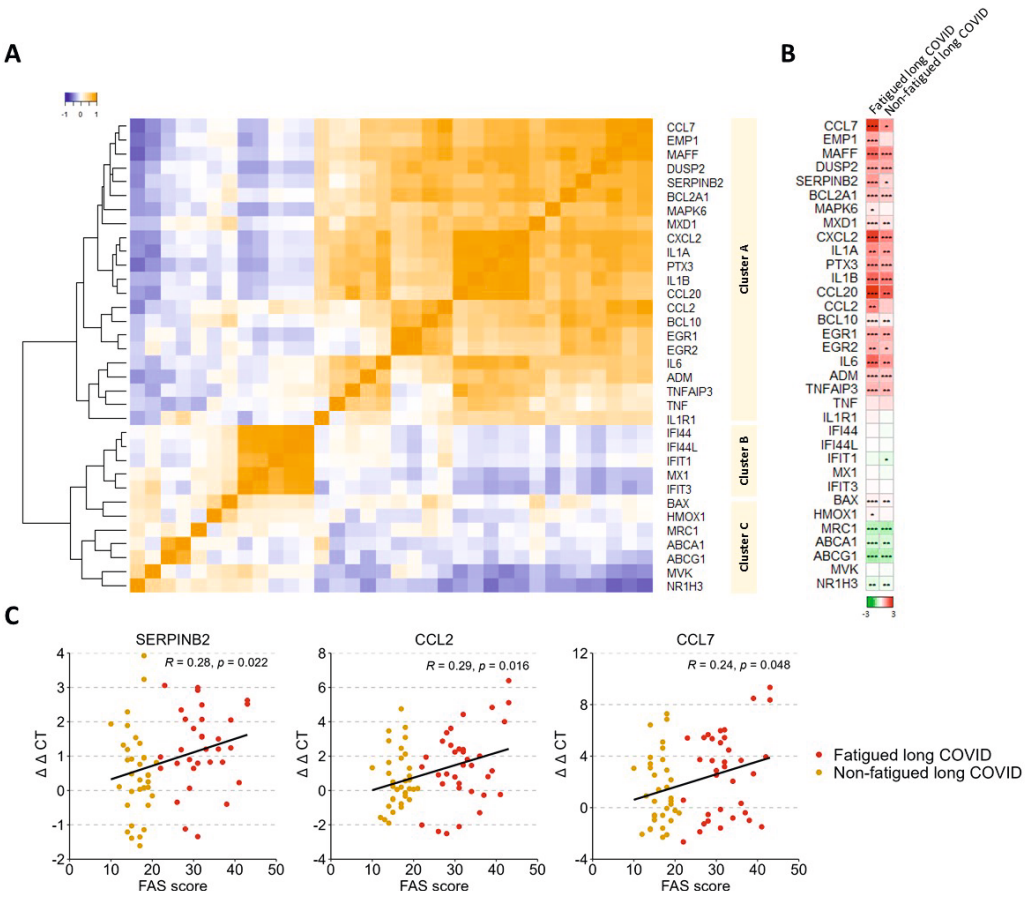

Figure 4. Gene expression levels in monocytes in fatigued and non-fatigued long COVID patients.
The expression level of genes were normalized to the housekeeping gene ABL1 (ΔCT values) and expressed relative to the average ΔCT value of healthy controls (ΔΔCT values). ***(A)*** *Three main clusters of mutually correlating monocyte genes can be identified. Cluster A comprises inflammation-regulation genes and genes related to adhesion, chemotaxis, apoptosis, and pyroptotic mechanisms of the cells. Cluster B comprises genes related to type 1 interferon driven inflammation. Cluster C comprises mainly genes related to mitochondrial anti-inflammatory action and cholesterol pump genes. Correlations between genes were assessed using Spearman's rank correlation coefficient.* ***(B)*** *Fatigue was defined as a total score of ≥22 on the Fatigue Assessment Scale (FAS) questionnaire. Single gene expression levels in fatigued (n=35) and non-fatigued (n=34) long COVID patients, data are presented as mean values and are expressed relatively to the expression level of healthy controls (n=42); the intensity of red reflects higher expression (upregulation) and green reflects lower expression (downregulation). No statistically significant differences were found in the gene expression levels in monocytes between fatigued and non-fatigued long COVID patients (data not shown). Significant differences in single gene expression levels in long COVID groups as compared to healthy controls were assessed with a Wilcoxon signed rank test using Benjamini-Hochberg-method for multiple testing, *p<0.05, **p<0.01, and ***p<0.001.* ***(C)*** *The correlation between gene expression levels in monocytes and the fatigue severity (total FAS score) in long COVID patients was assessed using Spearman's rank correlation coefficient.*

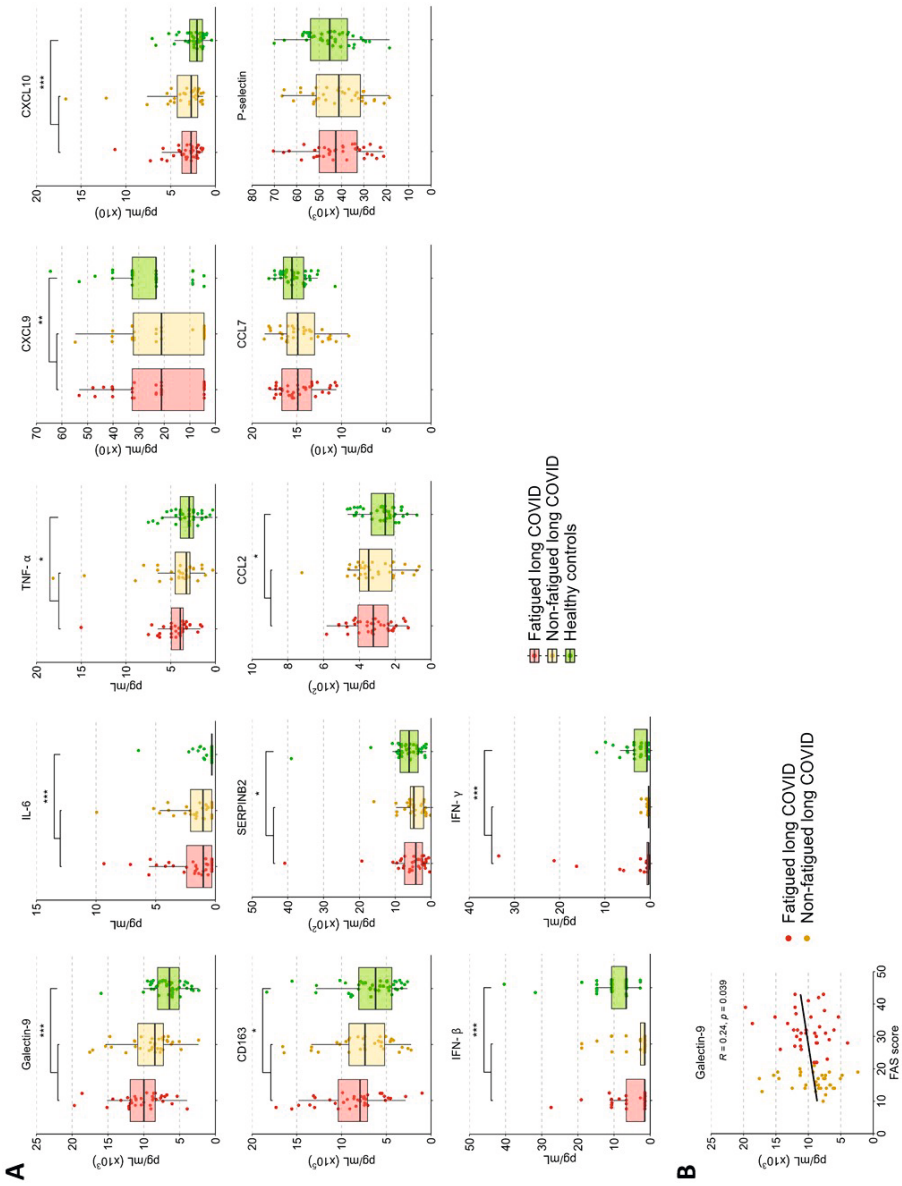

Figure 5. Serum cytokine and soluble cell surface molecule levels in fatigued and non-fatigued long COVID patients.

Fatigue was defined as a total score of ≥22 on the Fatigue Assessment Scale (FAS) questionnaire. ***(A)*** *Serum cytokine and soluble cell surface molecule levels are presented for groups of fatigued (n=37) and non-fatigued (n=35) long COVID patients and healthy controls (n=42). These serum levels did not differ significantly between groups of fatigued and non-fatigued long COVID patients. Significant group differences are presented for the entire group of long COVID patients as compared to healthy controls using the Mann-Whitney U test, *p<0.05, **p<0.01, and ***p<0.001.* ***(B)*** *The correlation between Galectin-9 levels and the fatigue severity (total FAS score) in long COVID patients was assessed using Spearman's rank correlation coefficient. CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; CD163, cluster of differentiation 163; IL, interleukin; IFN, interferon; TNF-a, tumor necrosis factor-alpha.*

Discussion

This study focused on long COVID patients with fatigue, one of the most disabling symptoms of long COVID, and provides insight into the clinical and immune profiles of fatigued and non-fatigued long COVID patients. Fatigued patients represent a more severe clinical profile of long COVID than non-fatigued patients and are characterized by many concurrent and generally persistent symptoms lasting up to one year of follow-up. On a group level, we did not find statistically significant differences between fatigued and non-fatigued long COVID patients in immune profiles at 3-6 months after hospital discharge, with both groups showing abnormalities only in comparison with HCs. Taken the fatigued and non-fatigued groups together, long COVID patients were characterized by a state of low grade inflammation and signs of T-lymphocyte senescence. As such, our long COVID patients exhibit immune disturbances that share similarities to immune disturbances seen in convalescent COVID-19 patients and patients with ME/CFS and MDD.[18,23,27,30,55]

Our study suggests thus that long COVID with fatigue is not associated with a clearly distinct immunotype but rather a part of the broader spectrum, as based on the immune parameters assessed in our study. Nevertheless, our data show that increased severity of fatigue associate with immune parameters involved in monocyte activation, although the observed correlation coefficients were weak. Altered monocyte activation is commonly reported in convalescent COVID-19 patients, but has not yet been linked to graded fatigue.[56,57] Of the observed immune parameters correlating to fatigue severity, non-classical monocytes interact with and patrol the vessel walls,[58] SERPINB2 (also known as plasminogen activator inhibitor-2; PAI-2) is a coagulation regulator,[59] and important in the interaction of monocytes with endothelium, while CCL2 and CCL7 are chemokines raised in monocytes passing through the vessel wall. Endotheliopathy and microvascular thrombosis have been proposed as the basis for long COVID symptoms.[60] It is known that endothelial damage and coagulation/thrombus formation do occur in the interaction of inflammatory monocytes with endothelial cells.[61] Moreover, the generally raised pro-inflammatory cytokines in serum can also induce processes that affect coagulation.[62]

Additionally, serum levels of Galectin-9 were also positively associated with fatigue severity in long COVID patients. Galectin-9 is considered a marker of severity of a variety of immune diseases and acute and chronic infectious diseases, including COVID-19 disease.[63,64] In a recent study, Du et al. suggested that Galectin-9 may potentially be involved in enhancing SARS-CoV-2 replication.[65] However, further studies are needed to better understand this potential mechanism. Patterson et al. found that the levels of intermediate and non-classical monocyte were significantly elevated in long COVID patients up to 15 months post-infection, with a significant number of non-classical monocytes containing SARS-CoV-2 S1 protein.[57] Individually, the observed immune parameters showed only a weak association with increased fatigue severity in our long COVID patients. However, collectively, they potentially point towards stronger monocyte-endothelial interaction, possibly viral-induced, in the more severe forms of long COVID characterized by considerable fatigue.

Few studies have explored the association between immune abnormalities and the fatigue symptom of long COVID, often evaluating fatigue as a dichotomous outcome rather than a graded outcome.[26,31,66-68] We have evaluated the published dataset of Su et al. to validate our findings on classical and non-classical monocyte subsets.[31] Similar to our findings, the percentage of these monocyte subsets did not differ significantly between their groups of fatigued and non-fatigued COVID-19 patients around 3 months after hospitalization. Sommen et al. found raised blood levels of MCP-1/CCL2 and IP-10/CXCL10 in non-hospitalized COVID-19 patients at 6 months follow-up, which levels did not correlate with fatigue severity,[66] similar to our findings in hospitalized patients. Consistent with a study conducted around a similar follow-up time,[68] we observed increased serum TNF-α levels in long COVID patients but we did not find an association between TNF-α levels and fatigue severity. Our findings in patients with increased fatigue severity were present against a background of various immune abnormalities common to the entire group of long COVID patients, in line with previous studies.[27,30,55,66]

The entire long COVID group also showed signs of T-lymphocyte senescence, characterized by decreased frequencies of naïve $CD4^+$ T-lymphocytes and $CD4^+FOXP3^+$ T_{reg}-lymphocytes. Moreover, the long COVID group displayed increased total blood numbers of $CD8^+$ cytotoxic T-lymphocytes and an increased frequency of (late stage differentiated) $CD8^+$ T_{EMRA}-lymphocytes, many of which showed signs of exhaustion/senescence ($CD279^+CD57^+$). Signs of T-lymphocyte exhaustion/senescence have been reported before in convalescent COVID-19 patients.[26,69] Phetsouphanh et al. also found that a proportion of their long COVID patients lacked naïve T-lymphocytes.[27] Wiech and colleagues reported an immuno-senescent profile of particularly the $CD8^+$ T-lymphocyte population in patients 6 months after severe COVID-19, but the authors did not to find an association with long COVID symptoms, including fatigue.[26]

Premature aging of the immune system is known to be induced by chronic viral infections, such as chronic CMV infection.[26,70] This type of immune activation may play a role in long COVID, since studies have shown re-activation of herpesviruses in long COVID patients.[50,71] However, we did not observe signs of EBV and CMV activation in our long COVID patients, similar to the study of Su et al.[31]. It is tempting to speculate that the here described T-lymphocyte abnormalities in long COVID patients are caused by an ongoing "hidden" SARS-CoV-2 infection, while also inducing low grade inflammation. This is in line with a current hypothesis on viral persistence as a potential causal factor in long COVID.[72]

The here found reduced levels of type I and type II IFNs in serum and the non-activation of the type I IFN gene cluster in monocytes is thus intriguing and we assume that this might be a sign of poor innate immunity to viral infection in long COVID patients.

The clinical and immune profile of our long COVID patients showed similarities to that of ME/CFS and MDD patients.[14,17,18,23,35,73,74] Therefore, we can learn from what is known in these conditions, which could potentially have implications for long COVID. Other associations found in ME/CFS and MDD between inflammation and abnormality in the central regulation of energy metabolism

in the brain stem and mood regulation in the limbic system may also be of interest to long COVID research.[75-79] However, future studies directly comparing clinical and immunologic profiles of long COVID with ME/CFS and MDD patients are needed to assess which characteristics, if any, are uniquely associated to long COVID.

The findings from our study may support potential pharmacological interventions in long COVID. Anti-inflammatory agents, such as minocycline, dexamethasone, and anti-IL6, might be instrumental in dampening the excessive inflammatory processes. Low dose IL-2 might be instrumental in correcting the reduced $CD4^+$ T_{reg} lymphocytes and reduced naïve $CD4^+$ T-lymphocytes.[80,81] Agents stimulating type 1 IFN production, such as TLR-7 and TLR-9 stimulators (e.g. rintatolimod), might be instrumental in inducing IFN production.[82,83] Rintatolimod has been used with some success in ME/CFS and will be tested for long COVID.[84,85] The described immune correcting agents may have to be combined with an antiviral agent to combat putative hidden viral reservoirs. Studies should be undertaken to further confirm the role of this putative reservoirs.

This study focused on long COVID patients with fatigue, one of the most common, disabling, and persistent symptoms in long COVID. Other strengths of our study include the comprehensive assessment of both clinical and immune characteristics in long COVID patients with graded fatigue severity. Given the high prevalence of overlapping symptoms in fatigued long COVID patients, the fatigue symptom may be a proxy for severe long COVID, indicating that our immunologic findings may be the consequence of severe long COVID. As diverse symptoms co-exist in long COVID patients, it is possible that the immune alterations found in our long COVID patients may also associate with symptoms other than fatigue, which we did not analyze in this study. However, other studies have described associations between immune alterations and symptoms other than fatigue in long COVID.[31,67,68] Our study is limited by the absence of an in-depth analysis of NK and B cells. The immunological assessment was performed at one point in time whereas other longitudinal studies reported interesting immune dynamics during convalescence of COVID-19.[27,30,31] Our study lacks a group of convalescent COVID-19 patients without signs of long COVID. We, therefore, cannot confirm that our findings can solely be attributed to the disease condition of long COVID rather than being a recovery sign of COVID-19 3-6 months after hospitalization. It is encouraging that other studies have found that excessive signs of low grade inflammation and high $CD8^+$ T-lymphocyte activity typify long COVID patients amongst the convalescent COVID-19 patients.[25,27,30] We conducted multiple tests to assess group differences in immune parameters using the Kruskal-Wallis test, followed by Bonferroni corrected post-hoc testing for multiple group comparisons. Since we did not correct the overall α threshold for the number of tested immune parameters across assay systems, this may increase the chances of false positive findings in our study. Notwithstanding, our findings are in line with previous studies on the immunological abnormalities in long COVID patients.[27,30,55] Long COVID patients should be followed for a longer period of time evaluating both clinical and immune profiles.

In conclusion, this study shows that long COVID patients with fatigue represent a more severe clinical profile of long COVID than non-fatigued patients, showing many concurrent and generally persistent

symptoms lasting up to one year of follow-up. Our findings suggest that fatigue is not associated with a clearly distinct immunotype of long COVID, but rather a part of the broader spectrum. On a group level, we observed no statistically significant differences in immune profiles between fatigued and non-fatigued long COVID patients. However, long COVID patients with increased fatigue severity correlated with stronger signs of monocyte activation and potentially point towards monocyte-endothelial interaction. As one group, patients with long COVID were characterized by a definite state of low grade inflammation and signs of T-lymphocyte senescence. The diversity of immune abnormalities indicates that personalized therapies combatting the diverse immune abnormalities may be required to alleviate the persisting disabling complaints of the patients.

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Chapter 12

General discussion

This thesis aimed to enhance our understanding of long-term health outcomes in patients hospitalized for COVID-19. The first confirmed case of SARS-CoV-2, causing COVID-19, was reported in December 2019 in Wuhan, China, and rapidly spread worldwide, leading to a global pandemic. In this timeframe, the CO-FLOW study was set up in which patients who survived hospitalization for COVID-19 in the Rotterdam–Rijnmond–Delft region in the Netherlands were longitudinally followed up through objectively assessed and self-reported health outcomes for up to 3 years after hospital discharge. CO-FLOW provides insights into the long-term health outcomes and aftercare pathways following hospitalization for COVID-19. The study findings are featured in two PhD theses, each addressing distinct topics, alongside some joint publications.

This thesis presents the CO-FLOW study protocol (**Chapter 2**). It focused on various health outcomes, including their trajectories, subgroup comparisons, and risk factors for health problems, up to 1 (**Chapter 3-5**), 2 (**Chapter 6-8**), and 3 years (**Chapter 9**) after hospital discharge. The rapid surge in COVID-19 cases and hospitalizations necessitated the quick development of aftercare pathways, which were primarily based on clinical expertise and opinion rather than evidence-based guidelines. The CO-FLOW study assessed patients' satisfaction and unmet needs regarding COVID-19 aftercare (**Chapter 10**). The long-term health problems following COVID-19, known as long COVID, remain poorly understood; however, biological mechanisms, including immune dysregulation, are likely involved. We therefore explored immunological abnormalities in patients with long COVID and their association with fatigue, one of its most prominent symptoms (**Chapter 11**). In this chapter, the main findings of this thesis are discussed, along with methodological considerations and clinical implications, and concludes with recommendations for future research.

Long-term health outcomes after hospitalization for COVID-19

The CO-FLOW study findings revealed that many patients went on to develop a wide range of symptoms after hospitalization for COVID-19 (**Chapter 4, 6, 9**). At the first visit, 3 months after hospital discharge, almost all patients (427/442 [97%]) reported at least one ongoing symptom. Despite some improvements, many symptoms remained highly prevalent throughout the follow-up period. Over 50% of patients continued to experience fatigue, impaired fitness, memory problems, and concentration problems, even up to 3 years after hospital discharge (**Chapter 9**).

Intriguingly, in the cognitive domain, self-reported memory and concentration problems (yes/no outcome) and cognitive failures (measured with a standardized questionnaire) showed no improvements after hospitalization and remained prevalent. In fact, memory problems (increasing from 51% to 59% of patients) and cognitive failures (increasing from 22% to 28%) worsened between the 2- and 3-year follow-up visits (**Chapter 9**). On the contrary, objectively assessed cognitive deficits, as measured with the Montreal Cognitive Assessment (MoCA), decreased over time from 40% (165/414) at 3 months to 12% (57/464) at 2 years. Of note, long-term comparisons between self-reported and objectively assessed outcomes are complicated, as the MoCA was not repeated during subsequent visits once a typical score was achieved (**Chapter 6**). Moreover, the MoCA is

a screening tool that may help identify potential cognitive issues but is not a diagnostic test. These results should therefore be interpreted with caution. We found that objectively assessed cognitive deficits and self-reported cognitive failures had only a weak correlation,[1] which aligns with the findings in the literature.[2,3] Objective tests of cognitive functioning assess cognitive ability in specific domains through standardized tasks, while self-reports capture a broader perception of one's cognitive abilities. Overall, our findings add to the growing evidence that cognitive problems are among the most common and persistent symptoms following hospitalization for COVID-19.[4,5]

Psychological factors may influence the subjective experience of health problems, including cognitive complaints. We found that self-reported cognitive failures were correlated with outcomes of anxiety, depression, and post-traumatic stress,[1] although these prevalences were relatively low (**Chapter 6, 9**). At 3 months, anxiety was reported in 13% (56/436) of patients, depression in 11% (49/436), and post-traumatic stress disorder in 12% (51/436), with these rates tending to remain stable or decline over time. While the COVID-19 pandemic has impacted mental health in the general population,[6,7] and patients with critical illness are typically at risk for developing mental health problems,[8] these concerns were not prominent in our cohort. Moreover, mental health problems may occur as a result of having long-term lingering symptoms and debilitating illness.

Physically, while self-reported symptoms of impaired fitness and muscle weakness remained highly prevalent during follow-ups, objective assessments indicated generally good recovery in physical function (**Chapter 6**) and activity (**Chapter 7**). Physical deconditioning and muscle weakness are well-known effects of critical illness following intensive care unit (ICU) treatment.[8] We observed that ICU-treated patients indeed showed poorer levels of physical fitness—particularly muscle weakness—(**Chapter 6**) and less physical activity (**Chapter 7**) than non-ICU-treated patients at 3-6 months follow-up. Nonetheless, these ICU-treated patients showed substantial physical improvements over time, reaching outcomes comparable to, or even better than, those of non-ICU-treated patients at the 1- and 2-year follow-ups. Most ICU-treated patients in our study had a good pre-COVID-19 health status and often were transferred to inpatient rehabilitation centers with intensive therapy, which may have contributed to favorable physical recovery. At 2 years, overall, patients reached 95% of normative values for cardiorespiratory fitness, as measured with the 6 min walk test (6MWT), and 108% for handgrip strength, aligning with other studies on physical function up to 2 years after hospitalization for COVID-19.[9-11]

Impact of COVID-19 on participation

The persistent health problems following COVID-19 adversely impact patients' ability to participate in social activities and return to work. The lockdowns during our study period restricted social activities, making it challenging to study the specific impact of COVID-19 on social participation.[12,13] A patient's ability to engage in work-related activities can be impacted by the severity of acute illness, persistent symptoms, the nature of work, work environments, and social support.[14,15] In the CO-FLOW study, still 30% (65/216) of patients had not returned to work, either full-time or part-time, at the 2-year follow-up (**Chapter 6**). In two other COVID-19 studies with a 2-year follow-up, one found that 11% (56/494) of hospitalized patients had not returned to work,[9] while another

reported that 32% (22/68) of ICU-treated patients had not fully returned to work.[16] Differences in COVID-19 populations may contribute to this discrepancy. For instance, ICU treatment has been linked to a lower likelihood of resuming work.[17] Our study is composed of a relatively large proportion of ICU-treated patients (42% [273/650]), and our findings align more closely with the latter study (which focused solely on ICU-treated patients) than with the former (which had only 3% ICU-treated patients). Nonetheless, these findings underscore the complex interplay of multiple factors that must be addressed in COVID-19 aftercare, focusing not only on symptom relief but also on the impact on daily life.

Overview of long-term health problems in the CO-FLOW study

Figure 1 shows the prevalence of health problems at 3 years after hospitalization for COVID-19 in the CO-FLOW study, with some outcomes limited to 2 years. It was striking to observe that 76% (225/297) of patients still felt not completely recovered from COVID-19 at 3 years, with many symptoms remaining highly prevalent. The prevalence of health problems in our cohort was relatively high compared to that in other cohort studies. For instance, fatigue was the most common symptom, reported by 66% (197/299) of patients at 3 years, whereas other studies found fatigue in 20%-45% of patients at 2 years and 17% and 18% at 3 years after hospitalization.[18-20] Notably, data up to 3 years after hospitalization are scarce, and differences in COVID-19 populations may contribute to these discrepancies. Nevertheless, the overall picture in the literature indicates that many patients experience long-term health problems after hospitalization for COVID-19.

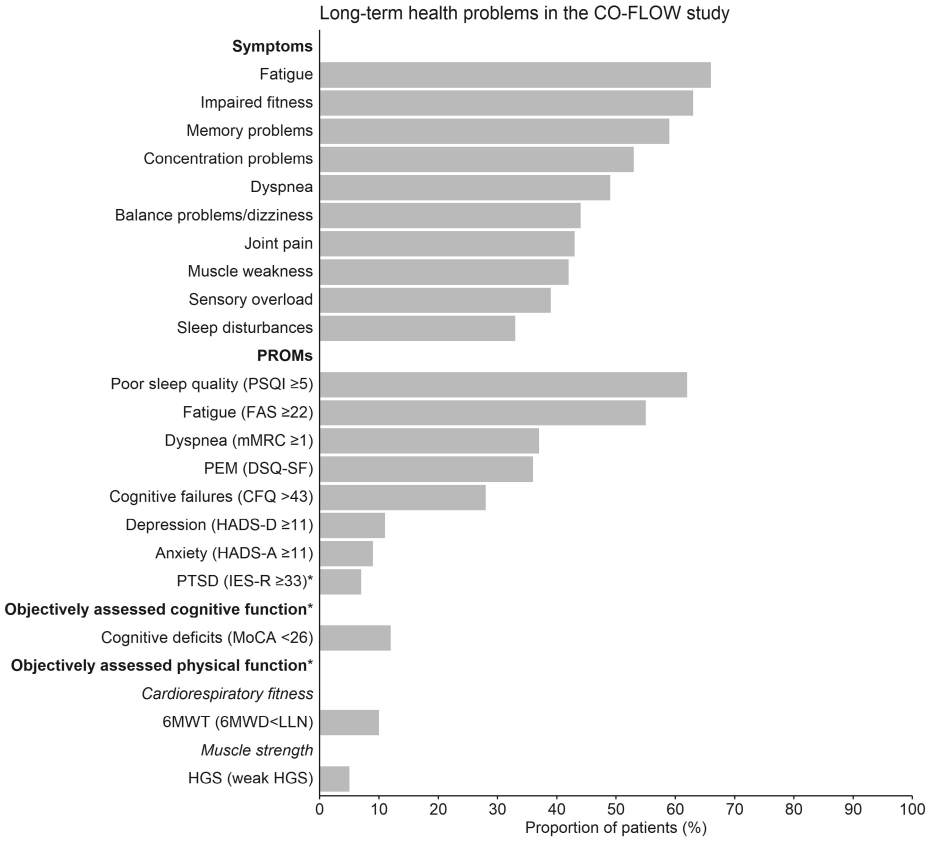

Figure 1. Long-term health problems after hospitalization for COVID-19.
*Data are presented for health outcomes at 3 years after hospital discharge, with some outcomes limited to 2 years as indicated by *. Symptoms were assessed on a binary scale (yes/no), whereas PROMs were assessed by a standardized questionnaire with cut-off value. Objectively assessed cognitive function was not repeated in subsequent visits once a normal score was reached, we used the last observation carried forward method to indicate the prevalence of cognitive deficits at 2 years. PROMs, Patient-Reported Outcome Measures; PSQI, Pittsburgh Sleep Quality Index; FAS, Fatigue Assessment Scale; PEM, Post-Exertional Malaise; DSQ-SF, DePaul Symptom Questionnaire-Short Form; mMRC, Modified Medical Research Council dyspnea scale; CFQ, Cognitive Failures Questionnaire; HADS-D, Hospital Anxiety and Depression Scale-subscale Depression; HADS-A, Hospital Anxiety and Depression Scale-subscale Anxiety; PTSD, Posttraumatic Stress Disorder; IES-R, Impact of Event Scale-Revised; MoCA, Montreal Cognitive Assessment; 6MWT, 6 Min Walk Test; 6MWD, 6 Min Walk Distance; LLN, Lower Limit of Normal; HGS, Handgrip strength.*

Long COVID

Long COVID is defined as a heterogeneous, chronic condition that occurs after SARS-CoV-2 infection, manifesting as a continuous, relapsing, remitting, or progressive disease state.[21] Long COVID is not the first post-acute infectious syndrome to emerge as a chronic condition.[22] Research has particularly highlighted its parallels with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), where fatigue and post-exertional malaise (PEM) are key features, contributing to a significant health burden.[21,23-26] PEM is a worsening or new-onset of symptoms after physical, cognitive, or

emotional exertion. These symptoms can occur immediately after the exertion or be delayed by up to 72 hours, which can last for days to weeks or even months. PEM is now also recognized as a distinctive feature of long COVID, and depending on the cohort, approximately half of patients with long COVID meet the diagnostic criteria for ME/CFS.[21,26] In the CO-FLOW study, 36% (105/292) of patients reported PEM at the 3-year follow-up, with many experiencing other concurrent health problems (**Chapter 9**). These findings contribute to the growing literature emphasizing that PEM is a distinctive feature of severe long COVID.[25,27-29] Therefore, early identification of PEM is essential for guiding personalized aftercare strategies and preventing any potential harm.[30]

One could question whether the ongoing symptoms in our cohort are due to COVID-19 or other factors, and what exactly characterizes long COVID. According to the definition, long COVID includes all new or worsened health problems, either continuous or with a delayed onset, that persist beyond three months after SARS-CoV-2 infection. Many of the symptoms overlap with those of post-intensive care syndrome (PICS), which involves physical, mental, and cognitive health problems following critical illness. Given that 42% of our patients were ICU-treated, some symptoms may be related to PICS. However, most symptoms were common across the entire cohort, regardless of ICU treatment, and most outcomes at the 2-year follow-up were comparable (**Chapter 6**), suggesting that the health problems cannot be solely attributed to PICS. Moreover, while patients hospitalized for COVID-19 are more likely to develop long COVID,[31-33] it can affect anyone, even those with an asymptomatic or mild SARS-CoV-2 infection.[21] While we did not compare our patients hospitalized for COVID-19 with those who had a mild infection, the relatively high prevalence of PEM and similar ongoing health problems (fatigue and cognitive problems) suggest that the long-term health problems in our study are primarily related to long COVID.

Fatigue: the most common symptom after hospitalization for COVID-19

Fatigue was the most common and persistent symptom in our cohort, with fatigue scores even worsening between the 2- and 3-year follow-ups (**Chapter 9**). However, fatigue is an unexplained symptom of long COVID, and the condition as a whole remains poorly understood. Several biological mechanisms are thought to contribute to long COVID, with abnormalities in the immune system linked to both long COVID and ME/CFS, potentially contributing to fatigue.[34-37] Therefore, in **Chapter 11**, we explored immunological abnormalities in patients with long COVID, compared with a control group of non-COVID-19 individuals, and assessed their association with fatigue at 3-6 months follow-up. Immunological abnormalities were found in the entire group of long COVID patients, irrespective of fatigue, showing immune activation characterized by low grade inflammation (increased inflammatory gene expression in monocytes and increased pro-inflammatory cytokines) and signs of T-lymphocyte senescence (increased exhausted $CD8^+$ TEMRA-lymphocytes). Our data thus provide supporting evidence for ongoing immune dysregulation in long COVID.[38-40] However, studies with longer follow-up periods are needed to assess the persistence and implications of a dysregulated immune system in patients who have been suffering from long COVID for several years.[41]

During hospitalization for COVID-19, various treatments were recommended over time to combat the effects of SARS-CoV-2. Since a dysregulated immune response and viral reservoirs have been hypothesized to play a role in long COVID, we explored the association between COVID-19 treatments during hospitalization, including steroids, anti-inflammatory treatments, and antivirals, and health outcomes up to 2 years after discharge (**Chapter 8**). Our findings indicated no significant effect of acute COVID-19 treatments on long-term fatigue scores or other health outcomes. Similarly, a large cohort study found no association between steroid use during hospitalization for COVID-19 and HRQoL one year later.[42] Given the high prevalence of persistent fatigue and other health problems after COVID-19, further research into the pathogenesis of long COVID, as well as effective prevention and treatment strategies, is urgently needed.[38]

Risk factors for poorer health outcomes

Female sex and pre-existing comorbidities were highly prevalent risk factors for poorer health outcomes in our studies (**Chapter 4, 6, 9**), including fatigue, cognitive failures, poorer sleep quality, PEM, and reduced HRQoL, aligning with previous research.[31,43,44] Enhancing our understanding of risk factors is essential, as this provides valuable insights into why some individuals are more vulnerable to developing long-term health problems. While males tend to experience more severe acute COVID-19 and have higher mortality rates,[45] long COVID is more common in females.[46,47] Sex-based differences in immune responses, influenced by hormonal, genetic, and environmental factors, may play a role. Generally, females have stronger immune responses than males, which may contribute to variations in the development of diseases, including long COVID.[48] Regarding comorbidities, pre-existing pulmonary disease was particularly associated with poorer health outcomes. COVID-19 can worsen pre-existing health conditions,[21] and the immune abnormalities associated with chronic pulmonary diseases may contribute to the development of long COVID.[49]

Hospitalization for COVID-19 has been associated with a higher risk of developing long COVID.[31,32] In the CO-FLOW study, ICU treatment was associated with an increased risk of PEM (**Chapter 9**) and a lower likelihood of fully resuming work[17] but was not linked to fatigue or cognitive failures (**Chapter 6**). Noteworthy, health outcomes were common across the entire cohort, regardless of ICU treatment (**Chapter 6**). Since long COVID can develop in anyone after COVID-19,[21] the severity of acute COVID-19 alone does not fully account for long-term health problems. Most long COVID cases occur in non-hospitalized patients with mild to moderate acute illness—the largest group of COVID-19 cases.[33] However, our study lacks a comparison group of these patients.

COVID-19 aftercare following hospitalization

COVID-19 has led to an overwhelming increase in hospitalizations. In 2020 alone, the Netherlands recorded over 770.000 confirmed COVID-19 cases, including more than 40.000 hospital admissions, which placed significant strain on the available clinical resources.[50-52] Patients were to be discharged from the hospital as soon as possible, either to their home environment or to inpatient rehabilitation facilities.

At hospital discharge, severely affected COVID-19 patients requiring prolonged hospitalization were typically referred to more intensive, multidisciplinary rehabilitation. Among 650 participants in the CO-FLOW study, 15% received in- or outpatient medical rehabilitation, 14% received inpatient rehabilitation in a skilled nursing facility, 52% returned home with support from community-based rehabilitation, and 20% did not participate in any form of rehabilitation after discharge. In **Chapter 5** we assessed 1-year trajectories of objectively assessed physical function across patients following these different aftercare pathways. Our findings showed that patients who participated in rehabilitation, particularly those with medical rehabilitation or rehabilitation in a skilled nursing facility, were more physically disabled at the 3-month follow-up. However, they showed improvements in cardiorespiratory fitness and muscle strength over time, with outcomes comparable to those of less affected patients in later follow-ups. Despite generally good recovery in these physical outcomes, many patients continued to experience a wide range of health problems, as discussed previously**.** The CO-FLOW study group later conducted a clinical randomized controlled pilot trial of a home-based computerized cognitive training program to explore its effect on persistent cognitive complaints; we are currently awaiting the results of this study.

Following hospitalization for COVID-19, our patients were routinely followed up by the hospital (**Chapter 6**), typically monitoring pulmonary sequelae.[53-55] Impaired diffusion capacity, the most common pulmonary function impairment after COVID-19, was observed in more than half of our patients 6 weeks after discharge (**Chapter 6**) and has been linked to more severe acute COVID-19 (**Chapter 3**).[9,56,57] Pulmonary impairments largely improved over time after hospital discharge.[57,58] In the CO-FLOW study, only 8% (55/650) of patients continued follow-up for up to 2 years due to persistent pulmonary dysfunction, though improvements were also observed in this group. In contrast, self-reported respiratory symptoms were commonly reported throughout follow-up, with 37% (110/296) of patients reporting dyspnea at 3 years (**Chapter 9**). A previous study found no association between respiratory symptoms and pulmonary dysfunction after hospitalization for COVID-19.[59]

Despite persistent health problems, patients were generally satisfied with the aftercare they received, rating this 8/10 at the 1-year follow-up (**Chapter 10**). Follow-up care by the hospital or by a general practitioner was associated with higher satisfaction with COVID-19 aftercare, offering an opportunity to address health concerns. Additionally, these healthcare providers play a vital role in secondary triage, facilitating referrals for tailored aftercare at a later stage (**Chapter 10**). It is to be noted that 35% (170/485) of our patients reported unmet needs, most frequently information needs (20%, 97/485) (**Chapter 10**). This number aligns with the broader COVID-19 population, including non-hospitalized patients.[60,61]

CO-FLOW study methodological considerations

Study design, participants, and measurements

The study's prospective multicenter longitudinal design, comprehensive assessment of objectively assessed and self-reported health outcomes, and the 3-year follow-up period after hospitalization for COVID-19 are key strengths. The comprehensive repeated assessments in a cohort of 650 patients have made valuable contributions to the research field of long-term health outcomes after hospitalization for COVID-19.

CO-FLOW participants were recruited from all COVID-19 survivors attending the outpatient clinic for routine follow-up at the participating hospitals. Data on the eligible recruitment population have not been reported as these numbers are largely unknown. However, recruitment was independent of the patient's disease severity or recovery status and primarily influenced by the availability of research personnel. Nevertheless, the potential for selection bias toward patients with lingering symptoms visiting the outpatient clinics cannot be ruled out.

Like many COVID-19 studies, we could not compare patients' health outcomes to their pre-morbid levels. Instead, we used normative reference values from the general population for objective measures and validated cut-off scores for patient-reported outcome measures to assess the severity of health outcomes. For instance, we used reference values obtained from the general population to interpret levels of physical fitness, which, while widely used, have limitations. Normative values for the 6MWT[62] date back to 1998 and may require updating. Given the evolving knowledge of PEM following COVID-19, we included the DePaul Symptom Questionnaire at the 3-year follow-up and, therefore, lacked evaluation of changes over time.

It is important to note that varying study designs, populations, and assessment tools challenge the comparison of findings between studies. Utilizing a harmonized test battery or a core outcome set could enhance the consistency and comparability of outcome measures across studies. Attempts to define a core outcomes set have been made; however, consensus on the instruments has not yet been achieved for all outcomes.[63,64]

Generalizability

CO-FLOW is composed of a relatively high proportion of ICU-treated patients (42%) compared to other cohort studies and the 14% ICU admission rate among patients hospitalized for COVID-19 in the Netherlands. This was likely due to our academic center's role as a regional referral center for ICU patients, and many participants were recruited from this center. However, this allowed for comparison between ICU- and non-ICU-treated patients on long-term health outcomes. We observed no noticeable disparity in health outcomes at 2 years between these groups; therefore, overestimation of poor outcomes is unlikely to play a major role. We recruited patients in a period where the original, alpha, and delta variants of SARS-CoV-2 were dominant, lacking the omicron variant, while the latter variant has been associated with less severe acute disease and long-term health outcomes.[65] Most patients were unvaccinated against COVID-19 at the time of hospital

admission, while vaccination has been shown to reduce the risk of long-term health problems.[66] Lastly, study participation required sufficient proficiency in Dutch or English, which may limit the generalizability of our findings to ethnic minorities. Despite this, 29% of our patients had a non-European migration background, enabling comparisons between European versus non-European patient groups.

Clinical implications

The CO-FLOW study findings revealed that many patients experience long-term health problems after hospitalization for COVID-19. The findings underscore the complex interplay of multiple factors that must be considered in COVID-19 aftercare, necessitating a personalized approach. This care should focus not only on symptom relief but also on the impact on daily life. Current guidelines recommend pacing and activity management strategies for long COVID patients with PEM to prevent post-exertional symptom exacerbation.[30,67,68] Pacing is a self-management strategy where patients engage in activities within their limits to avoid worsening their health, often involving planned rest periods to maintain energy throughout the day.[69,70] Given that many patients have been suffering from long COVID for several years now, for some patients, psychological support may help patients cope with the long-term challenges of long COVID. Importantly, psychological health should not be viewed as the cause of long COVID and should be offered only to those who are open to receiving such support.[71] Effective care strategies may require a multidisciplinary approach with close collaboration between healthcare professionals, covering medical, physical, cognitive, psychological, occupational, dietary, and vocational needs. Notably, multidisciplinary collaboration was considered essential for providing more comprehensive support to post-acute COVID-19 patients by healthcare providers.[72]

Long COVID is a complex, heterogeneous syndrome, and its exact underlying mechanisms remain elusive.[38-40] Our findings on immunological abnormalities in long COVID underscore the need for extensive research into its pathophysiology, which could guide more targeted treatment strategies. Without in-depth knowledge of the pathophysiology of long COVID, treatment will mainly rely on trial and error, focusing on symptom relief and optimizing daily functioning.

In late 2024, long COVID expert clinics opened in the Netherlands, integrating care with research by evaluating long-term health outcomes, collecting blood samples, and exploring the efficacy of pharmacological treatments on symptom reduction. Notably, the team also involves a rehabilitation physician to ensure integrated care. The initiative creates a care and research infrastructure that enables clinicians and researchers to collect comprehensive outcomes and enhance our understanding of long COVID, which may aid in identifying phenotypes, developing diagnostic tools, and ultimately designing personalized treatment strategies. Moreover, these clinics may enhance patient satisfaction with aftercare and help address their information needs. As the long COVID expert clinics are still in their early stages, their effectiveness in patient management has yet to be evaluated.

One-fifth of patients reported unmet information needs during COVID-19 aftercare. Online platforms, forums, and websites for COVID-19 support grew attention during the pandemic, offering evolving knowledge and self-management resources. We therefore recommend establishing a centralized, up-to-date online information source early during future outbreaks.

Conclusion and recommendations for future research

This thesis showed that many patients continued to experience health problems up to 3 years after hospitalization for COVID-19. More than half of the patients reported persistent fatigue, impaired fitness, memory problems, and concentration problems 3 years after hospital discharge. Long-term health problems, referred to as long COVID, were common across the entire cohort, regardless of ICU treatment. Females and individuals with pre-existing pulmonary disease were particularly at higher risk for poorer health outcomes. The findings highlight the urgent need for further research into long-term health problems after COVID-19 and effective management strategies.

At the time of writing, five years since the onset of COVID-19, long COVID remains poorly understood, and several research gaps persist. Large-scale cohort studies are essential for continuously monitoring long-term health impacts, ensuring that long COVID is not overlooked. In this context, the CO-FLOW study will continue to follow patients for up to 5 years after hospitalization. Future research should focus on identifying effective multidisciplinary care strategies, including personalized approaches, to support patients recovering from COVID-19. Extensive research is also needed into the underlying mechanisms of long COVID, as well as identifying its biomarkers and phenotypes, which could pave the way for more effective treatment strategies. Together, these insights could enhance our understanding of long COVID and improve the management of patients experiencing long-term health problems after COVID-19.

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Appendices

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Supplementary material

Scan the QR code below to access the supplementary material for this thesis.

Summary

COVID-19, caused by SARS-CoV-2, spread rapidly worldwide, resulting in a global pandemic and a sudden, substantial rise in hospitalizations. Early reports revealed that many patients experienced lasting health effects in the weeks or months after hospitalization for COVID-19. The CO-FLOW study aimed to comprehensively study long-term health outcomes and aftercare pathways following hospitalization for COVID-19. It performed longitudinal assessments of objectively assessed and self-reported health outcomes for up to 3 years after hospitalization, with study visits performed at 3 and 6 months and 1, 2, and 3 years after hospital discharge. The research presented in this thesis builds upon the findings of the CO-FLOW study.

This thesis aimed to enhance our understanding of long-term health outcomes in patients hospitalized for COVID-19. It focused on various health outcomes, assessing their trajectories, subgroup comparisons, and risk factors for health problems up to 1, 2, and 3 years after hospitalization for COVID-19. Additionally, it assessed patients' perspectives on COVID-19 aftercare and explored immunological abnormalities in patients with long COVID and their association with fatigue, one of its most prominent symptoms.

Chapter 1 provides background information on COVID-19, including the onset of the pandemic, clinical manifestations, and insights into health outcomes and aftercare pathways following hospitalization. It also describes the term "long COVID", referring to the condition of long-term health problems persisting after COVID-19. Additionally, the CO-FLOW study is introduced and an outline of this thesis is presented.

Chapter 2 presents a more detailed description of the CO-FLOW study, including an overview of its rationale, objectives, design, and methodology. The CO-FLOW study recruited patients who survived hospitalization for COVID-19 in the Rotterdam–Rijnmond–Delft region in the Netherlands. The study was performed in 10 centers, including 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities). Patients were longitudinally followed up through both objectively assessed and self-reported health outcomes at 3, 6, 12 and 24 months (later extended to 36 months) after hospital discharge. CO-FLOW aimed to study systematically: 1] trajectories of physical, cognitive, and psychological outcomes; 2] patient flows, healthcare utilization, and the perspective of patients and healthcare professionals on COVID-19 aftercare; 3] effects of physical, cognitive, and psychological outcomes on participation and health-related quality of life (HRQoL); and 4] predictors of long-term health outcomes, healthcare utilization, and patient satisfaction with aftercare.

In **Chapter 3** we studied the impact of pulmonary embolism (PE) during hospitalization for COVID-19 on health outcomes 3 months post-discharge. All patients were hospitalized during the first COVID-19 wave. In this study we aggregated data from existing databases across four Dutch academic hospitals. Patients with PE (102/465 [22%]) had poorer HRQoL, greater impairment in pulmonary functions, and more frequent radiological abnormalities compared to those without PE

(363/465 [79%]). In-depth analysis showed that the association between PE and HRQoL remained significant after adjusting for confounders, but not for the other outcomes. We discussed that PE may serve as a proxy for COVID-19 severity, which could suggest that the poorer outcomes at follow-up are more likely associated with the severity of acute COVID-19 itself rather than the direct effect of PE. Nonetheless, the presence of PE during hospitalization could indicate a risk of developing long-term health problems, as these patients show clinically meaningful poorer HRQoL.

Chapter 4 presents trajectories and clusters of symptoms up to 1 year after hospital discharge, along with predictors of prevalent symptoms. Most patients reported persistent symptoms after discharge, with 92% reporting at least one symptom at the 1-year follow-up. Muscle weakness, exertional dyspnea, fatigue, and memory and concentration problems were the most prevalent symptoms, reported by over 50% of patients during follow-up visits. Whereas physical and respiratory symptom clusters showed a slow gradual decline, this was not found for the fatigue and cognitive symptom clusters. Additionally, we found that female sex is the most prominent risk factor for persistent symptoms in our cohort. The findings emphasize the need for further research into the underlying mechanisms and treatments for long COVID, as well as the importance of conducting long-term cohort studies to better understand persistent symptoms after COVID-19.

COVID-19 has led to an overwhelming increase in hospitalizations, which challenged the clinical resources available. Patients were to be discharged from the hospital as soon as possible, either to their home environment or to inpatient rehabilitation facilities. Severely affected COVID-19 patients requiring prolonged hospitalization were typically referred to more intensive, multidisciplinary rehabilitation in medical rehabilitation centers or in skilled nursing facilities. Patients discharged home with persistent symptoms were referred to community-based rehabilitation, which typically included monodisciplinary treatments such as physiotherapy. In **Chapter 5** we studied the 1-year trajectories of objectively assessed physical function in patients following different aftercare pathways. Among the 582 patients in this study, 14% received in- or outpatient medical rehabilitation, 12% inpatient rehabilitation in a skilled nursing facility, 54% were discharged home with support from community-based rehabilitation, and 20% were discharged home and did not participate in any form of rehabilitation. We found that cardiorespiratory fitness and muscle strength improved after hospitalization for COVID-19 in the total cohort, with the largest improvement within 6 months post-discharge. At 3 months follow-up, patients who received rehabilitation, and particularly those with medical rehabilitation or rehabilitation in a skilled nursing facility, were more physically disabled than less affected patients, but group differences were no longer statistically significant in later follow-ups.

Chapters 6 and 7 present the trajectories of all collected health outcomes within the CO-FLOW study up to 2 years after hospitalization, including comparisons between intensive care unit (ICU)- and non-ICU-treated patients. In **Chapter 6** we found that despite many health outcomes improving over time, 73% of patients still felt not completely recovered from COVID-19 at 2 years. Cognitive problems, dyspnea, fatigue, and poor sleep quality were among the most prevalent problems. Most health outcomes were comparable between ICU- (273/650 [42%]) and non-ICU-treated (377/650

[58%]) patients at 2 years. However, ICU-treated patients tended to show slower recovery of neurocognitive symptoms, mental health outcomes, and resuming work compared to non-ICU-treated patients, while showing greater improvements in objectively assessed physical outcomes. Female sex and pre-existing pulmonary disease were identified as prominent risk factors of poorer health outcomes. The findings highlight the need for comprehensive aftercare strategies that address a wide range of long-term health effects. Further research into effective treatments is needed, including more personalized rehabilitation programs and potential pharmacological treatments. The findings also underscore the importance of continuous monitoring of health outcomes and we, therefore, extended the CO-FLOW study with additional follow-ups, including a survey conducted at 3 years post-discharge (**chapter 9**).

Chapter 7 presents the 2-year trajectories of device-assessed physical activity and sleep, and their association with HRQoL. Overall, physical and sleep behaviors seemed generally sufficient in the cohort up to 2 years after hospitalization, and outcomes did not change over time. However, ICU-treated patients started with less physical activity but improved over the first year post-discharge, reaching the levels of non-ICU-treated patients at 1 year, likely reflecting their recovery from critical illness. We found that less time spent in moderate-to-vigorous physical activity was associated with poorer HRQoL, even after adjusting for covariables, including concurrent health problems of fatigue, cognitive failures, anxiety, and depression.

During hospitalization for COVID-19, various treatments were recommended over time to combat the effects of SARS-CoV-2. Given that a dysregulated immune response and viral reservoirs have been hypothesized as underlying mechanisms of long COVID, we explored the association between COVID-19 treatments during hospitalization, including steroids, anti-inflammatory treatments, and antivirals, and long-term health outcomes in **Chapter 8**. We found no effect of acute COVID-19 treatments on self-reported outcomes, including dyspnea, fatigue, cognitive failures, HRQoL, or objectively assessed cardiorespiratory fitness (6 min walk test) up to 2 years after hospital discharge. Given the substantial number of patients suffering from long COVID, further research into its pathophysiology and effective prevention and treatment strategies are urgently needed.

The CO-FLOW study was extended with a survey conducted at 3 years after hospitalization for COVID-19. **Chapter 9** presents the trajectories of patient-reported health outcomes up to 3 years, focusing on changes between the 2- and 3-year follow-up visits. In addition, we assessed post-exertional malaise (PEM) at the 3-year follow-up, a prominent symptom of long COVID, assessing its prevalence, risk factors, and co-occurring health problems in patients with PEM. The findings showed that despite improvements over time, many health problems persisted up to 3 years. Fatigue and cognitive problems were the most frequently reported problems throughout follow-up and even worsened between the 2- and 3-year follow-up visits. At 3 years, 36% (105/292) of patients experienced PEM, with female sex, pre-existing pulmonary disease, and ICU admission identified as risk factors. Most patients with PEM reported other co-occurring health problems and they showed poorer health outcomes throughout the entire 3-year follow-up period compared to those without PEM at 3 years. Our findings, aligning with previous studies, suggest that PEM may

indicate a more severe phenotype of long COVID, emphasizing the importance of early identification to guide personalized aftercare. The findings highlight the need for further research into effective management strategies for long COVID, as well as the importance of ongoing health monitoring to better understand the long-term effects of COVID-19.

The COVID-19 pandemic and surge in hospitalizations necessitated a quick development of aftercare pathways, which were largely based on clinical expertise and opinion rather than evidence-based guidelines. In **Chapter 10** we studied COVID-19 aftercare from a patients' perspective, assessing satisfaction and its associated factors, and unmet needs at 1 year after hospital discharge. We used a self-developed questionnaire for this study: The *Satisfaction with COVID-19 Aftercare Questionnaire*. Despite persistent health complaints, patients were generally satisfied with the received aftercare (satisfaction score 8/10). Follow-up care by the hospital or by a general practitioner was associated with higher satisfaction with COVID-19 aftercare. It is to be noted that 35% (170/485) of patients reported unmet needs, most frequently information needs (97/485 [20%]). These insights in aftercare needs could have implications for enhancing COVID-19 aftercare and for the management of future infectious outbreaks.

Fatigue is a prominent but unexplained symptom of long COVID and the condition in general remains poorly understood. Biological mechanisms, including immune dysregulation, are likely involved. **Chapter 11** describes clinical outcomes and immunological abnormalities in patients with long COVID at 3-6 months after hospital discharge, and their association with fatigue. We compared immune parameters in our patients with an age- and sex-matched control group of non-COVID-19 individuals. Long COVID with fatigue represented a more severe clinical profile than the non-fatigued group, showing many concurrent and generally persistent symptoms. Immunological abnormalities were present in the entire group of long COVID patients, irrespective of fatigue, characterized by low grade inflammation (increased inflammatory gene expression in monocytes, increased pro-inflammatory cytokines) and signs of T-lymphocyte senescence (increased exhausted $CD8^+$ TEMRA-lymphocytes). However, increased fatigue severity was associated with stronger signs of monocyte activation and potentially points in the direction of monocyte-endothelial interaction, which should be further investigated in future research. These findings provide supporting evidence for ongoing immune dysregulation in long COVID.

In **Chapter 12**, the main findings of this thesis are discussed and contextualized within the existing literature. Additionally, it discusses methodological considerations and clinical implications, concluding with recommendations for future research.

Nederlandse samenvatting

COVID-19, veroorzaakt door het SARS-CoV-2 virus, verspreidde zich snel over de wereld, wat resulteerde in een wereldwijde pandemie en een overweldigende stijging van ziekenhuisopnames. Vroege inzichten toonden aan dat veel patiënten langdurige gezondheidsproblemen ervaarden in de weken of maanden na ziekenhuisopname voor COVID-19. Het CO-FLOW onderzoek had als doel om kennis te vergaren over de langetermijngevolgen en nazorg na ziekenhuisopname voor COVID-19. Het onderzoek bestudeerde longitudinaal zowel objectief gemeten als patiënt-gerapporteerde uitkomstmaten tot en met 3 jaar na ziekenhuisontslag. De meetmomenten vonden plaatsen op 3 en 6 maanden, en op 1, 2 en 3 jaar na ontslag. De onderzoeken die in dit proefschrift worden gepresenteerd, zijn gebaseerd op de bevindingen van het CO-FLOW onderzoek.

Dit proefschrift richtte zich op het verdiepen van inzichten in gezondheidsuitkomsten op de lange termijn na ziekenhuisopname voor COVID-19. We onderzochten uitkomsten in verschillende gezondheidsdomeinen, waaronder het bestuderen van trajecten over tijd, het vergelijken van subgroepen en het identificeren van voorspellers van uitkomsten, tot 1, 2, en 3 jaar na ziekenhuisontslag. Daarnaast onderzochten we patiënttevredenheid over COVID-19 nazorg en verkenden we immunologische afwijkingen bij patiënten met long COVID in relatie tot vermoeidheid, een van de meest voorkomende symptomen.

Hoofdstuk 1 beschrijft achtergrondinformatie van COVID-19, waaronder de opkomst van de pandemie, de verschillen in ziekteverschijnselen en inzichten in gezondheidsuitkomsten en nazorgtrajecten na ziekenhuisopname. De term "long COVID" wordt beschreven, wat de aandoening van langdurige klachten na COVID-19 infectie beschrijft. Daarnaast wordt in dit hoofdstuk het CO-FLOW onderzoek geïntroduceerd en wordt een overzicht van de inhoud van dit proefschrift gegeven.

Hoofdstuk 2 biedt een uitgebreid overzicht van de rationale, opzet, doelstellingen en methodologie van het CO-FLOW onderzoek. In dit onderzoek volgden we patiënten die voor COVID-19 in een ziekenhuis waren opgenomen in de regio Rotterdam–Rijnmond–Delft in Nederland. Het onderzoek werd uitgevoerd in 10 centra, waaronder 7 ziekenhuizen (1 academisch ziekenhuis, 6 regionale ziekenhuizen) en 3 revalidatiecentra (1 medisch specialistisch revalidatiecentrum en 2 geriatrische revalidatiecentra). Patiënten werden longitudinaal opgevolgd door middel van objectief gemeten en zelfgerapporteerde gezondheidsuitkomsten op 3, 6, 12 en 24 maanden (later uitgebreid met een extra meetmoment op 36 maanden) na ziekenhuisontslag. Het doel van CO-FLOW was het systematisch onderzoeken van: 1] trajecten van fysieke, cognitieve en psychologische uitkomsten; 2] patiëntenstromen, zorggebruik en het perspectief van patiënten en zorgverleners op de COVID-19 nazorg; 3] effecten van fysieke, cognitieve en psychologische uitkomsten op participatie en gezondheidsgerelateerde kwaliteit van leven; en 4] voorspellers van gezondheidsuitkomsten, zorggebruik en patiënttevredenheid met de nazorg.

In **Hoofdstuk 3** onderzochten we of het ontwikkelen van een longembolie tijdens ziekenhuisopname voor COVID-19 effect heeft op gezondheidsuitkomsten 3 maanden na ontslag. In dit onderzoek hebben we gegevens uit bestaande databases van vier Nederlandse academische ziekenhuizen samengevoegd. Alle patiënten waren opgenomen in het ziekenhuis tijdens de eerste COVID-19 golf. Van de patiënten ontwikkelde 22% (102/465) een longembolie tijdens hun opname. Deze patiënten rapporteerden een lagere gezondheidsgerelateerde kwaliteit van leven, toonden slechtere longfuncties en meer radiologische afwijkingen dan patiënten zonder longembolie (363/465 [79%]) bij het 3-maanden meetmoment. Verder onderzoek liet zien dat de associatie tussen longembolie en lagere kwaliteit van leven overeind bleef na het corrigeren voor andere factoren. Echter, de associatie tussen longembolie en andere uitkomsten verdween na correctie. We bediscussieerde dat een longembolie mogelijk een indicator is voor de ernst van COVID-19. Dit kan erop wijzen dat slechtere gezondheidsuitkomsten na ziekenhuisontslag meer gerelateerd zijn aan de ernst van COVID-19 in het algemeen, en niet specifiek aan de longembolie. Desondanks kan een longembolie tijdens ziekenhuisopname voor COVID-19 wijzen op een verhoogd risico op langdurige gezondheidsproblemen, aangezien deze patiënten een klinisch relevante lagere kwaliteit van leven vertonen.

In **Hoofdstuk 4** wordt het beloop van symptomen en clusters van symptomen tot 1 jaar na ziekenhuisontslag beschreven. Daarnaast onderzochten we voorspellers van veelvoorkomende symptomen. De meeste patiënten ervaarden langdurige klachten na ontslag, 92% van de patiënten rapporteerde ten minste één symptoom bij het 1-jaar meetmoment. Spierzwakte, inspanningsdyspnoe, vermoeidheid, geheugenproblemen en concentratieproblemen kwamen het meest voor, gerapporteerd door meer dan 50% van de patiënten op een van de meetmomenten. Hoewel symptomen in de fysieke en respiratoire clusters langzaam verbeterden, bleven symptomen in de vermoeidheid en cognitieve clusters duidelijk aanhouden. Daarnaast vonden we dat het vrouwelijk geslacht een belangrijk risicofactor is voor aanhoudende klachten. De bevindingen benadrukken het belang van langdurige opvolging en verder onderzoek naar de onderliggende mechanismen en effectieve behandelingen van long COVID, om de aandoening beter te begrijpen.

COVID-19 heeft geleid tot een overweldigende toename van ziekenhuisopnames, wat de beschikbare klinische middelen onder druk heeft gezet. Patiënten werden vaak zo snel mogelijk uit het ziekenhuis ontslagen, hetzij naar hun thuissituatie, hetzij naar een revalidatiecentrum. Ernstig aangedane patiënten met een langdurige ziekenhuisopname werden vaak doorverwezen naar intensieve, multidisciplinaire revalidatie in een medisch specialistisch of geriatrisch revalidatiecentrum. Patiënten die naar huis ontslagen werden en aanhoudende klachten ervaarden, werden vaak doorverwezen naar eerstelijns revalidatie, zoals fysiotherapie. In **Hoofdstuk 5** onderzochten we de 1-jaars trajecten van objectief gemeten fysieke uitkomsten tussen verschillende nazorgtrajecten. Van de 582 patiënten in dit onderzoek ontving 14% klinische of poliklinische medisch specialistische revalidatie, 12% klinische geriatrische revalidatie, 54% werd ontslagen naar huis en ontving eerstelijns revalidatie terwijl 20% naar huis ging zonder deelname aan revalidatie. We constateerden dat de cardiorespiratoire fitheid en spierkracht in het gehele cohort over de tijd verbeterden, met de grootste vooruitgang in de eerste 6 maanden na ziekenhuisontslag. Echter, bij het 3-maanden meetmoment vertoonden patiënten met

revalidatie, met name patiënten in medisch specialistische revalidatie of geriatrische revalidatie, meer fysieke beperkingen dan minder aangedane patiënten. Groepsverschillen waren echter op latere meetmomenten niet meer statistisch significant verschillend tussen de groepen.

De **Hoofdstukken 6 en 7** beschrijven de 2-jarige trajecten van alle verzamelde gezondheidsuitkomsten in het CO-FLOW-onderzoek, inclusief vergelijkingen tussen patiënten met en zonder intensive care (IC) opname. In **Hoofdstuk 6** vonden we dat ondanks verbeteringen in gezondheidsuitkomsten over tijd, veel patiënten langdurige gezondheidsproblemen bleven ervaren. Bij 2 jaar na ziekenhuisontslag gaf 73% van de patiënten aan niet volledig hersteld te zijn van COVID-19. De meest voorkomende klachten waren cognitieve klachten, kortademigheid, vermoeidheid en een slechte slaapkwaliteit. De meeste uitkomsten waren vergelijkbaar tussen IC- (273/650 [42%]) en niet-IC-behandelde (377/650 [58%]) patiënten bij het 2-jaar meetmoment. Echter, IC-behandelde patiënten vertoonden een langzamer herstel van cognitieve symptomen, mentale gezondheidsuitkomsten en werkhervatting in vergelijking met niet-ICU-behandelde patiënten. Aan de andere kant lieten zij meer vooruitgang zien in objectief gemeten fysieke uitkomsten. Vrouwelijk geslacht en reeds bestaande longaandoeningen bleken belangrijke risicofactoren voor gezondheidsproblemen. De bevindingen in **Hoofdstuk 6** benadrukken het belang van uitgebreide nazorgstrategieën die een breed scala aan langetermijngevolgen adresseren. Er is meer onderzoek nodig naar effectieve behandelingen, waaronder gepersonaliseerde revalidatieprogramma's en mogelijke farmacologische behandelingen. Langdurige opvolging van patiënten is van belang om het verdere verloop van gezondheidsuitkomsten na COVID-19 in kaart te brengen. Het CO-FLOW onderzoek werd daarom verlengd met extra meetmomenten, waaronder vragenlijsten die 3 jaar na ziekenhuisontslag werden afgenomen (**Hoofdstuk 9**).

Hoofdstuk 7 presenteert de 2-jarige trajecten van fysieke activiteit en slaap, gemeten met een accelerometer, en de relatie met gezondheidsgerelateerde kwaliteit van leven. Over het algemeen vertoonden de uitkomsten van fysiek- en slaapgedrag in het gehele cohort goede niveaus, en veranderden deze niet over de tijd. Echter, IC-behandelde patiënten vertoonden minder fysieke activiteit dan niet-IC patiënten 3-6 maanden na ziekenhuisontslag, maar verbeterden in het eerste jaar en bereikten bij 1 jaar vergelijkbare niveau als niet-IC-behandelde patiënten. Dit weerspiegelt waarschijnlijk het herstel na een ernstige ziekte. Daarnaast vonden we dat minder tijd besteed aan matig tot intensieve fysieke activiteit geassocieerd was met een lagere kwaliteit van leven. Deze associatie bleef bestaan, zelfs na correctie voor andere factoren, zoals klachten van vermoeidheid, cognitieve klachten, angst en depressie.

Tijdens ziekenhuisopname voor COVID-19 werden in de loop van de tijd verschillende behandelingen aanbevolen om de door SARS-CoV-2 veroorzaakte verstoringen in het lichaam te bestrijden. Aangezien afwijkingen in het immuunsysteem en virale reservoirs als mogelijke onderliggende mechanismen van long COVID worden beschreven, onderzochten we in **Hoofdstuk 8** het effect van ziekenhuisbehandelingen, waaronder steroïden, ontstekingsremmers en antivirale therapieën, op gezondheidsuitkomsten tot 2 jaar na ziekenhuisontslag. We vonden geen effect van deze behandelingen op zelfgerapporteerde uitkomsten zoals dyspneu, vermoeidheid, cognitieve klachten

en gezondheidsgerelateerde kwaliteit van leven, nog op objectief gemeten cardiorespiratoire fitheid (6 min wandeltest). Gezien het grote aantal patiënten met langdurige klachten (long COVID), is verder onderzoek naar de pathofysiologie ervan en effectieve preventie- en behandelstrategieën van cruciaal belang.

Het CO-FLOW onderzoek werd verlengd met een meetmoment bij 3 jaar na ziekenhuisontslag. **Hoofdstuk 9** beschrijft de 3-jarige trajecten van zelfgerapporteerde gezondheidsuitkomsten, met de focus op veranderingen tussen de 2- en 3-jaar meetmomenten. Daarnaast onderzochten we post-exertionele malaise (PEM), een prominent symptoom van long COVID, bij het 3-jaar meetmoment, waarbij we gekeken hebben naar het aantal patiënten met PEM, risicofactoren en de relatie met andere gezondheidsuitkomsten. Ondanks verbeteringen in meerdere uitkomsten over tijd, bleven veel klachten aanhouden, zelfs tot 3 jaar na ontslag. Vermoeidheid en cognitieve klachten waren de meest gerapporteerde klachten gedurende de follow-up periode en verergerden zelfs tussen de 2- en 3-jaar meetmomenten. Bij 3 jaar ervaarde 36% (105/292) van de patiënten klachten die duiden op PEM, waarbij vrouwelijk geslacht, reeds bestaande longaandoeningen en IC-opname voor COVID-19 als risicofactoren werden geïdentificeerd. De meeste patiënten met PEM rapporteerden andere gelijktijdige klachten en rapporteerden slechtere gezondheidsuitkomsten gedurende de gehele 3-jaar follow-up periode in vergelijking met degenen zonder PEM bij 3 jaar. Onze bevindingen, in combinatie met eerdere onderzoeken, suggereren dat PEM duidt op een ernstiger fenotype van long COVID. Dit benadrukt het belang van vroege identificatie van PEM om gepersonaliseerde nazorg te optimaliseren. De bevindingen onderstrepen de noodzaak voor onderzoek naar effectieve managementstrategieën voor long COVID, evenals het belang van langdurige opvolging van deze patiëntengroep om de langetermijneffecten van COVID-19 beter te begrijpen.

De COVID-19 pandemie en de toename van ziekenhuisopnames vereisten een versnelde ontwikkeling van nazorgtrajecten, die grotendeels gebaseerd waren op klinische expertise en opinie in plaats van evidence-based rijchtlijnen. **Hoofdstuk 10** beschrijft patienttevredenheid met COVID-19 nazorg, waaronder factoren die hiermee geassocieerd zijn, en onvervulde behoeften 1 jaar na ziekenhuisontslag. Voor dit onderzoek hebben we een zelfontwikkelde vragenlijst gebruikt om de relevante gegevens te verzamelen: de *Satisfaction with COVID-19 Aftercare Questionnaire*. Ondanks de aanhoudende klachten waren patiënten over het algemeen tevreden met de ontvangen nazorg (tevredenheidsscore 8/10). Nazorg in het ziekenhuis of door de huisarts was geassocieerd met een hogere tevredenheid. Echter, 35% (170/485) van de patiënten rapporteerde onvervulde behoeften, vooral op het gebied van informatievoorziening (97/485 [20%]). Deze inzichten in de nazorgbehoeften kunnen helpen bij het optimaliseren van de COVID-19 nazorg en het ontwikkelen van effectieve nazorgstrategieën voor toekomstige uitbraken van infectieziekten.

Vermoeidheid is een veelvoorkomend maar onverklaard symptoom van long COVID, en de aandoening in het algemeen wordt nog slecht begrepen. Biologische mechanismen, zoals verstoringen in het immuunsysteem, spelen waarschijnlijk een rol. In **Hoofdstuk 11** onderzochten we klinische uitkomsten en immunologische afwijkingen bij patiënten met long COVID 3-6 maanden na ziekenhuisontslag, evenals de relatie tussen vermoeidheid en immunologische uitkomsten. We

vergeleken de immuunrespons van patiënten met long COVID met een controlegroep van niet-COVID-19-individuen, gematcht op leeftijd en geslacht. De long COVID groep met vermoeidheid vertoonde een ernstiger klinisch profiel dan niet-vermoeide patiënten, met veel gelijktijdige en aanhoudende symptomen over tijd. Immunologische afwijkingen kwamen voor in de gehele groep van long COVID patiënten, ongeacht vermoeidheid, gekenmerkt door "low grade inflammation" (verhoogde inflammatoire genexpressie in monocyten, verhoogde levels van pro-inflammatoire cytokinen) en tekenen van verouderde T-lymfocyten (verhoogde uitgeputte $CD8^+$ TEMRA-lymfocyten). Echter, een hogere ernst van vermoeidheid was geassocieerd met sterkere tekenen van monocytenactivatie en wijst mogelijk in de richting van monocyten-endotheel interactie, wat in toekomstig onderzoek verder onderzocht zou moeten worden. De bevindingen sluiten aan bij eerdere studies over aanhoudende verstoringen in het immuunsysteem bij long COVID

Tenslotte worden in **hoofdstuk 12** de belangrijkste bevindingen van dit proefschrift besproken en in de context van de van de bestaande literatuur geplaatst. Daarnaast worden methodologische overwegingen, klinische implicaties en aanbevelingen voor toekomstig onderzoek besproken.

CO-FLOW Collaboration Group

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List of publications

Publications included in this thesis

Bek LM*, **Berentschot JC***, Hellemons ME, Huijts SM, Aerts JGJV, van Bommel J, van Genderen ME, Gommers DA, Ribbers GM, Heijenbrok-Kal MH, van den Berg-Emons RJG; CO-FLOW Collaboration Group. CO-FLOW: COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch health care system: study protocol of a multicenter prospective cohort study following patients 2 years after hospital discharge. *BMC Health Serv Res.* 2021;21(1):1-10.

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Hellemons ME*, Huijts S*, Bek LM, **Berentschot JC**, Nakshbandi G, Schurink CAM, Vlake JH, van Genderen ME, van Bommel J, Gommers DAMPJ, Odink A, Ciet P, Shamier MC, Geurts van Kessel C, Baart SJ, Ribbers GM, van den Berg-Emons RJG, Heijenbrok-Kal MH, Aerts JGJV. Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for COVID-19: A Longitudinal Study of Respiratory, Physical, and Psychological Outcomes. *Ann Am Thorac Soc.* 2022;19(4):551-61.

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*Authors share first authorship, **Authors share last authorship

PhD portfolio

PhD candidate

Name	J.C. Berentschot
University	Erasmus University Rotterdam
Department	Respiratory Medicine
Period	November 2020 – November 2024
Promotors	Prof.dr. J.G.J.V. Aerts
	Dr. H.J.G. van den Berg-Emons
Co-promotors	Dr. M.E. Hellemons
	Dr. M.H. Heijenbrok-Kal

Summary of PhD training and teaching activities

Courses	**Year**	**Workload (ETCS)**
eBROK®, Basic course Rules and Organisation for Clinical researchers *(NFU)*	2021	1.5
Using R for Statistics in Medical Research *(NIHES)*	2021	1.4
Repeated Measurements *(NIHES)*	2021	1.7
Biomedical English Writing *(Erasmus MC MolMed)*	2021	2.5
Logistic Regression *(NIHES)*	2021	1.4
Joint Models for Longitudinal and Survival Data *(NIHES)*	2021	0.7
Scientific Integrity *(Erasmus MC)*	2021	0.3
Fundamentals in Medical Decision Making *(NIHES)*	2022	0.7
Data Science in Epidemiology *(NIHES)*	2022	0.7
Causal Mediation Analysis *(NIHES)*	2023	1.4
eBROK® Hercertificatie *(NFU)*	2024	0.2
Good Clinical Practice *(5x, Smelt Academy)*	2020-2025	0.5
Presentations		
ERS, poster presentation (*online*)	2021	0.5
DCRM, poster presentation (*online*)	2021	0.5
RehabWeek, poster presentation	2022	0.5
Moodstratification.EU, oral presentation	2022	0.5
ERS conference, poster presentation	2022	0.5
DCRM, oral presentation	2022	0.5
ICAMPAM, poster presentation	2022	0.5
Biomedical Science PhD day, poster presentation	2022	0.5
DCRM, poster presentation	2023	0.5
Wetenschapsdag Longziekten, 2x oral presentation	2022-2023	1.0
ESPRM, oral presentation	2024	0.5
DCRM, oral presentation	2024	0.5
Nederlandse Long COVID dag	2025	0.5

Conferences and symposia		
ERS (*online*)	2021	0.9
DCRM (*online*)	2021	0.6
RehabWeek	2022	0.9
Moodstratification.EU	2022	0.6
ERS	2022	0.9
DCRM	2022	0.6
Biomedical Science PhD day	2022	0.3
DCRM	2023	0.6
Erasmus MC PhD day	2022-2023	0.6
Wetenschapsdag Longziekten	2022-2024	0.9
Symposium Wetenschappelijk Onderzoek Post-COVID	2024	0.3
Nederlandse Long COVID dag	2024-2025	0.6
ESPRM	2024	1.0
DCRM	2024	0.6
Teaching activities		
Lecturer Minor Rehabilitation Medicine	2021-2023	1.5
Bachelor Clinical Technology, lecturer and supervising practicum	2023-2025	1.5
Daily Supervisor students	2020-2023	16.0
Master thesis medical students (8x)		
Research internship technical medicine student (1x)		
Other		
Communication training *(Science Gallery Rotterdam)*	2021	0.3
Public Speaking *(The Speech Republic)*	2022	0.7
Organizing Long COVID Meetings	2024	2.0
Participation in Research Meetings Rehabilitation Medicine	2020-2024	9.0
Total ETCS		**60.4**

About the author

Julia Berentschot was born on February 11, 1994, in Leidschendam. She grew up in a lively family of six, with two older sisters and a younger brother. From an early age, Julia participated in various sports, but speed skating was the one that stuck. After completing her secondary education at Dalton College in 2012, she took some time to explore her next academic step while pursuing speed skating. She began her studies in Human Movement Sciences at the University of Groningen and decided to stop speed skating during the final year of her bachelor's to fully focus on academics. After obtaining her master's degree in 2020, she moved back to South Holland in the midst of the COVID-19 pandemic.

In November 2020, she started as a PhD candidate at the department of Respiratory Medicine at Erasmus University Medical Center in Rotterdam, under the supervision of promotors prof.dr. J.G.J.V. Aerts and dr. H.J.G. van den Berg-Emons, and co-promotors dr. M.E. Hellemons and dr. M.H. Heijenbrok-Kal. Her PhD project focused on the prospective multicenter CO-FLOW study, which aimed to gain insights into long-term health outcomes and aftercare pathways following hospitalization for COVID-19. The research presented in this thesis builds upon the findings of this study.

Since January 2025, Julia has been working as a postdoctoral researcher at the department of Respiratory Medicine at Erasmus University Medical Center. Her main research focuses on deepening the understanding of long COVID.

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Majanka, ontzettend fijn dat ik altijd bij je terechtkon, vaak met vragen over statistiek. Samen de data induiken en analyses bespreken was enorm leerzaam. Extra leuk dat we nu samenwerken aan een nieuw onderzoek, ik kijk uit naar de resultaten.
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we met veel plezier en gezelligheid hard en zo efficiënt mogelijk hebben gewerkt aan het CO-FLOW onderzoek. Dank voor de fijne samenwerking, ik had me geen betere buddy kunnen wensen! Knap hoe goed je de afgelopen jaren alles hebt gedaan, en ik ben trots dat we ons promotietraject samen gaan afsluiten. Heel leuk dat we onze samenwerking voortzetten in onderzoek naar long COVID.

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