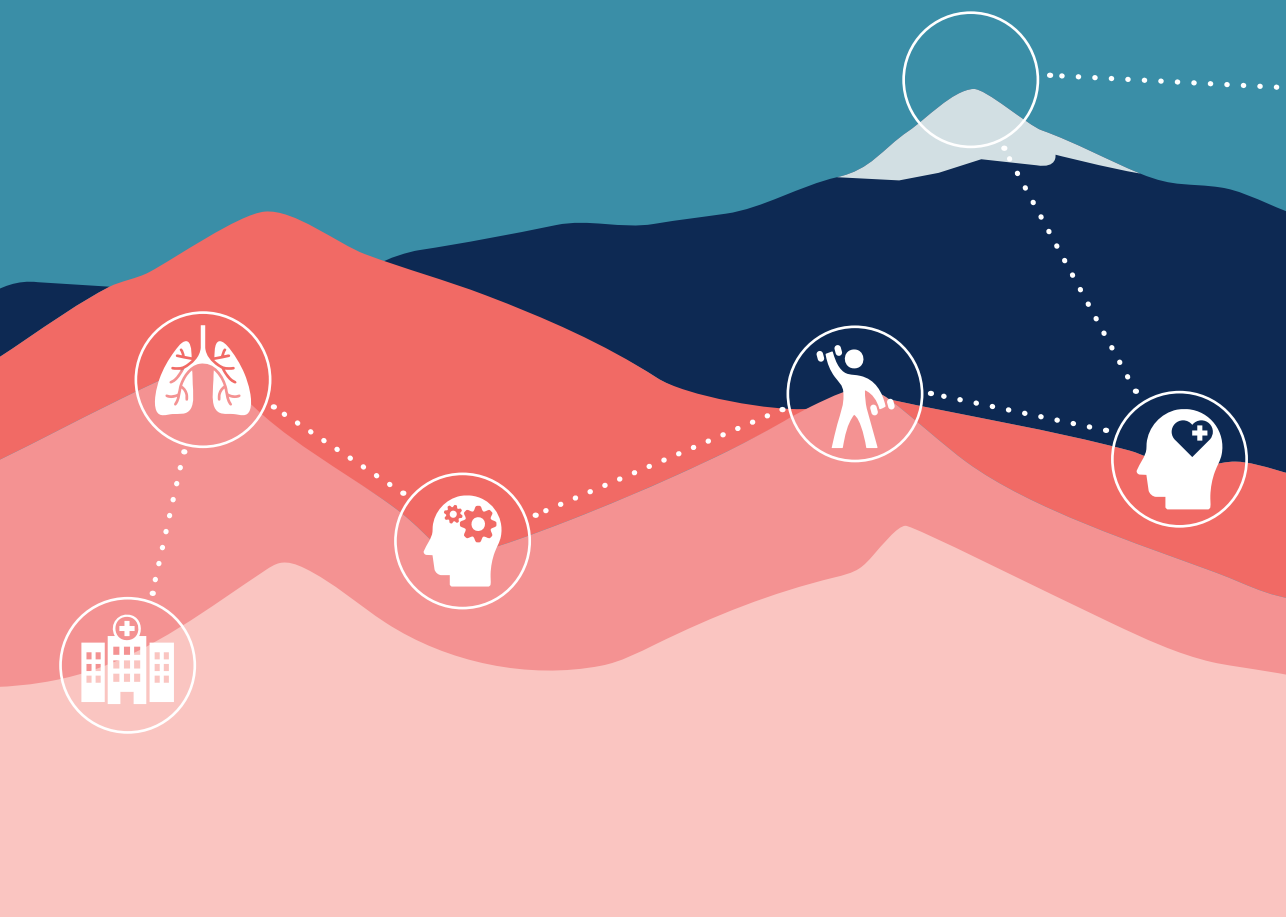
Health Outcomes after Hospitalization for COVID-19:

A prospective cohort study

Martine Bek



Health Outcomes after Hospitalization for COVID-19: A prospective cohort study

Martine Bek

The research presented in this thesis is funded by COVID-19 Program Care and Prevention of The Netherlands Organization for Health Research and Development (ZonMw, Grant number 10430022010026), and Rijndam Rehabilitation and Laurens, Rotterdam, the Netherlands.

Cover design: Hanneke van der Meer

Layout and printing: Ridderprint

ISBN: 978-94-6522-395-7

Health Outcomes after Hospitalization for COVID-19: A prospective cohort study

Gezondheidsuitkomsten na ziekenhuisopname voor COVID-19: Een prospectief cohortonderzoek

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr.ir. A.J. Schuit

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

Dinsdag 9 december 2025 om 13:00 uur

door

Lotte Martine Bek
geboren te Maassluis.

Erasmus University Rotterdam

Promotiecommissie

Promotoren:	Prof.dr. G.M. Ribbers
	Dr. H.J.G. van den Berg-Emons
Overige leden:	Prof.dr. H.F. Lingsma
	Prof.dr. R. Dekker
	Prof.dr. J.G. van der Bom
Copromotoren:	Dr. M.H. Heijenbrok-Kal
	Dr. M.E. Hellemons

TABLE OF CONTENTS



CHAPTER 1

General introduction

GENERAL INTRODUCTION

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, which causes Coronavirus Disease 2019 (COVID-19), marked the onset of an unprecedented global health crisis.[1] Originated from Wuhan, China, SARS-CoV-2 spread rapidly around the world and the World Health Organization (WHO) declared this a pandemic on March 11, 2020. Since the outbreak, over 775 million cases of confirmed SARS-CoV-2 infection have been reported by the WHO.[2] The pandemic of unparalleled scale and impact demanded a coordinated international response to contain the spread of the virus, limit its impact, and develop effective interventions. Worldwide, governments implemented a range of public health measures, including lockdowns, travel restrictions, social distancing, and mask mandates to slow viral dissemination and protect public health, thereby alleviating the strain on healthcare systems which were overwhelmed by COVID-19 cases. Within a short time period the COVID-19 pandemic had a large social, economic, and health impact. In the Netherlands, the first confirmed case of COVID-19 was reported on February 27, 2020, and since then, an estimated 8.6 million individuals have been infected with SARS-CoV-2.[2] To manage the pandemic, the Netherlands implemented a multifaceted approach, which involved the establishment of COVID-19 response teams, task forces, and advisory bodies, including the National Coordination Center for Infectious Disease Control, the Outbreak Management Team, and the Regional Health Services. These agencies were responsible for providing accurate and up-to-date information, developing and updating guidelines and protocols for testing, quarantine, and COVID-19 treatment, advising the government on public health measures, coordinating collaboration among stakeholders, monitoring the epidemiological situation, and facilitating widespread testing. In addition, the national coordination center for patient distribution was established to coordinate and optimize healthcare resources by monitoring hospital capacity and coordinating patient transfers.

Pathophysiology

Transmission of SARS-CoV-2 occurs primarily via respiratory droplets and to a lesser extent contaminated surfaces.[3] Upon initial infection with SARS-CoV-2, the viral spike protein binds to the angiotensin-converting enzyme 2 receptor, enabling the virus to infiltrate host cells lining the respiratory tract, such as nasal and bronchial epithelial cells and pneumocytes (Fig. 1.1).[1,3,4] In the early stages of infection, viral RNA is replicated within host cells and may spread

throughout the upper respiratory tract. At this stage, infected individuals may experience symptoms of fever, dry cough, fatigue, headache, nausea, myalgia, and olfactory and/or gustatory dysfunctions.[3,5-7] The innate immune system responds by producing proinflammatory cytokines and antiviral interferons, which activates the adaptive immune response.[3] If the immune response is strong enough, the host can effectively control viral proliferation and limit disease severity at this phase.[4] However, in some individuals the host defense mechanism fails to eliminate the virus, allowing its spread to the lower respiratory tract. The resulting inflammatory environment often triggers a cytokine storm and activates the coagulation cascade in the lungs, moreover, host cells may undergo persistent apoptosis or necrosis.[8] These processes can lead to severe complications such as pneumonia, acute respiratory distress syndrome (ARDS), acute lung injury, disseminated intravascular coagulation, and pulmonary embolism.[4]

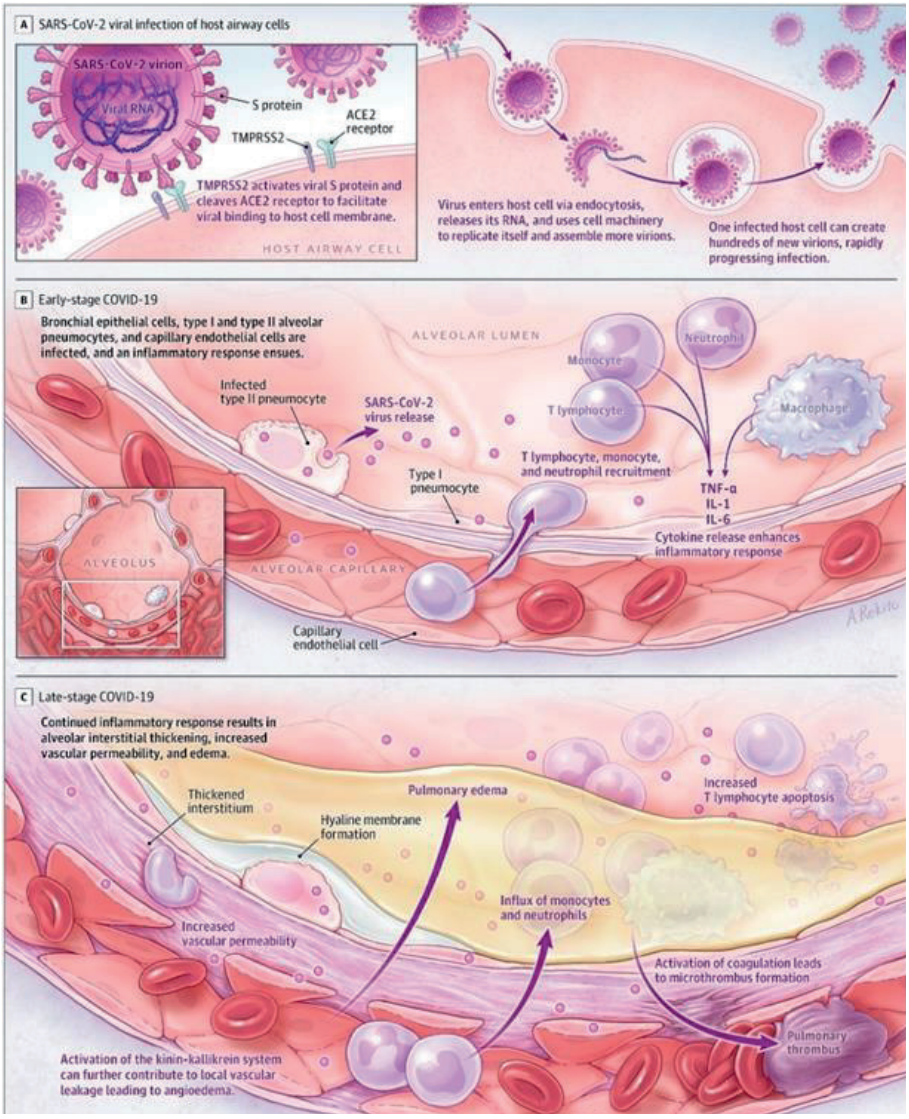


Figure 1.1 Pathogenesis of COVID-19.[3]

Hospital admission

Symptoms of SARS-CoV-2 infection varied, ranging from mild symptoms like fever, headache, dry cough, anosmia and/or ageusia, to severe symptoms such as pneumonia, ARDS, and multiorgan failure.[9,10] Individuals with mild symptoms often recovered at home without the need for acute medical care. However, worldwide millions of individuals developed moderate to severe symptoms which led to a significant surge in hospital admissions.[11,12] Patients

not only suffered from pulmonary symptoms, such as dyspnea, cough, and lung abnormalities characterized by ground-glass opacity or consolidations, but could also experience organ dysfunction, coagulation dysfunction, septic shock, and even multiorgan failure.[1,13] Where oxygen by masks or nasal prongs mostly proved sufficient for those with moderate symptoms, more advanced interventions, including non-invasive ventilation or high-flow nasal oxygen might be required for those with severe manifestations. Patients who developed ARDS, septic shock, or multiorgan failure required intensive care unit (ICU) treatment with mechanical ventilation.[9] As of March 30, 2023, over 143 000 hospitalizations due to COVID-19 have been documented in the Netherlands, with almost 20 000 (13.9%) patients who required ICU treatment.[14]

Previous corona outbreaks

Previous coronavirus outbreaks, including SARS in late 2002 and Middle East respiratory syndrome (MERS) in 2012 also concerned patients suffering from atypical acute pneumonia, which could progress to ARDS,[15,16] and were accompanied by extrapulmonary symptoms.[16] Especially elderly individuals and those with comorbidities were vulnerable to poor disease outcomes.[17] These previous coronavirus outbreaks provided valuable insights into the pathogenesis,[18] vaccine efficacy and safety,[17] and underscored the necessity of vigilance against novel pathogens, which can emerge from heterogenous zoonotic reservoirs due to close interaction between humans and animals in markets and restaurants.[16] Furthermore, survivors of SARS or MERS infections have reported long-term health impairments,[19,20] such as lung abnormalities, reduced exercise capacity, mental health problems, and reduced health-related quality of life (HRQoL). Given these observations, it was anticipated that patients with COVID-19 could also encounter long-term health problems for which aftercare would be required.

Post-COVID health problems

Initially, only patients treated in the ICU were considered at risk of developing long-term symptoms, especially considering the increased duration of mechanical ventilation and sedation in ARDS from COVID-19.[21] Patients were thought vulnerable for post-intensive care syndrome, characterized by long-term physical, cognitive, and psychological symptoms.[22] However, over time it became clear that irrespective of ICU treatment patients could experience health problems after hospitalization for COVID-19.[23-25] In general, patients suffered from a spectrum of sequelae; pulmonary complications included dyspnea, cough, fibrotic lung damage, and ventilator-induced damage.[26]

Coagulopathies, such as pulmonary embolism and ischemic stroke were also observed, along with cardiovascular problems like chest pain and myocardial injury.[27] Neurological symptoms were common, including headaches, cognitive impairment, ageusia, anosmia, dizziness, skeletal muscular complications, and cerebrovascular disease.[28,29] Moreover, the extreme and unique circumstances faced by severely ill patients – prolonged hospitalization, isolation from loved ones, care provided by healthcare professionals in full protective equipment, and the fear of death – were predisposing risk factors for psychiatric sequelae, such as anxiety, depression, posttraumatic stress, and insomnia.[30] The persistence of health problems after a COVID-19 infection is now referred to as *Post-COVID-19 condition* or *Long COVID*. The most recent definition of long COVID, as described by the National Academies of Sciences, Engineering, and Medicine, described it as an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing, and remitting, or progressive disease state that affects one or more organ systems.[31,32] The growing understanding of long COVID highlights its complexity, revealing that patients with COVID-19 face a broad spectrum of potential long-term health problems.

COVID-19 post-hospital aftercare

The primary focus was on acute medical care and managing the surge of patients with COVID-19 overwhelming healthcare facilities. However, as the pandemic progressed, the diverse set of symptoms, including physical, cognitive, and mental health domains, underscored the need for comprehensive COVID-19 post-hospital aftercare. Yet, in absence of evidence-based guidelines, formal aftercare pathways for patients hospitalized for COVID-19 were lacking. Consequently, in a short time period and mostly based on expert opinion, novel rehabilitation care pathways were rapidly established in medical rehabilitation centers, skilled nursing facilities, community-based rehabilitation centers, and sheltered care facilities.[33-35] Whether these newly developed aftercare pathways would suffice in minimizing potential long-term health problems remained to be established.

AIMS AND OUTLINE OF THIS THESIS

Within this context the “COVID-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system: a combined rehabilitation, pulmonary, and intensive care perspective” (CO-FLOW) study was designed

to evaluate COVID-19 aftercare pathways and potential long-term health problems in patients hospitalized for COVID-19 (Fig. 1.2).

The CO-FLOW study is a multicenter prospective cohort study conducted across 7 hospitals (1 academic and 6 regional hospitals) and 3 rehabilitation centers (1 medical rehabilitation center and 2 skilled nursing facilities) in the Rotterdam-Rijnmond-Delft region in the Netherlands. Initially designed to follow up patients hospitalized for COVID-19 for 2 years, the study was later extended to 3 years, offering a multidimensional, longitudinal evaluation of patient-reported outcome measures (PROMs) and objectively assessed functional measures. Eligible participants included adults who survived hospitalization for COVID-19, with sufficient proficiency in Dutch or English, and were within 6 months post-discharge. Incapacitated patients (e.g., dementia) were excluded. Participants were informed of the CO-FLOW study upon hospital discharge and were recruited either during routine follow-up at the outpatient clinic of one of the participating centers or during their inpatient stay in a rehabilitation center. The Medical Ethical Committee of the Erasmus Medical Center approved the CO-FLOW study (MEC-2020-0487) and the extension of the study. Between July 2020 and October 2021, during the first to third COVID-19 waves in the Netherlands, we included 650 patients. Study visits were scheduled at 3, 6, 12, and 24 months post-discharge, and, if applicable, at rehabilitation discharge. These visits included objectively assessed physical and cognitive tests, recovery and symptom checklists, and a survey of validated PROMs. By 2 years, recovery in objectively assessed physical and cognitive outcomes showed marked improvement, but PROMs remained impaired, therefore, at 3 years, only a survey of PROMs was administered. The 2-year follow-up was completed in June 2023 and data collection of the 3-year surveys was finalized in June 2024.

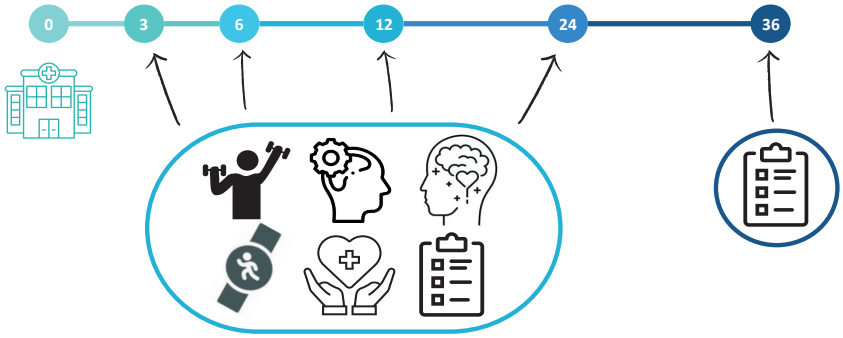


Figure 1.2 CO-FLOW study design.
The CO-FLOW study monitored patients with COVID-19 from hospital discharge up to 3 years, with follow-up assessments at 3, 6, 12, 24, and 36 months post-discharge. The first four visits included objectively assessed physical and cognitive evaluations, monitoring of physical activity via wrist-worn accelerometer, and administration of survey of validated patient-reported outcome measures (PROMs). Additionally, data on the COVID-19 post-hospital aftercare pathways were collected. At 36 months, patients were only followed up with the survey of PROMs.

Aims

The overall aim of the CO-FLOW study was to set up a registry and to systematically and comprehensively evaluate the COVID-19 aftercare pathways and the long-term health outcomes of patients hospitalized for COVID-19 in the Rotterdam-Rijnmond-Delft region in the Netherlands. The study had four aims: to assess 1] trajectories and identify predictors of physical, cognitive, and psychological recovery; 2] patient flows, healthcare utilization, and the perspective of healthcare professionals and patients on the COVID-19 post-hospital aftercare; 3] the effects of physical, cognitive, and psychological outcomes on social participation and health-related quality of life (HRQoL); and 4] predictors of healthcare utilization and patient satisfaction with aftercare. The CO-FLOW study has been a collaborative effort led by two PhD students who have coordinated its various aspects. Consequently, the objectives of the CO-FLOW study have been examined collectively and independently by each PhD student. Fig. 1.3 provides a visual representation of the topics covered within the CO-FLOW study, illustrating the individual as well as overlapping areas of focus within each thesis.

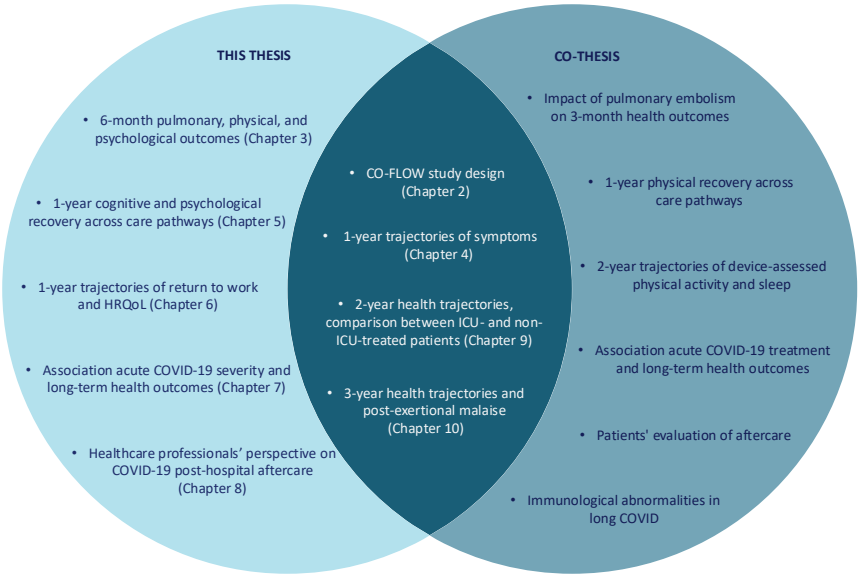


Figure 1.3 The research topics of the CO-FLOW study described in this thesis, in both theses and in the co-thesis.

Outline

The CO-FLOW study initially followed up patients with COVID-19 up to 2 years after hospital discharge, later extended to 3 years; its protocol is described in **Chapter 2**. Interim analyses were performed during the 2-year follow-up period, which are outlined in Chapters 3 through 7. **Chapter 3** presents outcomes of pulmonary, physical, and psychological outcomes up to 6 months after hospital discharge. In **Chapter 4** we focus on persisting symptoms up to 12 months post-discharge. In **Chapter 5** we present the 1-year trajectories of cognitive and psychological outcomes across care pathways. **Chapter 6** describes return to work, its risk factors, and its association with HRQoL up to 12 months post-discharge. Lastly, **Chapter 7** evaluates the association between severity of acute COVID-19 and PROMs up to 12 months. In **Chapter 8** the perspective of healthcare professionals on the organization of the COVID-19 post-hospital aftercare pathways is presented. In **Chapter 9 and 10** the trajectories of health outcomes up to 2 and 3 years, respectively, are described. **Chapter 9** additionally focusses on the trajectories in ICU- and non-ICU patients. **Chapter 10** also shows the prevalence, risk factors, and co-occurring health problems of post-exertional malaise at 3 years post-discharge. In the concluding **Chapter 11**, the main findings of the preceding chapters are integrated and interpreted. Methodological considerations, clinical implications, and directions for future research are discussed.

REFERENCES

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-15.
2. WHO. WHO Coronavirus (COVID-19) Dashboard. [updated 2024 May 19; accessed on 2025 Feb 04]. Available from: https://data.who.int/dashboards/covid19/cases
3. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;324(8):782-93.
4. Zhu Y, Sharma L, Chang D. Pathophysiology and clinical management of coronavirus disease (COVID-19): a mini-review. *Front Immunol*. 2023;14:1116131.
5. Annemarie BD, Ewen MH, Christopher AG, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985.
6. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.
7. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open*. 2021;4(5):e2111417.
8. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607-13.
9. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med*. 2021;49(3):503-16.
10. Baj J, Karakuła-Juchnowicz H, Teresiński G, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. *J Clin Med*. 2020;9(6).
11. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. *Crit Care*. 2020;24(1):516.
12. CDC. COVID-NET Laboratory-confirmed COVID-19 hospitalizations: Centers for Disease Control and Prevention. Available from: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network.
13. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-7.
14. NICE. COVID-19 op de Nederlandse verpleegafdelingen; Patiëntkarakteristieken en uitkomsten. [updated 30 March 2023; cited 2025 Feb 04]. Available from: https://stichting-nice.nl/.
15. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;361(9371):1767-72.
16. Cheng VC, Chan JF, To KK, Yuen KY. Clinical management and infection control of SARS: lessons learned. *Antiviral Res*. 2013;100(2):407-19.
17. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol*. 2013;11(12):836-48.
18. Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antiviral Res*. 2013;100(1):286-95.
19. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med*. 2020;52(5):jrm00063.
20. Zhang P, Li J, Liu H, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Research*. 2020;8(1):8.
21. Vasilevskis EE, Ely EW, Speroff T, et al. Reducing iatrogenic risks: ICU-acquired delirium and weakness--crossing the quality chasm. *Chest*. 2010;138(5):1224-33.
22. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference*. *Crit Care Med*. 2012;40(2):502-9.
23. Carfì A, Bernabei R, Landi F, for the Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020;324(6):603-5.

24. Ballering AV, van Zon SKR, olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *The Lancet*. 2022;400(10350):452-61.
25. de Graaf MA, Antoni ML, ter Kuile MM, et al. Short-term outpatient follow-up of COVID-19 patients: A multidisciplinary approach. *eClinicalMedicine*. 2021;32.
26. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis*. 2020;20(10):1135-40.
27. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J emerg Med*. 2020;38(7):1504-7.
28. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19(9):767-83.
29. Pinzon RT, Wijaya VO, Buana RB, et al. Neurologic Characteristics in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis. *Front Neurol*. 2020;11:565.
30. Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun*. 2020;89:594-600.
31. National Academies of Sciences Engineering, and Medicine. A long COVID definition: a chronic, systemic disease state with profound consequences. 2024.
32. Ely EW, Brown LM, Fineberg HV, et al. Long Covid Defined. *N Engl J Med*. 2024;391(18):1746-53.
33. FMS: Langdurige klachten en revalidatie na COVID-19 Richtlijnendatabase [Internet]. The Netherlands. Federatie Medisch Specialisten; [updated 2022 March 21; cited 2025 Feb 04]. Available from:https://richtlijnendatabase.nl/richtlijn/covid-19/startpagina_-_langdurige_klachten_en_revalidatie_na_covid-19.html.
34. NHG-Richtlijnen: Langdurige klachten na COVID-19 [Internet]. The Netherlands. NHG-Richtlijnen: Nederlands Huisartsen Genootschap; [updated 2022 March; cited 2025 Feb 04]. Available from: https://richtlijnen.nhg.org/standaarden/langdurige-klachten-na-covid-19
35. VerenSo. COVID-19 / Coronavirus [Internet]. The Netherlands. Vereniging van specialisten ouderengeneeskunde; [updated 2022 Sep 07; cited 2025 Feb 04]. Available from: https://www.verenso.nl/kwaliteit/thema-s-en-projecten/infectieziekten/covid-19-coronavirus



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

L. Martine Bek*
Julia C. Berentschot*
Merel E. Hellemons
Susanne M. Huijts
Joachim G.J.V. Aerts
Jasper van Bommel
Michel E. van Genderen
Diederik A.M.P.J. Gommers
Gerard M. Ribbers
Majanka H. Heijenbrok-Kal
Rita J.G. van den Berg-Emons
On behalf of the CO-FLOW Collaboration Group***

* Authors share first authorship
*** Listed in Appendix

BMC Health Services Research. 2021;21(1):847

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, 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.[15,11,23,24] 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 2.1. 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 wristwatch (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 Index (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 Questionnaire (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 2.1 *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	x	x	*			
Patient characteristics		x	*			
Clinical characteristics		EPR[$]	*			
General questions, health care path, recovery		x	x	x	x	x
Pre-morbid physical activity class (SGPALS)			x			
COVID-19 Symptom Checklist		x	x	x	x	x
Questionnaires: online or postal mail						
Independency general daily life activities: BI		▫	x	x	x	x
Physical activity: IPAQ-short form			x	x	x	x
Physical fitness: IFIS		x	x	x	x	x
Fatigue: FAS		x	▫	x	x	x
Mood: HADS		▫	▫	x	x	x
Post-Traumatic Stress Syndrome: IES-R		▫	▫	x	x	x
Cognition: CFQ		x	x	x	x	x
Coping: CISS					x	
Health-related quality of life: SF-36, EQ-5D-5L		▫	▫/x	x	x	x
Burden of disease: ABC-tool			▫	x	x	x
Sleep quality: PSQI		x	x	x	x	x
Participation: USER-P			x	x	x	x

	Discharge hospital	Discharge inpatient rehabilitation	3m after discharge hospital	6m after discharge hospital	12m after discharge hospital	24m after discharge hospital
Health Care utilization: iMCQ, iPCQ			x	x	x	x
Patient satisfaction with COVID-19 aftercare: SCAQ					x	
Clinical tests at hospital, inpatient rehabilitation, or at home						
Mobility: DEMMI		▫	x	x	x	x
Antropometry: body mass index, arm circumference		▫	x	x	x	x
Nutritional status: SNAQ		▫	x	x	x	x
Cognition: MoCA		▫	x	x*	x*	x*
Cognition: TMT, LLT a.o.[&]		▫	▫		▫	
Pulmonary function: spirometry[&]		▫	▫	▫	▫	▫
Radiographic abnormality: CT-scan[&], X-ray[&]			▫	▫	▫	▫
Neuromuscular fitness: handgrip strength, MRC*		▫	x	x*	x*	x*
Cardiorespiratory fitness: 6MWT, 1MSTS		▫	x	x	x	x
Physical activity and sleep: accelerometry			x	*	x	x

*▫ = 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.

REFERENCES

1. Stam HJ, Stucki G, Bickenbach J, European Academy of Rehabilitation M. Covid-19 and Post Intensive Care Syndrome: A Call for Action. *J Rehabil Med*. 2020;52(4):jrm00044.
2. Kosinski S, Mohammad RA, Pitcher M, et al. What Is Post-Intensive Care Syndrome (PICS)? *Am J Respir Crit Care Med*. 2020;201(8):P15-P6.
3. Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med Surg*. 2019;6(3):233-46.
4. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama*. 2020;323(16):1574-81.
5. Disser NP, De Micheli AJ, Schonk MM, et al. Musculoskeletal Consequences of COVID-19. *J Bone Joint Surg Am*. 2020;102(14):1197-204.
6. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell*. 2020;183(1):16-27 e1.
7. Schandl A, Hedman A, Lyngå P, et al. Long-term consequences in critically ill COVID-19 patients: A prospective cohort study. *Acta Anaesthesiol Scand*. 2021.
8. Kiekens C, Boldrini P, Andreoli A, et al. Rehabilitation and respiratory management in the acute and early post-acute phase. "Instant paper from the field" on rehabilitation answers to the COVID-19 emergency. *Eur J Phys Rehabil Med*. 2020;56(3):323-6.
9. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis Research*. 2020;191:148-50.
10. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020;81(6):e4-e6.
11. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-32.
12. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2020.
13. Belli S, Balbi B, Prince I, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalisation. *Eur Respir J*. 2020;56(4).
14. Arenivas A, Carter KR, Harik LM, Hays KM. COVID-19 neuropsychological factors and considerations within the acute physical medicine and rehabilitation setting. *Brain Inj*. 2020;34(8):1136-7.
15. Han X, Fan Y, Alwalid O, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology*. 2021;299(1):E177-E86.
16. Taboada M, Cariñena A, Moreno E, et al. Post-COVID-19 functional status six-months after hospitalization. *J Infect*. 2021;82(4):e31-e3.
17. Yan X, Huang H, Wang C, et al. Follow-up study of pulmonary function among COVID-19 survivors 1 year after recovery. *Journal of Infection*. 2021.
18. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Network Open*. 2021;4(5):e2111417-e.
19. Batawi S, Tarazan N, Al-Raddadi R, et al. Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (MERS). *Health Qual Life Outcomes*. 2019;17(1):101.
20. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247-61.
21. Ngai JC, Ko FW, Ng SS, et al. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15(3):543-50.
22. Park WB, Jun KI, Kim G, et al. Correlation between Pneumonia Severity and Pulmonary Complications in Middle East Respiratory Syndrome. *J Korean Med Sci*. 2018;33(24):e169.
23. Sonnweber T, Sahanic S, Pizzini A, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. *Eur Respir J*. 2021;57(4).
24. Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*. 2021.
25. Gautam N, Madathil S, Tahani N, et al. Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection. *Clin Infect Dis*. 2021.

26. Schofield-Robinson OJ, Lewis SR, Smith AF, et al. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. *Cochrane Database Syst Rev*. 2018;11(11):CD012701.
27. Simpson R, Robinson L. Rehabilitation After Critical Illness in People With COVID-19 Infection. *Am J Phys Med Rehabil*. 2020;99(6):470-4.
28. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-43.
29. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3).
30. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and Ageing*. 2011;40(4):423-9.
31. Fess E, Moran C. American Society of Hand Therapists Clinical Assessment Recommendations. 1981.
32. James MA. Use of the Medical Research Council muscle strength grading system in the upper extremity. *J Hand Surg Am*. 2007;32(2):154-6.
33. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.
34. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. *Clin Physiol Funct Imaging*. 2002;22(2):115-24.
35. Lyra CO, Lima SC, Lima KC, et al. Prediction equations for fat and fat-free body mass in adolescents, based on body circumferences. *Ann Hum Biol*. 2012;39(4):275-80.
36. Gomez-Campos R, Santi-Maria T, Arruda M, et al. Fat-Free Mass and Bone Mineral Density of Young Soccer Players: Proposal of Equations Based on Anthropometric Variables. *Front Psychol*. 2019;10:522.
37. de Morton NA, Davidson M, Keating JL. The de Morton Mobility Index (DEMMI): an essential health index for an ageing world. *Health Qual Life Outcomes*. 2008;6:63.
38. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16.
39. Ponds R, Boxtel M, Jolles J. De 'Cognitive Failure Questionnaire' als maat voor subjectief cognitief functioneren. *Tijdschrift voor Neuropsychologie*. 2006;1:37-45.
40. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-9.
41. Army US. Army individual test battery. *Manual of directions and scoring*. 1944.
42. Partington JE, Leiter RG. Partington's Pathways Test. *Psychological Service Center Journal*. 1949.
43. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull*. 1991;109(2):163-203.
44. Stroop JR. Studies of interference in serial verbal reactions. *Journal of experimental psychology*. 1935;18(6):643.
45. Jolles J, Houx PJ, van Boxtel MPJ, Ponds R. The Maastricht Aging Study: Determinants of Cognitive Aging. The Netherlands. Neuropsych Publishers Maastricht; 1995.
46. Wechsler D. Wechsler adult intelligence scale. 1955.
47. Capitani E, Rosci C, Saetti MC, Laiacona M. Mirror asymmetry of category and letter fluency in traumatic brain injury and Alzheimer's patients. *Neuropsychologia*. 2009;47(2):423-9.
48. Robinson G, Shallice T, Bozzali M, Cipolotti L. The differing roles of the frontal cortex in fluency tests. *Brain*. 2012;135(7):2202-14.
49. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-70.
50. Weiss DS, Marmar CR, Wilson JP, Keane TM. Assessing psychological trauma and PTSD. *The Impact of Events Scale—Revised*. 1997;19:399-411.
51. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J*. 1965;14:61-5.
52. Vandelanotte C, Bourdeaudhuij I, Philippaerts R, et al. Reliability and Validity of a Computerized and Dutch Version of the International Physical Activity Questionnaire (IPAQ). *J Phys Act Health*. 2005;2:63-75.
53. Merellano-Navarro E, Collado-Mateo D, García-Rubio J, et al. Validity of the International Fitness Scale "IFIS" in older adults. *Exp Gerontol*. 2017;95:77-81.
54. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. *Eur Respir J*. 2012;40(1):255-63.

55. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055-68.
56. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
57. Slok AHM, Kotz D, van Breukelen G, et al. Effectiveness of the Assessment of Burden of COPD (ABC) tool on health-related quality of life in patients with COPD: a cluster randomised controlled trial in primary and hospital care. *BMJ Open*. 2016;6(7):e011519.
58. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
59. Post MW, van der Zee CH, Hennink J, et al. Validity of the utrecht scale for evaluation of rehabilitation-participation. *Disabil Rehabil*. 2012;34(6):478-85.
60. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med*. 2021;49(3):503-16.
61. Grimby G, Börjesson M, Jonsdottir IH, et al. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports*. 2015;25 Suppl 4:119-25.
62. de Ridder DTD, van Heck GL. Coping inventory for stressful situations. CISS Handleiding: Swets Test Publishers; 2004.
63. Endler NS, Parker JDA. Coping inventory for stressful situations (CISS) : manual. Toronto: Multi-Health Systems; 1990.
64. Kruizenga HM, Seidell JC, de Vet HCW, Wierdsma NJ. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ©). *Clinical nutrition*. 2005;24(1):75-82.
65. Wilson M-MG, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *The American journal of clinical nutrition*. 2005;82(5):1074-81.
66. Bouwmans CA, Hakkaart-van Roijen L, Koopmanschap MA, et al. Manual of the iMTA medical consumption questionnaire (iMCQ). *Rotterdam: iMTA, Erasmus University Rotterdam*. 2013.
67. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.
68. Vanhaecht K, De Witte K, Depreitere R, et al. Development and validation of a care process self-evaluation tool. *Health Serv Manage Res*. 2007;20(3):189-202.



CHAPTER 3

Persistent health problems beyond pulmonary recovery up to 6 months after hospitalization for SARS-CoV-2; a longitudinal study of respiratory, physical and psychological outcomes

Merel E. Hellemons*
Susanne M. Huijts*
L. Martine Bek
Julia C. Berentschot
Gizal Nakshbandi
Carin A.M. Schurink
Johan H. Vlake
Michel E. van Genderen
Jasper van Bommel
Diederik A.M.P.J Gommers
Arlette E. Odink
Pierluigi Ciet
Marc C. Shamier
Corine H. Geurts van Kessel
Sara J. Baart
Gerard M. Ribbers
Rita J.G. van den Berg-Emons
Majanka H. Heijenbrok-Kal
Joachim G.J.V. Aerts

* Authors share first authorship

Annals of the American Thoracic Society. 2022;19(4):551-61.

ABSTRACT

Rationale Data on longitudinal recovery after hospitalization for coronavirus disease (COVID-19) currently remain scarce, just as outcomes beyond 3 months of follow-up do.

Objectives To evaluate the sequelae up to 6 months after hospitalization for COVID-19 by considering 1) recovery as it relates to pulmonary function, radiological abnormalities, physical and mental health status, and health-related quality of life (HRQoL) and 2) the predictors of the most clinically relevant sequelae.

Methods Patients were evaluated at 6 weeks, 3 months, and 6 months after hospitalization by using pulmonary function testing, radiological evaluation, and online questionnaires on the physical and mental health status and HR-QoL. Outcomes were analyzed using repeated-measurement analyses.

Results Ninety-two patients were included (mean age, 58.2 ± 12.3 yr; 58 [63.0%] men). The estimated percentage of patients with impaired forced vital capacity improved from 25% at 6 weeks to 11% at 6 months; for impaired diffusion capacity, this percentage improved from 63% to 46%. Radiologically, ground-glass opacity decreased but fibrosis persisted. The majority of patients (89.1%) still reported one or more symptoms 6 months after discharge. Fatigue decreased significantly over time (P = 0.006). Nonetheless, fatigue remained in 51% of the patients at 6 months. HR-QoL (nearly) normalized in most domains at 6 months, except for physical role functioning, with persistent fatigue and the length of hospitalization being the most important predictors.

Conclusions During the first 6 months after hospitalization for COVID-19, most patients demonstrated continuing recovery across all health domains, but persistent sequelae were frequent. Fatigue was the most frequent residual and persistent symptom up to 6 months after hospitalization, importantly impacting HR-QoL.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic overwhelmed the world in 2020, and the pandemic is still ongoing, affecting millions of people. Infection with COVID-19 in humans is associated with respiratory symptoms that range from very mild symptoms to severe bilateral pneumonia. In 5–14% of patients, the infection is severe, requiring oxygen supplementation or even prolonged ventilatory support.[1,2] Progressive respiratory failure is the primary cause of death after COVID-19 infection, with overall hospital mortality being approximately 15–20%.[2]

Knowledge on the sequelae of the COVID-19 infection is still scarce. However, it becomes increasingly clear that up to 10% of patients experience persistent symptoms 3 months after infection or even longer.[3] These numbers are even higher (approaching 50%) in patients who were more severely affected, such as those who survived hospitalization, with dyspnea and fatigue being the most prevalent symptoms.[4] In addition, impaired mental health (including anxiety, depression, post-traumatic stress, and cognitive dysfunction) and health-related quality of life (HR-QoL) have been reported.[5,6]

Because persistent symptoms and impairment of pulmonary function are known to last for months or even years in survivors from other coronavirus pneumoniae (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome),[7,8] we hypothesize that there are long-lasting sequelae from COVID-19 as well and that there is a relation between the severity of COVID-19 and outcomes.

However, longitudinal data on recovery after hospitalization for COVID-19 remain scarce, just as outcomes beyond 3 months of follow-up (FU) do.[9-11] Moreover, it is unclear to what extent patients suffer from persistent pulmonary sequelae, especially in the mid to long term, and how hospitalization for COVID-19 affects the physical and mental health status and HR-QoL. Early reports indicate that at discharge after hospitalization for COVID-19, a considerable proportion of patients had impaired pulmonary function, especially reduced diffusion capacity (47%).[12] Similarly, at 3 months of FU, restrictive defects (7–13%), diffusion impairment (24–34%), and development of pulmonary fibrosis (19–26%) have been reported and are more frequent after critical COVID-19.[6,11,13,14] Recently, similar numbers of persistent pulmonary function impairment and residual radiological abnormalities at 6 and 12 months after hospitalization

were reported, but whether recovery over time occurs and to what extent remains unclear.[9-11]

Given the lack of long-term longitudinal data on recovery after hospitalization for COVID-19, we aimed to evaluate 1) recovery as it relates to pulmonary function, radiological abnormalities, physical and mental health status, and HR-QoL over time up to 6 months after hospitalization for COVID-19 and 2) the predictors of the most clinically relevant sequelae in these domains.

METHODS

Study design and participants

This was a prospective cohort study of patients with COVID-19 who were discharged from the Erasmus Medical Center (MC) (University MC, Rotterdam, the Netherlands) in the first phase of the pandemic. We collected data as part of CO-FUS (COVID-19 FU Study). Within the Erasmus MC, there was universal opt-out informed consent established regarding all clinical data of patients who had been hospitalized for COVID-19 (Erasmus MC COVID-19 Observational Research). The medical ethics committee of our center reviewed this study and found it not to be subject to the Medical Research Involving Human Subjects Act (MEC-2020-0511). Nonetheless, participants could use opt-out online consent before filling out the questionnaires, and in addition, written informed consent was given at the outpatient clinic during FU.

All consecutive patients who were discharged between February 28 and July 31, 2020, were potential candidates for the study, and FU was completed on January 31, 2021. Patients were eligible for inclusion if they visited the outpatient clinic for FU after hospitalization for COVID-19, were over 18 years old, and had an established diagnosis of COVID-19. This diagnosis either was based on a positive reverse transcription–polymerase chain reaction result or detection of nucleic acid from COVID-19 before or during the initial hospitalization or was based on a multidisciplinary team decision regarding symptoms and chest computed tomography (CT) scan findings during hospitalization, which were later confirmed with positive serology results.

Study procedures

FU visits were scheduled around 6 weeks and 3 and 6 months after hospitalization. Patients without signs of residual radiological or pulmonary

function abnormalities at one of the FU visits were not scheduled for continuing visits. Before all the outpatient visits, patients were asked to fill out several online questionnaires. Patients who were discharged from clinical FU continued completing the online questionnaires.

Pulmonary function tests were performed at all outpatient visits and consisted of spirometry measuring forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and the diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin (DLCOc). Radiographic FU consisted of chest radiography at 6 weeks, which was followed by thin-section noncontrast chest CT scans at 3 and 6 months.

Measurements

Pulmonary sequelae

Pulmonary function tests were performed to assess the FVC and FEV1 in liters and the DLCOc in mmol/ (min kPa).We performed measurements according to the current guidelines from the American Thoracic Society and the European Respiratory Society.[15] The Global Lung Function Initiative Network reference values were used to express the percentages of predicted values of FVC, FEV, and DLCOc% (FVC%, FEV1%, DLCOc%), the z-scores, and the lower limit of normal (LLN).[16,17] A zscore below 21.64 indicated a measurement under the LLN.

Experienced chest radiologists interpreted the CT scans during FU by using a standardized assessment. Chest radiographs were classified as normal or as demonstrating moderate or severe abnormalities on the basis of their report. CT scans were classified as normal; as demonstrating the presence of ground-glass opacities (GGO) (moderate/severe) only or GGO with other abnormalities, including bronchiectasis or bronchiolectasis (moderate/severe), consolidations, reticulation/fibrosis, and subpleural lines and bands; or as demonstrating other abnormalities only. To assess the antibody kinetics over time, sera were collected at every FU visit. Qualitative enzyme-linked immunosorbent assays were performed for the detection of total antibodies and immunoglobulin M (IgM) class antibodies to COVID-19 (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.). Optical density ratios above 1 were interpreted as positive results, as indicated by the manufacturer. In this assay, total IgM class antibodies above 10 indicate the presence of neutralizing antibodies.[18]

Physical and mental health status

Together with patients, a new Corona Symptom Checklist was developed on "novel symptoms since the onset of COVID-19" during the first 3 months, which was added to the online questionnaires with the answer options of "yes" or"no" (see the online supplement for the complete questionnaires).

Fatigue was assessed by using the Fatigue Assessment Scale (FAS), which is a 10-item self-report questionnaire and has been validated in patients with chronic lung disease.[19,20] The items are scored on a Likert scale ranging from 1 to 5, and the total score ranges from 10 to 50, increasing with more frequent fatigue problems. Total scores of >22 are considered to represent substantial fatigue. A change in the FAS score of 4 points or more indicates a clinically significant change in fatigue.[21]

Anxiety and depression were measured by using the Hospital Anxiety and Depression Scale (HADS).[22] The HADS is a 14-item self-report measure and is commonly used to determine the degree of anxiety (HADS anxiety subscale) and depression (HADS depression subscale) (each including 7 items, which are scored on a Likert scale ranging from 0 to 3). A sum score >8 on either the HADS anxiety subscale or the HADS depression subscale is classified as clinically relevant anxiety or depression, respectively.[22] The HADS has demonstrated its validity in many settings, including during the aftermath of a critical illness.[23]

Symptoms of post-traumatic stress disorder (PTSD) were assessed by using the Impact of Event Scale–Revised (IES-R).[24] The IES-R is a self-report measure consisting of 22 items, which are scored on a Likert scale ranging from 0 to 4, assessing subjective distress caused by a traumatic event, and has previously been validated in intensive care unit (ICU) survivors.[25] The IES-R consists of three subscales, indicating symptoms of intrusion, avoidance, and hyperarousal. Total scores range from 0 to 88, with higher scores indicating more severe symptoms. An IES-R total score >24 is considered clinically meaningful PTSD, with mild (score of 24–32), moderate (score of 33–38), or severe (score of 39–88) complaints.

HR-QoL

HR-QoL was assessed by using the 36-item Short Form Health Survey (SF-36).[26,27] The SF-36 is a 36-item patient-reported survey and consists of eight domains: physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general

health perception.[27] Each domain score is directly transformed to a scale score ranging from 0 (worst score) to 100 (best score). The SF-36 has been extensively validated in the Dutch population.[28]

Data collection

Patient characteristics (age at admission, sex, and body mass index [BMI]) and clinical data (medical history, laboratory values and chest radiography findings at admission, occurrence of thrombosis and delirium during hospitalization, ICU admission, invasive ventilation, prone positioning, ICU length of stay [LOS], hospital LOS, in-hospital COVID-19–directed treatment, and pulmonary function and radiology at FU) were collected in Castor EDC software. Questionnaires on physical and mental health status and HR-QoL were completed online and directly collected in Castor EDC. All data were pseudonymized before storing and were not directly retraceable to the individual patient.

Statistical analysis

Normally distributed variables were reported as means with standard deviations or were otherwise reported as medians with interquartile ranges, and categorical variables were reported as numbers with percentages. For longitudinal analyses, we used linear mixed model (LMM) analyses and generalized LMM (GLMM) analyses to take into account the correlation within and between repeated measurements and to use all available measurements despite missing data. The LMM and GLMM can handle missing data, under the missing-at-random (MAR) assumption, by estimating the within- and between-subject covariance matrix on the basis of the observed data that are all included in these repeated measurement analyses. Missing data were assumed to be MAR, as the missing data at 6 months depend on the observations at 3 months and 6 weeks of FU. We performed LMM analyses to assess recovery over time for variables on an interval scale (pulmonary function, fatigue, anxiety/depression, PTSD, and HR-QoL), and these results are presented as estimated means with standard errors. We used a GLMM for dichotomous outcomes to model the probability of abnormal outcomes over time, and these results are presented as estimated proportions with standard errors. The dependent variables in these models were the observed outcomes at 6 weeks, 3 months, and 6 months. The measurement time point was entered as a factor into each model to evaluate changes over the total FU time and to make pairwise comparisons between the time points in post hoc analyses. Fixed baseline risk factors (sex, age, BMI, length of hospital

stay, length of ICU stay) and time-varying covariates (FVC%, DLCOc%, FAS, HADS, IES-R, chest CT abnormalities) were added to these models one by one to assess their predictive value. Subsequently, all significant predictors were entered into multivariable models for each outcome of interest to assess their independent predictive value. Goodness of fit was checked by using the Akaike information criterion. For all analyses, a P value of ,0.05 was considered to indicate statistical significance. All analyses were performed by using SPSS version 25 software (IBM SPSS Statistics).

RESULTS

Study sample

Between February 28 and July 31, 2020, 171 patients were discharged from the Erasmus MC after admission for COVID-19. Our center served as a referral center for mostly ICU patients, and because of many transfers from other regions during the first phase of the pandemic, a portion of these patients did not undergo FU in our hospital. Supplementary Fig. 3.1 the numbers of patients during each FU visit at the outpatient clinic. At 6 weeks after hospitalization, 92 patients were included in this study and had a mean age of 58.2 6 12.3 years, 58 (63.0%) were male, 74 (80.4%) had one or more comorbidities, 36 (39.1%) had two or more comorbidities, and the median LOS in the hospital was 21.5 (13.0–40.8) days (Table 3.1). Of the included patients, 61 (66.3%) had been admitted to the ICU and had a median LOS of 20 (11.0–33.0) days. At admission, radiographic abnormalities were seen in 80 (87.0%) patients, and 30 (32.6%) had a thrombotic event during admission. In total, 25 (27.2%) patients received one or more COVID-19–directed drug therapies, with therapies consisting of (hydroxy)chloroquine in 3 (3.3%) patients, antivirals in 3 (3.3%) patients (remdesivir in 1, lopinavir/ritonavir in 2), steroids in 17 (18.5%) patients (dexamethasone in 1, prednisone in 6, and high-dose methylprednisolone in 10), and other anti-inflammatory agents in 4 (4.3%) patients (anti-IL6 in 1 and anti-IL1 in 3).

Table 3.1 *Baseline characteristics of patients hospitalized for SARS-CoV-2*

	n	All (N=92)
Patient characteristic		
Age, years		58.2 ± 12.3
Sex *(male)*		58 (63.0)
BMI		29.9 (6.6)
Comorbidities		
None		18 (19.6)
Comorbidities > 1		36 (39.1)
Obesity (BMI>30)		37 (40.2)
Diabetes		15 (16.7)
Cardiovascular disease and/or hypertension		28 (31.1)
Pulmonary disease		14 (15.6)
Renal disease		5 (5.4)
Gastrointestinal disease		1 (1.1)
Neuromuscular disease		3 (3.3)
Malignancy		4 (4.3)
In-hospital characteristics		
PCR-confirmed COVID-19		86 (93.5)
Serology-confirmed COVID-19		6 (6.5)
Laboratory values		
Creatinine, umol/L	87	83.0 (68.0–102.0)
(CKD-EPI) eGFR, ml/min	87	85.0 (64.0–92.0)
CRP, mg/L	82	108.5 (53.8–195.3)
Ferritin, ug/L	63	839.0 (454.0–1565.0)
ALAT, U/L	87	30.0 (22.0–51.0)
Hemoglobin, mmol/L	86	8.0 (7.5–8.9)
MCV, fl	83	89.0 (86.0–91.0)
Thrombocytes, 10^9/L	84	224.5 (171.0–294.8)
Lymphocytes absolute count, 10^9/L	66	0.90 (0.68–1.2)
D-dimer, mg/L	24	0.72 (0.52–1.5)
NT-pro-BNP, pmol/ml	18	14.5 (7.3–41.3)
IL-6, pmol/ml	25	58.0 (29.0–153.5)
Chest x-ray abnormalities	86	
Normal		6 (7.0)
Moderate		15 (17.4)
Severe		65 (75.6)
Thrombosis		30 (32.6)
Deep vein thrombosis		4 (4.3)
Pulmonary embolism		25 (27.2)

Table 3.1 *Continued*

	n	All (N=92)
Sub-segmental pulmonary embolism		18 (19.6)
Segmental pulmonary embolism		10 (10.9)
Saddle pulmonary embolism		3 (3.3)
Delirium		48 (52.2)
Requiring oxygen supplementation		85 (92.4)
Requiring high flow nasal cannula		20 (22.5)
ICU admission		61 (66.3)
Invasive mechanical ventilation		55 (90.2)
Prone positioning		47 (52.2)
Length of intubation, days		15.0 (10.0–31.5)
Tracheostomy		33 (54.1)
Length of ICU stay, days		20.0 (11.0–33.0)
Length of hospital stay, days		21.5 (13.0–40.8)
In-hospital Treatment		
(Hydroxy)chloroquine		3 (3.3)
Antivirals		3 (3.3)
Steroids		17 (18.5)
Anti-inflammatory therapy		4 (4.3)
Time interval between discharge and follow-up visit		
6 Weeks visit, days	92	48.0 ± 10.0
3 Months visit, days	89	92.3 ± 11.7
6 Months visit, days	46	171.2 ± 17.0

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 less than 92. BMI, body mass index; PCR, Polymerase Chain Reaction; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ALAT, alanine aminotransferase; MCV =mean corpuscular volume; NT-pro-BNP, N-terminal-pro hormone B-type natriuretic peptide; IL-6, interleukin 6; ICU, intensive care unit.

Pulmonary function

Spirometry was available for 77 (83.7% of patients with an FU visit), 89 (100%), and 43 (89.5%) patients at 6 weeks, 3 months, and 6 months of FU, respectively. The estimated results from the LLMs over time are presented in Table 3.2. At 6 weeks, the FVC was below the LLN in 25% (64.7%) of the patients, decreasing to 21% (64.3%) and 11% (65.3%) after 3 and 6 months, respectively. The estimated mean FVC increased significantly over time from 3.4 L (60.11 L) to 3.7 L (60.12 L) at 6 months ($P < 0.001$), and the estimated mean FVC% predicted increased from 86.3% (61.64%) at 6 weeks to 93.8% (61.98%) ($P < 0.001$) at 6 months (Fig. 3.1A). Likewise, the mean estimated FEV1% predicted improved significantly

from 6 weeks to 6 months (P = 0.001) (Fig. 3.1A). Spirometry results improved similarly across the whole range of pulmonary function.

Diffusion capacity at 6 weeks was below the LLN in 63.0% (±5.5%) of the patients, decreasing to 51% (±5.4%) and 46% (±7.0%) at 3 and 6 months, respectively. The mean value estimate increased significantly over time from 5.9 mmol/(min · kPa) [±0.20 mmol/(min · kPa)] at 6 weeks to 6.8 mmol/ (min · kPa) [±0.22 mmol/ (min · kPa)] (P < 0.001) at 6 months, and the estimated DLCOc% predicted increased from 69.5% (±1.78%) at 6 weeks to 79.9% (±1.81%) at 6 months (P <0.001) (Fig. 3.1B).

Table 3.2 *Pulmonary function at 6-week and 3- and 6-month follow-up in patients hospitalized for COVID-19*

	6 Weeks	3 Months	6 Months	*p-value*
Spirometry				
FVC, L	3.4 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	<0.001
FVC% predicted	86.3 ± 1.6	90.0 ± 1.6	93.8 ± 2.0	<0.001
FVC *z*-score	–1.0 ± 0.1	–0.69 ± 0.1	–0.44 ± 0.1	<0.001
FVC% <LLN	25 (0.047)	21 (0.043)	11 (0.053)	0.127
FEV_1, L	2.7 ± 0.08	2.8 ± 0.08	2.8 ± 0.1	0.319
FEV_1% predicted	88.4 ± 1.7	89.6 ± 1.6	92.6 ± 1.9	0.001
FEV_1 *z* -score	–0.80 ± 0.1	–0.70 ± 0.1	–1.4 ± 0.9	0.061
FEV_1% <LLN	18 (0.046)	16 (0.039)	12 (0.048)	0.663
Gas exchange				
DLCOc, mmol/(min*kPa)	5.9 ± 0.2	6.2 ± 0.2	6.8 ± 0.2	<0.001
DLCOc% predicted	69.5 ± 1.8	73.0 ± 1.8	80.0 ± 1.8	<0.001
DLCOc *z* -score	–2.3 ± 0.2	–2.0 ± 0.1	–1.4 ± 0.1	<0.001
DLCOc%<LLN	63 (0.055)	51 (0.054)	50 (0.062)	0.021

Data are presented as estimated mean ± standard error or proportion (standard error). Estimates and P values were obtained by using linear mixed model analyses in cases of continuous outcomes and by using generalized linear mixed model analyses in cases of binary outcomes. FVC, Forced Vital Capacity; LLN, Lower Limit of Normal; FEV_1, Forced Expiratory Volume in one second; DLCOc, Diffusing Lung Capacity for Carbon monoxide, haemoglobin adjusted.

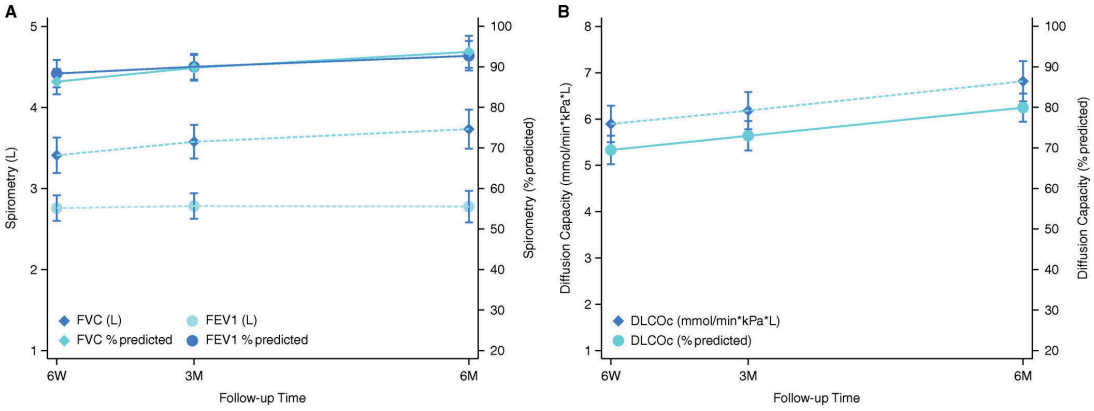


Figure 3.1 Pulmonary function at 6 weeks, 3 months, and 6 months.
(A) FVC and FEV1 values in liters (scale on the left side, dashed lines) and the percent-predicted values (scale on the right side, solid lines) are shown. (B) DLCOc values in mmol/min□kPa/L (scale on the left side, dashed line) and the percent-predicted values (scale on the right side, solid line) are shown. FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in 1 second; DLCOc, Diffusing Lung Capacity for Carbon monoxide, haemoglobin adjusted.

Radiology

Six weeks after hospitalization, chest radiography findings had normalized in 17 (21.3%) patients. Chest CT scans were available in 87 (94.6%) and 46 (95.8%) patients at 3 and 6 months, respectively (Table 3.3). After 3 months, chest CT scans were normal in 12 (13.8%) patients, and persistent GGO were seen in 50 (57.5%) patients, of whom 12 (24.0%) had severe GGO. Bronchiectasis or bronchiolectasis was present in 31 (35.6%) patients, consolidations were present in 13 (14.9%) patients, reticulation and fibrotic changes were present in 29 (33.3%) patients, and subpleural lines and bands were present in 27 (31.0%) patients. Patients with minimal residual abnormalities and normalized pulmonary function did not undergo a repeat chest CT scan. Among patients with chest CT scans (n= 45) at both 3 and 6 months, 32 (71.0% ±6.8%]) patients had GGO at 3 months, which decreased to 27 patients (60.0% [±7.3%]) at 6 months (P = 0.126), and the presence of consolidation decreased from 27% (±6.6%) to 13.0% (±5.1%) (P = 0.030). Fibrotic changes did not decrease over time (P = 0.763).

Table 3.3 *Radiographic characteristics at 6-week and 3- and 6-month follow-up in patients hospitalized for COVID-19*

	6 Weeks	3 Months	6 Months
Chest x-ray abnormalities, n	80		
Normal	17 (21.3)		
Moderate	37 (46.3)		
Severe	26 (32.5)		
*Chest CT-scan abnormalities, n**		87	46
Normal		12 (13.8)	1 (1.2)[a]
GGO			
Moderate		38 (43.7)	19 (21.8)
Severe		12 (13.8)	8 (9.2)
Bronchi(ol)ectasis			
Moderate		20 (23.0)	14 (16.1)
Severe		11 (12.6)	7 (8.0)
Consolidation		13 (14.9)	6 (6.9)
Reticulation/ fibrosis		29 (33.3)	22 (25.3)
Subpleural lines and bands		27 (31.0)	19 (21.8)
Chest CT scan abnormalities, n†		45	45
Normal		1 (2.2)	1 (2.2)
GGO			
Moderate		22 (48.9)	19 (42.2)
Severe		10 (22.2)	8 (17.8)
Bronchi(ol)ectasis			
Moderate		14 (31.1)	14 (31.1)
Severe		11 (24.4)	7 (15.6)
Consolidation		12 (26.7)	6 (13.3)
Reticulation/fibrosis		21 (46.7)	22 (48.9)
Subpleural lines and bands		20 (44.4)	18 (40.0)

*Data are presented as n (%).*Patients without signs of radiological abnormalities at 3-month follow-up were not scheduled for continuing visits; the percentage of abnormalities at 6-month follow-up are based on the total number of patients at 3-month follow-up. †For 45 patients, chest CT-scan was available at both 3 and 6 months. CT, Computed Tomography; GGO, Ground Glass Opacity.*

Antibody kinetics

Sera were tested for 76 (83%), 75 (84%), and 47 (98%) patients at 6 weeks, 3 months, and 6 months, respectively. At 6 months after discharge, all tested patients had detectable total antibodies to COVID-19, and 96% showed optical density ratios above 10, which correlated with the presence of neutralizing antibodies (18). IgM class antibodies to COVID-19 showed gradual waning, with positivity decreasing from 78% at 6 weeks to 36% at 6 months (*see* Supplementary Fig. 3.2).

Physical and mental health symptoms

Through the newly developed Corona Symptom Checklist, 89.1% of the patients at 6 months still reported one or more physical or mental symptoms since COVID-19 infection (Table 3.4). Patients most frequently experienced reduced fitness (71.9%), followed by muscle weakness (54.7%), concentration and/or memory problems (53.1%), and joint complaints (46.9%). Reduced taste and/or smell was still reported by 17.2% of patients at 6 months. Several patients were discharged with supplemental oxygen during rest or exercise. This could be weaned in all patients during the first 6 weeks after discharge.

The mean FAS score was higher than the cutoff score at all FU visits, indicating the presence of overt fatigue (Fig. 2A). Fatigue measured by using the FAS did not decrease significantly between 6 weeks and 3 months (P = 0.863), with a decrease only being shown from 3 months to 6 months (P = 0.002). At 6 months, a large proportion of the patients (50.8%) still experienced fatigue, as indicated by FAS score >22 (Supplementary Table 3.1).

Symptoms of PTSD, as measured by using the IES-R, decreased significantly over time (P < 0.001), as presented in Fig. 2B. Of all patients, 28.6% had signs and symptoms of PTSD at 6 weeks (which decreased to 16.4% and 3.6% at 3 and 6 months, respectively) (Supplementary Table 3.1).

Both mean anxiety (P = 0.003) and depression (P < 0.001) scores decreased significantly over time (Fig. 3.2C and 3.2D; Supplementary Table 3.1). The prevalence rates of anxiety were 20.6%, 19.6%, and 14% at 6 weeks, 3 months, and 6 months, respectively, and the prevalence rates of depression were 23.5%, 16.1%, and 16.1% at 6 weeks, 3 months, and 6 months, respectively.

HR-QoL

Fig. 3 shows the profiles of the domain scores of the SF-36 for each time point compared with the Dutch norm. Most domains improved significantly over time (P < 0.001), except for emotional role functioning (P = 0.292) and mental health (P = 0.103) (Supplementary Table 3.1). The degrees of impairment for both emotional role functioning and mental health were limited and were similar to the degrees of impairment among the norm population at all time points. In addition, most domains (nearly) normalized at 6 months of FU, except for physical role functioning. Although gradual improvement over time was evident, a gap was still seen between its 6-month outcome and the Dutch norm outcome.

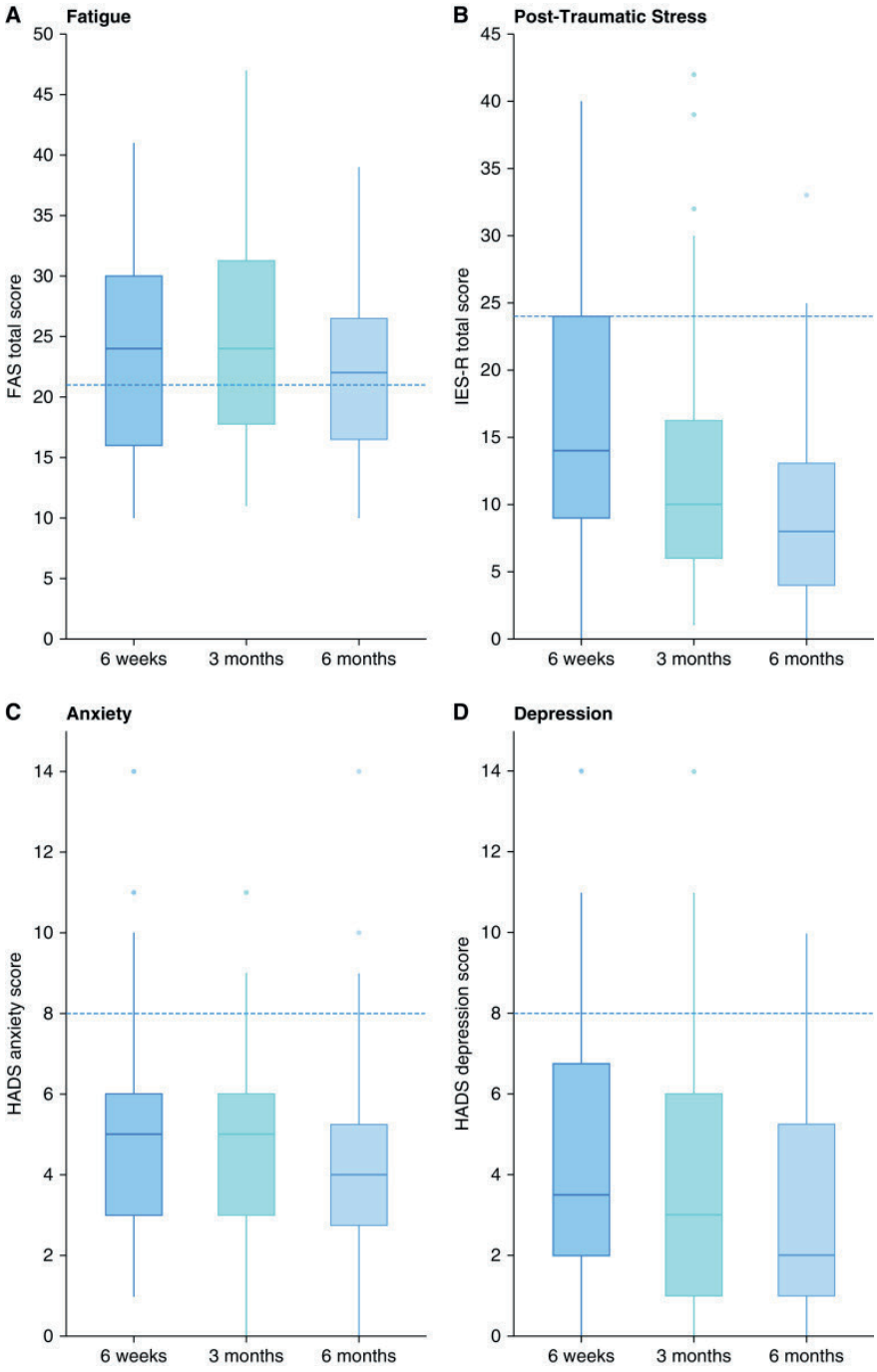


Figure 3.2 Fatigue (A), post-traumatic stress (B), anxiety (C), and depression (D) at 6 weeks, 3 months, and 6 months.
For each domain the cutoff score is shown. FAS, Fatigue Assessment Scale; IES-R, Impact of Event Scale-Revised; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS-Anxiety subscale; HADS-D, HADS-Depression subscale.

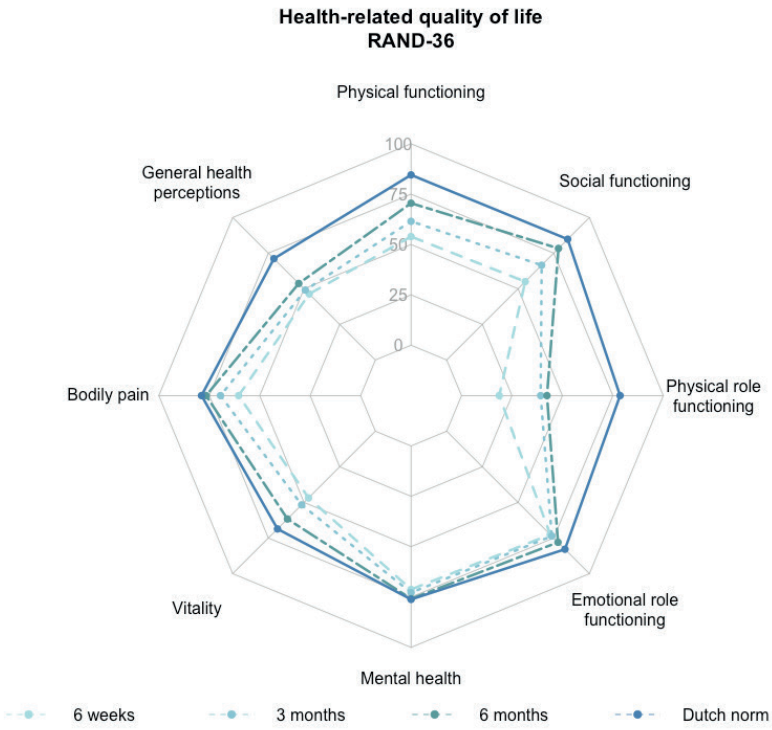


Figure 3.3 Scores for the SF-36 health-related quality of life domains at 6 weeks, 3 months, and 6 months compared with the Dutch norm population. *SF-36, 36-item Short Form Health Survey.*

Predictors

We analyzed the predictors of the most clinically relevant sequelae after hospitalization for COVID-19: namely DLCOc, fatigue measured by using the FAS, and physical role functioning as measured by using the SF-36. Table 3.5 shows the results of the LMM analyses.

DLCOc was the most frequently and significantly affected pulmonary function parameter. Bivariate predictors for a lower DLCOc% were a longer time since hospitalization ($P < 0.001$), a longer hospital LOS ($P < 0.001$), and more chest CT scan abnormalities ($P = 0.048$). In the multivariable analysis, a longer time since hospitalization ($P < 0.001$) and a longer hospital LOS ($P = 0.007$) remained independent predictors for a lower DLCOc%.

Fatigue was the most frequent symptom during FU. Female sex was the only significant predictor of fatigue over time (mean difference of 4.05 between

women and men on a FAS scale; P = 0.027). Decreased pulmonary function and chest CT scan abnormalities were not predictors of fatigue.

Physical role functioning was the most affected domain of the SF-36 after hospitalization for COVID-19 at all time points. The hospital LOS (P = 0.015), the FAS score (P < 0.001), depression (P < 0.001), and PTSD (P = 0.003) over time were bivariate predictors for physical role functioning, whereas ICU admission and reduced pulmonary function were not. In the multivariable analyses, a longer LOS in the hospital (P = 0.007) and a higher FAS score (P < 0.001) persisted as independent predictors of a lower physical role functioning score over time.

Table 3.4 *Prevalence of symptoms at 6 months follow-up in patients hospitalized for COVID-19*

	6 Months
Symptoms *(new since COVID-19 infection)*	**n=64**
≥ 1 Symptom	57 (89.1)
Reduced fitness	46 (71.9)
Muscle weakness	35 (54.7)
Concentration and/or memory problems	34 (53.1)
Joint complaints	30 (46.9)
Sleeping problems	25 (39.1)
Dizziness	22 (34.4)
Skin rash	22 (34.4)
Tingling and/or pain in extremities	22 (34.4)
Hoarseness	16 (25.0)
Reduced vision	16 (25.0)
Hairloss	14 (21.9)
Reduced taste and/or smell	11 (17.2)
Reduced hearing	9 (14.1)

Data are presented as n (%), indicating the number of patients with symptoms.

Table 3.5 *Multivariate analyses for DLCOc%, fatigue, and physical role function up to 6 months*

	DLCOc% (N obs = 122)		FAS (N obs = 176)		SF-36 RP (N obs = 132)	
	β	*P value*	β	*P value*	β	*P value*
Time						
6 weeks			*Ref*		*Ref*	
3 months	*Ref*[*]		0.18	0.863	15.70	0.019
6 months	7.13	<0.001	–2.11	0.046	17.83	0.017
Sex *(female)*			4.05	0.027		
LOS hospital *(days)*	–0.23	0.007			–0.42	0.007
Chest CT scan abnormalities		0.145				
Normal	*Ref*					
GGO	2.24	0.632				
GGO + others	–3.44	0.361				
Others	–5.21	0.169				
FAS score					–2.88	<0.001
HADS-A score						
HADS-D score					–1.58	0.122
IES-R score					0.53	0.089

Ref, reference category; DLCOc, Diffusing Lung Capacity for Carbon monoxide, haemoglobin adjusted; FAS, Fatigue Assessment Scale; SF-36, 36-item Short Form Health Survey; RP, Physical Role Function; LOS, Length of Stay; CT, Computer Tomography; GGO, Ground Glass Opacity; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; IES-R, Impact of Event Scale-Revised. Models are estimated with linear mixed models, using time as a factor. Predictive value of fixed baseline risk factors and time-varying covariates was assessed. [*] The 3-month time point is the reference category as chest CT scan was added to the model, only having data at 3 and 6 months.

DISCUSSION

We assessed recovery in relation to pulmonary function, radiological abnormalities, the physical and mental health status, and HR-QoL during the first 6 months after hospitalization for COVID-19 in a prospective cohort study and demonstrated recovery across all health domains in most patients.

Our data on persistent pulmonary injury are in line with earlier reports, with restrictive defects, diffusion impairment, and pulmonary fibrosis being

reported in a proportion of patients depending on the cohort and occurring more frequently after critical COVID-19.[6,11,13,14] This is also very much in line with outcomes after severe acute respiratory syndrome and Middle East respiratory syndrome infection.[7,8] Given the large numbers of persistent physiological and radiological signs of pulmonary fibrosis, a large cohort of patients with pulmonary fibrosis after COVID-19 with persistent and potentially progressive impairment was feared by experts.[29,30] In our cohort, reassuringly, no progressive impairment was noted. On the contrary, despite the presence of some fibrosis in almost a quarter of the patients, pulmonary function and other residual radiological abnormalities improved significantly over time.

This leads to speculation of the underlying pathophysiology of the pulmonary injury, as purely fibrotic changes do not improve over time. In a series of autoptic lungs from patients with severe endothelial injury caused by COVID-19 (associated with the presence of intracellular virus), disrupted cell membranes as well as widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries were demonstrated.[1] At the same time, the lungs from patients with COVID-19 had significant new vessel growth. Decreased diffusion and groundglass abnormalities are possibly due to vascular damage and microangiopathy, with angiogenesis explaining partial recovery in many. Other changes, such as the parenchymal bands and reticulation, are more likely purely fibrotic in origin and remain stable over time, causing permanent physiological impairment. This impairment is mild in most patients, even after critical COVID-19, and was not related to symptoms such as dyspnea in rest or during exercise or HR-QoL, indicating limited clinical significance.

A substantial number of patients reported impaired physical and mental health up to 6 months after hospitalization. Although this may be expected as a general fitness degree after a severe illness, the number of patients reporting symptoms (including, but not limited to reduced fitness, muscle weakness, joint complaints, dizziness, and concentration and/or memory problems) was remarkable. Our findings are in line with those of various studies reporting on mid-term/long-term symptoms. We demonstrate evident recovery over time among most evaluated symptoms, such as anxiety and depression.

Notably, this was not as much the case for fatigue, which was the most frequent and persistent symptom. There was significant improvement after 3 months, but at 6 months, 51% of the patients still had fatigue on the basis of the FAS score. The phenomenon that female sex is predictive for fatigue has been

described before, and further investigation of the differences in outcomes between sexes is needed.[31,32] More research into the underlying biological mechanisms is warranted, especially because of its significant impact and the distressing finding that the high prevalence did not substantially decrease over time.

Many patients after ICU treatment suffer from post–intensive care syndrome. Although it is not possible to discriminate between common sequelae of post–intensive care syndrome and effects specific to the post–COVID-19 period in these patients, we observed long-lasting physical, cognitive, and psychological consequences from COVID-19 in patients who survived ICU treatment as well as in those who did not undergo ICU treatment. It is as yet unclear how longer term recovery will develop and whether the reduced health status will persist chronically. Earlier studies demonstrated that survivors of acute respiratory distress syndrome continued to have persistent exercise limitations and a reduced physical quality of life 5 years after their discharge from the ICU, but pulmonary function usually normalized over time.[33,34] Early mobility and rehabilitation are promising interventions for ameliorating such impairments, but it remains unclear how rehabilitation programs should be tailored to meet the needs of these patients. Given that the virus may affect multiple body systems beyond the pulmonary system, such as the cardiac, neurological, and renal systems, a one-size-fits-all approach probably will not suffice. Rather, rehabilitation programs should be individualized and integrated into care pathways aimed at early discharge from the hospital with a focus beyond restoring physical and respiratory function alone, thereby addressing fatigue, anxiety, depression, and the return to participation in society.[35] Many questions remain regarding the clinical effectiveness of multimodal post–COVID-19 rehabilitation and the optimal timing of rehabilitation interventions, which will hopefully be addressed in the near future.[36] This question is deemed a research priority by many societies.[36,37]

Lastly, our findings confirm that the majority of the hospitalized patients with COVID-19 develop a sustained humoral response, with detectable antibodies being found in all tested patients at 6 months after discharge. This is in agreement with a recent report that describes the evolution of COVID-19 immunity up to 6.2 months after symptom onset.[38] IgM antibodies gradually wane after clinical recovery. In this population, IgM antibodies were still detectable in 36% of cases at 6 months. This illustrates that the utility of COVID-

19 IgM as a marker of acute infection is limited. Because of the assay used in this study, no quantitative data are reported on (neutralizing) antibody titers.

Strengths and limitations

We believe this study adds important knowledge about recovery after hospitalization for COVID-19. A strength of the current study is the repeated measurements over time in patients with a broad range of COVID-19 severity degrees. At the same time, compared with all patients admitted for COVID-19 in the Netherlands, the number of patients who were admitted to the ICU were overrepresented in this cohort.[39] Our center mostly served as a referral center for ICU patients, hence explaining the large numbers of patients who received ICU treatment in this cohort. Furthermore, patients who had normalized pulmonary outcomes were no longer followed up in the clinic, leading to missing FU measurements. Under the MAR assumption, we used all observed data of this cohort in repeated measurement analyses. These analyses can handle this kind of missing data by using the within- and between-subject covariance under the assumption that subjects with (nearly) normalized pulmonary outcomes at 3 months will still have good outcomes at 6 months. However, other unobserved reasons for dropout cannot be completely ruled out, and the results should therefore be interpreted with caution. Likewise, given the relatively small numbers of patients, the results of the multivariable models should be considered as explorative and hypothesis-generating, and they need further in-depth evaluation and confirmation. We will continue to prospectively follow up with a large cohort of (>500) patients within 10 hospitals, rehabilitation centers, and nursing homes in our region up to 2 years after hospitalization in the CO-FLOW (COVID-19 FU care Paths and Long-term Outcomes within the Dutch Healthcare System) study (Netherlands trial registration number NL74252.078.20), assessing long-term sequelae after COVID-19 infection, care paths, and the effects of various rehabilitation interventions.

CONCLUSIONS

In conclusion, in this prospectively followed Dutch cohort, we longitudinally describe recovery as it relates to pulmonary function, radiological abnormalities, physical and mental health status, and HR-QoL after hospitalization for COVID-19 and its main predictors. Persistent pulmonary impairment can be found for up to 6 months, but gradual improvement is seen over time. Similarly, the majority of patients reported persistent symptoms and reduced HR-QoL related to COVID-19 infection. Most of these improved over time, but fatigue was not only the most frequent but also the most persistent symptom, also seriously affecting HR-QoL. Fatigue could not be explained by the severity of COVID-19 or pulmonary function at FU. The underlying cause and optimal treatment need to be established and will be the topic of further investigations.

REFERENCES

1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120–128.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324: 782–793.
3. Yelin D, Margalit I, Yahav D, Runold M, Bruchfeld J. Long COVID-19: it's not over until? *Clin Microbiol Infect*. 2021;27:506–508.
4. Xiong Q, Xu M, Li J, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect*. 2021;27:89–95.
5. Mazza MG, De Lorenzo R, Conte C, et al. COVID-19 BioB Outpatient Clinic Study group. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. *Brain Behav Immun*. 2020;89:594–600.
6. Van Den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2021;73: e1089–e1098.
7. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128:2247–2261.
8. Park WB, Jun KI, Kim G, et al. Correlation between pneumonia severity and pulmonary complications in Middle East respiratory syndrome. *J Korean Med Sci*. 2018;33:e169.
9. Huang C, Huang L, Wang Y, et al. 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397:220–232.
10. Han X, Fan Y, Alwalid O, et al. Six-month follow-up chest CT findings after severe COVID-19 pneumonia. *Radiology*. 2021; 299:E177–E186.
11. Wu X, Liu X, Zhou Y, et al. 3-Month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*. 2021;9:747–754.
12. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J*. 2020;55:2001217.
13. Marvisi M, Ferrozzi F, Balzarini L, Mancini C, Ramponi S, Uccelli M. First report on clinical and radiological features of COVID-19 pneumonitis in a Caucasian population: factors predicting fibrotic evolution. *Int J Infect Dis*. 2020;99:485–488.
14. Lerum TV, Aaløkken TM, Brønstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J*. 2021;57: 2003448.
15. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49:1600016.
16. Quanjer PH, Stanojevic S, Cole TJ, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40: 1324–1343.
17. Stanojevic S, Graham BL, Cooper BG, et al. Global Lung Function Initiative TLCO working group; Global Lung Function Initiative (GLI) TLCO. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50:1700010.
18. GeurtsvanKessel CH, Okba NMA, Igloi Z, et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. *Nat Commun*. 2020;11:3436.
19. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. *J Psychosom Res*. 2003;54:345–352.
20. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. *Eur Respir J*. 2012;40:255–263.
21. de Kleijn WPE, De Vries J, Wijnen PAHM, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med*. 2011;105:1388–1395.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–370.
23. Scragg P, Jones A, Fauvel N. Psychological problems following ICU treatment. *Anaesthesia*. 2001;56:9–14.
24. Zilberg NJ, Weiss DS, Horowitz MJ. Impact of Event Scale: a cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol*. 1982;50: 407–414.

25. Brück E, Schandl A, Bottai M, Sackey P. The impact of sepsis, delirium, and psychological distress on self-rated cognitive function in ICU survivors: a prospective cohort study. *J Intensive Care*. 2018;6:2.
26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–1736.
27. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. conceptual framework and item selection. *Med Care*. 1992; 30:473–483.
28. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055–1068.
29. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*. 2020;8: 807–815.
30. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. *Lancet Respir Med*. 2020;8: 839–842.
31. Yoshida Y, Gillet SA, Brown MI, et al. Clinical characteristics and outcomes in women and men hospitalized for coronavirus disease 2019 in New Orleans. *Biol Sex Differ*. 2021;12:20.
32. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2021;93: 1013–1022.
33. Herridge MS, Cheung AM, Tansey CM, et al. Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348:683–693.
34. Herridge MS, Tansey CM, Matté A, et al. Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364:1293–1304.
35. Gorna R, MacDermott N, Rayner C, et al. Long COVID guidelines need to reflect lived experience. *Lancet*. 2021; 397:455–457.
36. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021;372:n136.
37. Kennisagenda COVID-19. Utrecht, the Netherlands: Federatie Medisch Specialisten; 2021 [accessed 2021 Mar 17]. Available from: https:// www.demedischspecialist.nl/sites/default/files/Kennisagenda% 20COVID-19.pdf.
38. Gaebler C, Wang Z, Lorenzi JCC, et al. Evolution of antibody immunity to SARS-CoV-2. *Nature*. 2021;591: 639–644.
39. Ontwikkeling COVID-19 in grafieken. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu; 2021 [updates 2021 Nov 2; accessed 2021 Mar 17]. Available from: https://www.rivm.nl/ coronavirus-covid-19/grafieken.



CHAPTER 4

Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study

L. Martine Bek[*]
Julia C. Berentschot[*]
Majanka H. Heijenbrok-Kal
Susanne M. Huijts
Michel E. van Genderen
Johan H. Vlake
Jasper van Bommel
Joachim G.J.V. Aerts
Gerard M. Ribbers
Rita J.G. van den Berg-Emons[**]
Merel E. Hellemons[**]
On behalf of the CO-FLOW Collaboration Group[***]

[*] Authors share first authorship
[**] Authors share senior authorship
[***] Listed in Appendix

ERJ Open Research. 2022;8(4):00355-2022.

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), 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 appendix 3.1 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. Differences 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. Of 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 4.1. 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 Fig. 4.1.

Persisting symptoms

Table 4.2 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 4.2 and Fig. 4.2. Symptoms that significantly declined over time were muscle weakness, hair loss, and exertional dyspnoea (p<0.001).

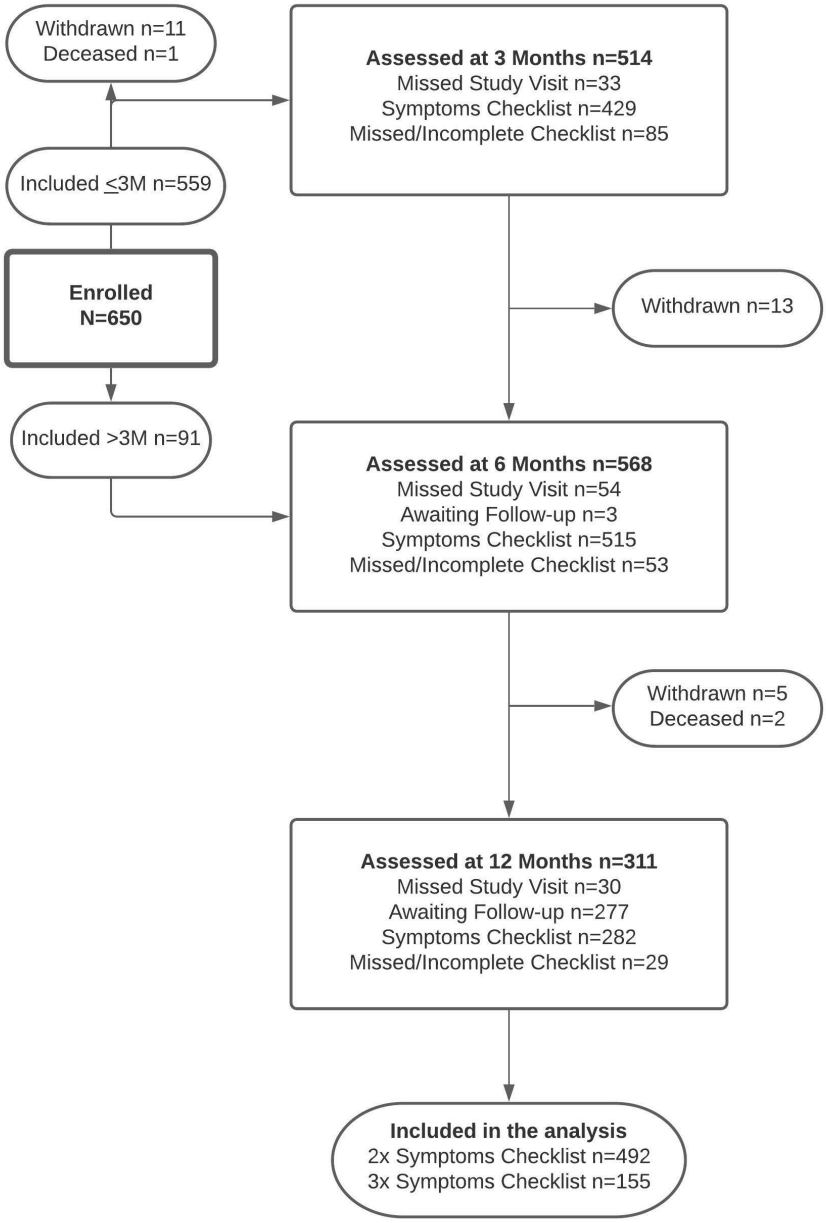


Figure 4.1 Flowchart of the patients in the CO-FLOW study during the interim analysis.

Table 4.1 *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/m²	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)
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)

	n[a]	All (N=492)
(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)
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.*

Table 4.2 *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**
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.*

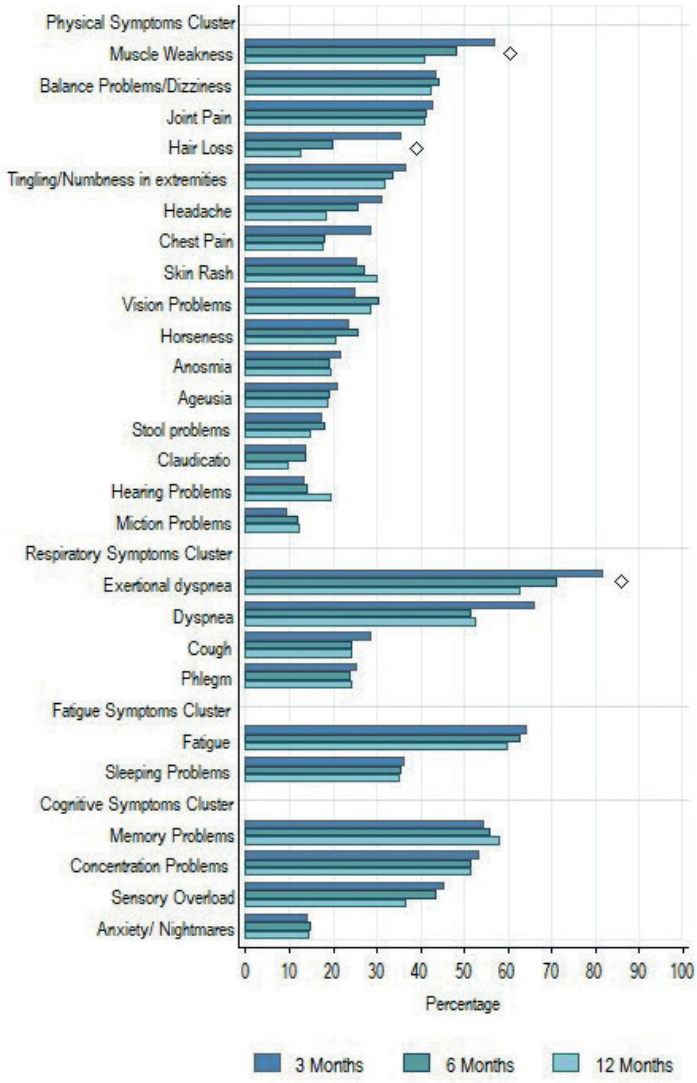


Figure 4.2 Symptom prevalence over time.
Prevalence of COVID-19-related symptoms at 3-, 6- and 12-month follow-up in patients after hospitalisation for COVID-19, sorted by symptoms cluster and from most to least frequently reported. Data are presented as percentage of patients with symptoms. Symptoms 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 Fig. 4.2. 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 (Fig. 4.3). 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) (Fig. 4.3). 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 4.1 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 (Fig.4.4). 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 (Fig. 4.4).

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 (Fig. 4.4).

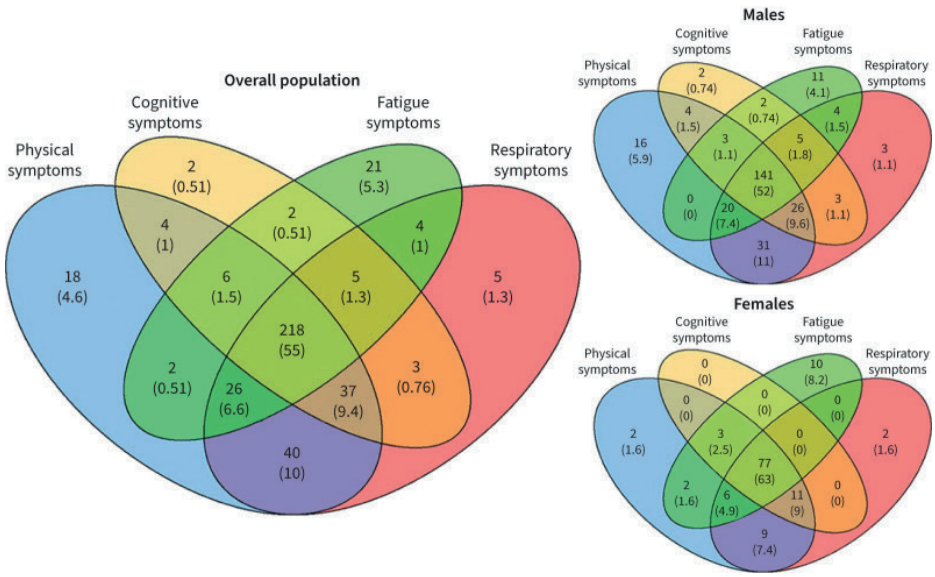


Figure 4.3 Venn diagrams showing overlap between the symptom clusters (physical symptoms, cognitive symptoms, fatigue symptoms and respiratory symptoms) for the entire cohort, males and females.
Data are presented as n (%) indicating the number of patients with symptoms. Data are presented as n (%) indicating the number of patients with symptoms.

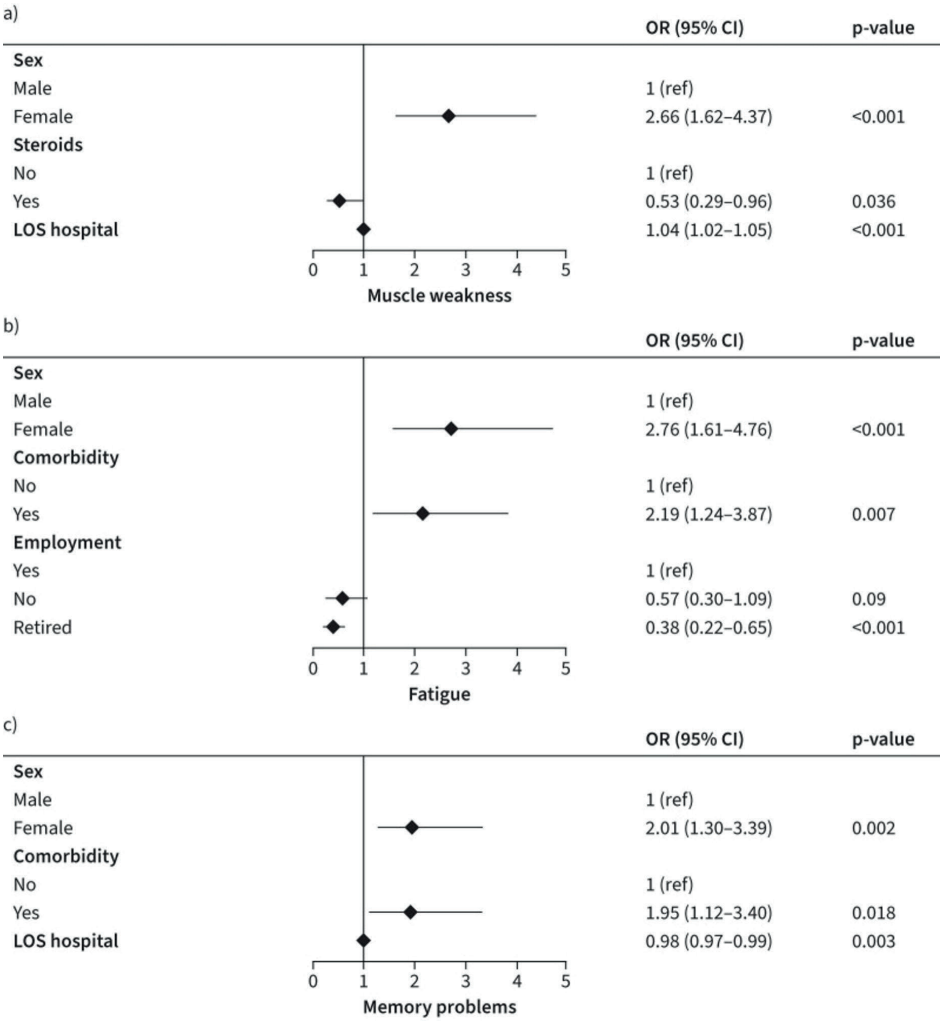


Figure 4.4 Forest plot of the patient and admission characteristics associated with the most prevalent symptoms for the a) physical, b) fatigue and c) cognitive symptoms clusters obtained by multivariable logistic regression analyses. *LOS: length of stay.*

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 hospitalisation.[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 into 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.

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *JAMA*. 2020; 324: 782–793.
2. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *BMJ*. 2020, 370: m3026.
3. Shah W, Hillman T, Playford ED, et al. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021; 372: n136.
4. WHO. A clinical case definition of post COVID-19 condition by a Delphi consensus. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
5. Sudre CH, Murray BA-OX, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med*. 2021; 27: 626–631.
6. van der Maaden T, Mutubuki EN, de Bruijn S, et al. Prevalence and severity of symptoms 3 months after infection with SARS-CoV-2 compared to test-negative and population controls in the Netherlands. *medRxiv*. 2022; preprint [https://doi.org/10.1101/2022.06.15.22276439].
7. Hellemons ME, Huijts S, Bek L, et al. Persistent health problems beyond pulmonary recovery up to 6 months after hospitalization for SARS-CoV-2; a longitudinal study of respiratory, physical and psychological outcomes. *Ann Am Thorac Soc*. 2022; 19: 551–561.
8. Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open*. 2021; 4: e2128568-e.
9. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022; in press [https://doi.org/10.1016/S2213-2600(22)00126-6].
10. Comelli A, Viero G, Bettini G, et al. Patient-reported symptoms and sequelae 12 months after COVID-19 in hospitalized adults: a multicenter long-term follow-up study. *Front Med (Lausanne)*. 2022; 9: 834354.
11. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021; 38: 101019.
12. Estiri H, Strasser ZH, Brat GA, et al. Evolving phenotypes of non-hospitalized patients that indicate long COVID. *BMC Med*. 2021; 19: 249.
13. Taquet M, Dercon Q, Luciano S, et al. Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med*. 2021; 18: e1003773.
14. Bek LM, Berentschot JC, Hellemons ME, et al. 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: 847.
15. De Kleijn WPE, De Vries J, Wijnen PAHM, et al. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med*. 2011; 105: 1388–1395.
16. Wynberg E, van Willigen H, Dijkstra M, et al. Evolution of COVID-19 symptoms during the first 12 months after illness onset. *Clin Infect Dis*. 2022 Aug 24;75(1):e482-e490.
17. Logue JK, Franko NM, Mcculloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open*. 2021; 4: e210830.
18. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022; 10: 761–775.
19. Blomberg B, Mohn KG-I, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med*. 2021; 27: 1607–1613.
20. Bardel A, Wallander MA, Wallman T, et al. Age and sex related self-reported symptoms in a general population across 30 years: patterns of reporting and secular trend. *PLoS One*. 2019; 14: e0211532.
21. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis*. 2021; 22: 43–55.
22. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021; 27: 601–615.
23. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med*. 2014; 370: 1626–1635.



CHAPTER 5

Cognitive and psychological recovery patterns across different care pathways 12 months after hospitalization for COVID-19: a multicenter cohort study (CO-FLOW)

L. Martine Bek
Merel E. Hellemons
Julia C. Berentschot
Marieke M. Visser
Susanne M. Huijts
Jasper van Bommel
Michel E. van Genderen
Joachim G.J.V. Aerts
Gerard M. Ribbers
Rita J.G. van den Berg-Emons*
Majanka H. Heijenbrok-Kal*
On behalf of the CO-FLOW Collaboration Group**

* Authors share senior authorship
** Listed in Appendix

Annals of Physical and Rehabilitation Medicine. 2023;66(5):101737

ABSTRACT

Background The comparison of recovery patterns for different care pathways following COVID-19 is necessary for optimizing rehabilitation strategies.

Objectives To evaluate cognitive and psychological outcomes across different care pathways up to 12 months after hospitalization for COVID-19.

Methods CO-FLOW is an ongoing multicenter prospective cohort study with assessments at 3, 6, and 12 months after hospitalization for COVID-19. The main outcomes are cognitive deficits (Montreal Cognitive Assessment, score <26), cognitive failure (Cognitive Failure Questionnaire, score >43), posttraumatic stress disorder (PTSD; Impact of Event Scale-Revised, score ≥33), and anxiety and depression (Hospital Anxiety and Depression Scale, subscale score ≥11).

Results In total, data from 617 participants were analyzed. Mean age was 59.7 (SD 11.4) years and 188 (31%) were female. Significant recovery occurred within the first 6 months post-discharge (p≤0.001). Cognitive deficits persisted in 21% (101/474), and psychological problems in 15% (74/482) of people at 12 months. Significantly improved cognition scores were reported for people who did not receive rehabilitation ('No-rehab'; 124/617, 20%; mean difference, MD 2.32, 95% CI 1.47 to 3.17; p<0.001), those who received community-based rehabilitation ('Com-rehab'; 327/617, 53%; MD 1.27, 95% CI 0.77 to 1.78; p<0.001), and those who received medical rehabilitation ('Med-rehab'; 86/617, 14%; MD 1.63, 95% CI 0.17 to 3.10; p=0.029). Med-rehab participants experienced more cognitive failure from 3 to 6 months (MD 4.24, 95% CI 1.63 to 6.84; p=0.001). Com-rehab showed recovery for PTSD (MD −2.43, 95% CI −3.50 to −1.37; p<0.001), anxiety (MD −0.67, 95% CI −1.02 to −0.32; p<0.001), and depression (MD −0.60, 95% CI −0.96 to −0.25; p<0.001), but symptoms persisted at 12 months.

Conclusions Survivors of COVID-19 showed cognitive and psychological recovery, especially within the first 6 months after hospitalization. Most persistent problems were related to cognitive functioning at 12 months. Recovery differed rehabilitation settings. Additional cognitive or psychological support might be warranted in people who medical or community-based rehabilitation.

INTRODUCTION

Many cases of coronavirus disease 2019 (COVID-19) involve long-term symptoms[1] and 6 months after hospitalization, 70-89% of people report at least one persistent symptom, and this figure is 49% at 12 months.[2-5] One of the most common symptoms is cognitive dysfunction, manifesting as problems with concentration, memory and brain fog.[6-9] Studies that objectively measure cognitive functioning have reported cognitive deficits in 31-69% of people during, or shortly after, hospitalization[10-13] and in ≥80% of people in rehabilitation settings.[14,15] Cognitive deficits were present in 50-75% of hospitalized survivors in at least one cognitive domain at 6 months,[16,17] and in 16% at 12 months.[18] At 12 months after intensive care unit (ICU) discharge, 16% of people experienced self-reported cognitive failure.[19]

In addition to cognitive deficits and failure, people with COVID-19 frequently report psychological impairments[7,8,20-22] with 43% of people experiencing posttraumatic stress disorder (PTSD), 46% reporting anxiety, and 30% reporting depression up to 6 months after hospitalization for COVID-19.[4,16,23-25] Longitudinal studies that follow-up people hospitalized for COVID-19 for 15 months report that up to 10% of people experience PTSD and 26% report anxiety and/or depression.[5,18,19,26] However, there is a lack of large, multicenter, prospective cohort studies comparing recovery across multiple rehabilitation settings.[10,14]

At the onset of the COVID-19 pandemic, care pathways were rapidly established without sufficient knowledge of people's clinical and rehabilitation needs, or long-term sequelae. Guidelines about who would need what type of rehabilitation did not yet exist. After hospitalization, most people are discharged home and if they receive community-based rehabilitation, it is usually monodisciplinary physical therapy. More severely affected, and younger, people are referred for medical rehabilitation while vulnerable people with more comorbidities are referred for skilled nursing facilities (SNF), where they receive multidisciplinary rehabilitation.[27]

In the Netherlands, rehabilitation programs are highly tailored to an individual's needs and goals. Rehabilitation intensity and total duration depend on factors such as disease characteristics or personal context, eg, the presence of a care-giver. Rehabilitation has been shown to improve cognitive performance in people with acute respiratory distress syndrome and sepsis.[28] Exploring

the variations and outcomes among different care pathways for people with COVID-19 is necessary to optimize rehabilitation strategies as variations in post-COVID rehabilitation may lead to different outcomes. Studies of COVID rehabilitation programs have been conducted within specific settings like hospitals and rehabilitation centers[12,14,18] but, to date, long-term outcomes across settings have not been compared.

We hypothesized that people who followed multidisciplinary rehabilitation will have a longer recovery time than those to whom either no rehabilitation, or monodisciplinary rehabilitation, was offered. Therefore, we aimed to evaluate the cognitive (objective and subjective) and psychological recovery patterns among survivors of COVID-19 across multiple care pathways up to 12 months after hospitalization.

MATERIAL AND METHODS

Study design and population

The COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system (CO-FLOW) study is an ongoing, multicenter prospective cohort study in which participants are monitored at 3, 6, 12, and 24 months after hospital discharge and at rehabilitation discharge, if applicable, within the Rotterdam-Rijnmond-Delft area of the Netherlands. Eligible participants are people within 6 months of hospitalization for COVID-19 (diagnosed by laboratory or clinical findings), ≥18 years old, and fluent in Dutch or English. The CO-FLOW protocol has been described in detail elsewhere.[29]

Here we present interim results from people up to 12 months after hospital discharge with at least one study measurement between July 1, 2020, and June 13, 2022. All participants provided written informed consent before the first study measurement. The Medical Ethics Committee of the Erasmus Medical Center study (MEC-2020-0487) approved this study. The study is registered on the World Health Organization International Clinical Trials Registry Platform (NL8710) and is reported in accordance with the STROBE guidelines.

Procedure

Demographics and clinical characteristics were collected at study visits and from electronic patient records (EPR). Demographics included age, sex, body mass index (BMI), migration background, and pre-COVID educational and

employment status. Clinical characteristics included medical history, length of stay (LOS) in hospital, treatment during admission, oxygen support, ICU admission, LOS in ICU, delirium, and thrombosis. Healthcare use was collected via face-to-face interview, EPR, and the iMTA Medical Cost Questionnaire (iMCQ).[30] Medication use was collected via iMCQ. After being discharged from hospital, participants were grouped according to their care pathway (Supplementary Fig. 5.1):

1. No rehabilitation (No-rehab) group: participants returned home independently and did not receive rehabilitation.
2. Community-based rehabilitation (Com-rehab) group: participants received outpatient rehabilitation to support their recovery to premorbid functional levels; they were usually offered monodisciplinary rehabilitation programs (lasting from weeks to months) of psychotherapy, physical or occupational therapy
3. In- and outpatient medical rehabilitation (Med-rehab) group: participants received intensive in- or outpatient multidisciplinary rehabilitation to support independence and functional recovery to premorbid levels; the aim of inpatient rehabilitation is to return home. Rehabilitation programs are individualized and person-centered as functional goals determine the type and duration of treatment. The program is guided by a multidisciplinary team and, depending on the individual's care needs, includes a rehabilitation physician, physical, occupational, movement, and speech and language therapists, psychologists, nurses, dieticians, and social workers. Inpatient rehabilitation treatment is often provided 4-5 times per day for approximately 4-6 weeks. Outpatient rehabilitation programs usually last 8-12 weeks. After inpatient rehabilitation, people may continue onto outpatient medical or community-based rehabilitation programs.
4. Inpatient skilled nursing rehabilitation (SNF-rehab) group: participants received moderately intensive inpatient multidisciplinary rehabilitation to support independence and recovery to premorbid functional levels in order to return home. Rehabilitation programs are individualized as the functional goals determine the type and duration of treatment. Rehabilitation programs are guided by a multidisciplinary team that includes an elderly-care physician, therapists (physical, occupational, movement, and speech and language), psychologists, nurses, dieticians, and social workers, as necessary. During inpatient rehabilitation, treatment is provided up to 5 times a week for 4-8 weeks; afterwards people may follow community-based rehabilitation programs.

Study visits were scheduled at 3, 6, and 12 months and included non-invasive functional tests assessing physical and cognitive abilities. Participants also received questionnaires via email or by post. Data were stored using an electronic data capture system (Castor EDC, Amsterdam, The Netherlands).

Outcome measures

The Montreal Cognitive Assessment (MoCA) is a screening tool that objectively evaluates 8 cognitive domains.[31] The total score ranges from 0-30; a score <26 indicates cognitive deficits. A point is added if the patient has participated in education for ≤12 years. The MoCA was administered at the first possible visit with the participant, and subsequently repeated only for those with a score of <26, to follow clinical practice as closely as possible and reduce participant burden at the next study visit. We used a different MoCA version each time.

The Cognitive Failure Questionnaire (CFQ) subjectively assesses the frequency of experienced cognitive failures in everyday life.[32,33] It contains 25 items, each scored using a 5-point Likert scale from 0 (“never”) to 4 (“very often”). The total score ranges from 0-100, a score >43 indicates cognitive failure.

Psychological status included PTSD, anxiety, and depression. PTSD was assessed using the Impact of Event Scale-Revised (IES-R) which includes 22 items rated by a 5-point Likert scale from 0 (“not at all”) to 4 (“extremely”).[34,35] The total score ranges from 0-88, and a result ≥33 indicates clinically significant PTSD. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) subscales for anxiety (HADS-A) and depression (HADS-D). Each subscale score ranges from 0-21; for either a score ≥11 indicates clinically significant anxiety or depression.[36]

Data analysis

Data were analyzed from participants with at least 1 follow-up outcome of interest. Variables are presented as means with standard deviation (SD), medians with interquartile range (IQR), numbers (n) with percentage (%), or estimated means with standard error (SE), as appropriate. We used Generalized Estimating Equations (GEE), with repeated measurements of MoCA, CFQ, IES-R, HADS-A, and HADS-D scores, to assess recovery patterns over time for the full cohort and across care pathways. GEE accounted for within-person correlations using a working correlation matrix between repeated measurements, and included all observed outcomes, despite missing values. We considered the unstructured correlation matrix the best option for our

data. We entered visit time (3, 6, and 12 months) as aa fixed factor in the GEE for the full cohort. We entered care pathway (No-, Com-, Med-, or SNF-rehab) as a fixed factor, and the interaction of care pathway and visit time (3, 6, and 12 months), and adjusted for age at admission, sex, BMI at admission, pre-COVID employment, and length of hospital stay in the GEE for subgroup analyses. Post-hoc analyses included pairwise comparisons between follow-up visits and care pathways. Only significant results between care pathways are reported.

The main GEE analysis of MoCA data included only participants who scored <26 during their first assessment after hospital discharge or, for some, upon their discharge from inpatient rehabilitation to show recovery over time, as MoCA testing was not repeated when a participants scored ≥26. Twenty-two people scored ≥26 (22/86) at their first assessment at inpatient rehabilitation discharge, thus this was re-used as their 3-month outcome. In addition, an exploratory GEE was performed for the full cohort in which scores ≥26 were carried over and used for all future study time points.

We calculated Spearman's correlations (r; <0.5, mild; 0.5-0.7, moderate; and >0.7, strong) to evaluate associations between the outcomes of interest at 12 months. All statistical tests were 2-sided, and statistical significance was defined as a p-value of <0.05. The Bonferroni correction was applied to group comparisons of baseline characteristics. We used SPSS (version 28, SPSS Inc, Chicago, IL, USA) for the statistical analyses.

RESULTS

Study population

Of the 650 participants enrolled in CO-FLOW, 617 (95%) were analyzed as they had at least 1 study measurement as of June 13, 2022 (Fig. 5.1). The mean age was 59.7 (11.4) years, 188 (31%) were female, and the median hospital LOS was 12.0 (6.0–27.0) days. Distribution of the care pathways was: No-rehab, 124/617 (20%); Com-rehab, 327/617 (53%); Med-rehab, 86/617 (14%); and SNF-rehab, 80/617 (13%) (Table 1). Median (IQR) inpatient rehabilitation times were: Med-rehab, 33 (25–45) days and SNF-rehab, 33 (20–41) days. Twelve participants in the Med-rehab group received outpatient rehabilitation only. Compared to other care pathways, participants in the SNF-rehab group were significantly older, 66.1 (9.6) years, and had more comorbidities (91%). Participants in the Med-rehab group had the longest hospital LOS at 44 (31.5–55.3) days, the most

men (78%), and the highest incidence of ICU admission (95%), obesity (61%), and employment (86%), compared to other care pathways.

Cognitive functioning outcomes

Cognitive deficits

Among participants with cognitive deficits at their first assessment, we observed improvement over time (MD 1.30, 95% CI 0.89 to –1.72; p<0.001), significant improvement from 3 to 6 months (MD 0.79, 95% CI 0.4 to 1.19; p<0.001), and from 6 to 12 months (MD 0.51, 95% CI 0.16 to 0.86; p=0.004) (Table 5.2). At 3 months, 42% (179/428) of participants had cognitive deficits; at 6 months the frequency was 30% (145/487); and at 12 months it was 21% (101/474) (Fig. 5.2; Supplementary Table 5.1). Participants with cognitive deficits at their 12-month follow-up were more often unemployed or retired compared to participants without cognitive deficits; they also more often had a non-European migration background and lower pre-COVID educational status (Supplementary Table 5.2). The lowest MoCA scores were in memory, executive functioning, and language cognitive domains (Supplementary Table 5.3). Participants with an overt language barrier (23/617) were not evaluated with the MoCA tool.

The Med-rehab group had the lowest percentage of participants with cognitive deficits, and the SNF-rehab group had the worst cognitive scores and highest percentage of participants with cognitive deficits at all follow-up times (Fig. 5.3A; Supplementary Tables 5.4 and 5.5). At 3 months, the cognitive scores between the care pathways did not differ significantly. At 12 months, the Med-rehab group scored significantly higher than the SNF-rehab group (MD 1.11, 95% CI 0.07 to 2.15; p=0.036).

Table 5.1 *Demographics and clinical characteristics for 617 people who had been hospitalized for COVID-19. Data were grouped according to care pathway followed after hospital discharge as part of the CO-FLOW study*

	n	Total cohort	No-rehab	Com-rehab	Med-rehab	SNF-rehab	p-value [b]
Number (n)	617	617 (100.0)	124 (20.1)	327 (53.0)	86 (13.9)	80 (13.0)	
Demographics							
Age at admission in years, mean (SD)	617	59.7 (11.4)	58.5 (12.8)	59.4 (11.4)	57.0 (8.2)	66.1 (9.6)	<0.001*
Sex, female	613	188 (31)	30 (24)	117 (36)	19 (22)	22 (28)	0.020
Body mass index (BMI), mean (SD)	559	29.3 (5.3)	28.1 (5.0)	29.1 (5.3)	31.1 (5.3)	29.6 (5.6)	<0.001*
Migration background	608						0.910 [a]
European		442 (73)	86 (71)	238 (74)	62 (72)	56 (71)	
(North) African		23 (4)	5 (4)	16 (5)	1 (1)	1 (1)	
Dutch Caribbean		83 (14)	19 (16)	39 (12)	13 (15)	12 (15)	
Asian		38 (6)	6 (5)	16 (5)	8 (9)	8 (10)	
Turkish		22 (4)	5 (4)	13 (4)	2 (2)	2 (3)	
Pre-COVID educational level	506						0.360
Low		210 (35)	42 (35)	109 (34)	25 (29)	34 (44)	
Middle		213 (35)	40 (33)	110 (34)	35 (41)	28 (36)	
High		183 (30)	39 (32)	103 (32)	25 (29)	16 (21)	
Pre-COVID employment	608						<0.001*
Unemployed		94 (15)	16 (13)	57 (17)	4 (5)	17 (22)	
Employed		364 (60)	73 (60)	189 (59)	73 (86)	29 (37)	
Retirement		150 (25)	32 (26)	77 (24)	8 (10)	33 (42)	

Table 5.1 *Continued*

	n	Total cohort	No-rehab	Com-rehab	Med-rehab	SNF-rehab	p-value [b]
Clinical characteristics							
Comorbidities	617						
≥1 comorbidity		501 (81)	84 (68)	272 (83)	72 (84)	73 (91)	<0.001*
Obesity (BMI ≥30)		234 (38)	29 (23)	122 (37)	52 (61)	31 (39)	<0.001*
Diabetes		120 (19)	21 (17)	65 (20)	13 (15)	21 (26)	0.273
Cardiovascular disease and/or hypertension		240 (39)	35 (28)	126 (39)	35 (41)	44 (55)	0.002
Pulmonary disease		152 (25)	19 (15)	89 (27)	21 (24)	23 (29)	0.052
Renal disease		58 (9)	11 (9)	33 (10)	5 (6)	9 (11)	0.606
Gastrointestinal disease		30 (5)	6 (5)	16 (5)	7 (8)	1 (1)	0.224
Neurological disease		65 (11)	9 (7)	30 (9)	8 (9)	18 (23)	0.003
Malignancy		68 (11)	9 (7)	38 (12)	9 (11)	12 (15)	0.360
Autoimmune and/or inflammatory disease		66 (11)	12 (10)	33 (10)	8 (9)	13 (16)	0.392
Mental disorder		29 (5)	3 (2)	16 (5)	6 (7)	4 (5)	0.445
Length of stay hospital in days	617						
mean (SD)		19.4 (20.1)	8.8 (7.8)	12.6 (11.5)	46.6 (24.0)	34.4 (21.9)	<0.001*
median (IQR)		12.0 (6.0-27.0)	7.0 (4.0-10.0)	9.0 (5.0-16.0)	44.0 (31.5-55.3)	29.0 (20.3-46.8)	
Treatment	617						0.109 [a]
No treatment		134 (22)	35 (28)	61 (19)	17 (20)	21 (26)	
(Hydroxy)chloroquine		12 (2)	2 (2)	3 (1)	7 (8)	NA	
Antivirals		93 (15)	28 (23)	58 (18)	5 (6)	2 (3)	
Steroids		434 (70)	80 (65)	248 (76)	51 (59)	55 (69)	
Anti-inflammatories		74 (12)	3 (2)	35 (11)	17 (20)	19 (24)	

	n	Total cohort	No-rehab	Com-rehab	Med-rehab	SNF-rehab	p-value [b]
Convalescent plasma		8 (1)	2 (2)	4 (1)	NA	2 (3)	
Oxygen supplementation	617	596 (97)	116 (94)	315 (97)	86 (100)	78 (98)	0.069
High-flow nasal cannula	576	190 (33)	19 (16)	86 (28)	41 (53)	44 (56)	<0.001*
Intensive Care Unit (ICU) admission	617	252 (41)	18 (15)	90 (28)	82 (95)	62 (78)	<0.001*
Length of stay in ICU in days mean (SD) median (IQR)	249	 21.7 (17.6) 16.0 (9.0-31.0)	 11.4 (12.4) 8.0 (3.5-11.8)	 12.7 (10.9) 9.0 (6.0-16.3)	 32.1 (20.0) 29.0 (17.5-40.5)	 24.2 (15.2) 19.0 (13.0-38.3)	<0.001*
Invasive mechanical ventilation	617	216 (35)	11 (9)	67 (21)	79 (92)	59 (74)	<0.001*
Duration of intubation in days mean (SD) median (IQR)	209	 19.5 (14.2) 14.0 (8.0-28.0)	 13.4 (12.2) 8.0 (6.0-18.0)	 12.6 (8.5) 9 (6.0-19.0)	 25.9 (16.0) 24.0 (13.0-34.3)	 20.4 (13.5) 14 (10.0-32.5)	<0.001*
Tracheostomy	601	79 (13)	3 (2)	15 (5)	39 (47)	24 (33)	<0.001*
Delirium	615	148 (24)	16 (13)	40 (13)	51 (63)	41 (54)	<0.001*
Thrombosis	601	94 (16)	8 (7)	36 (11)	29 (35)	21 (27)	<0.001*
Time interval between hospital discharge and study follow-up in days, mean (SD)							
3-month visit	431	95.5 (14.4)	95.4 (13.4)	93.6 (25.2)	98.1 (16.9)	98.6 (20.0)	0.317
6-month visit	510	185.1 (27.6)	186.4 (13.1)	184.2 (34.4)	186.0 (17.8)	186.1 (18.5)	0.888
12-month visit	489	368.5 (18.4)	365.1 (12.0)	369.4 (20.9)	366.7 (9.7)	372.1 (21.1)	0.080

*Data are presented as n (%) unless otherwise indicated. Com-rehab, group with community-based rehabilitation in care pathway; Med-rehab, group with medical rehabilitation in care pathway; NA, Not Applicable; No-rehab, group without rehabilitation in care pathway; SNF-rehab, group with skilled nursing rehabilitation in care pathway. [a] Because of small group sizes per care pathway we analyzed migration background as 'European' versus all non-European data, and treatment as 'No treatment' versus all other treatment data combined. * Significant p-values with Bonferroni correction (p≤0.001). [b] p-values are based on independent t-test, Kruskal-Wallis test, Chi-square test, or Fisher's Exact test as appropriate.*

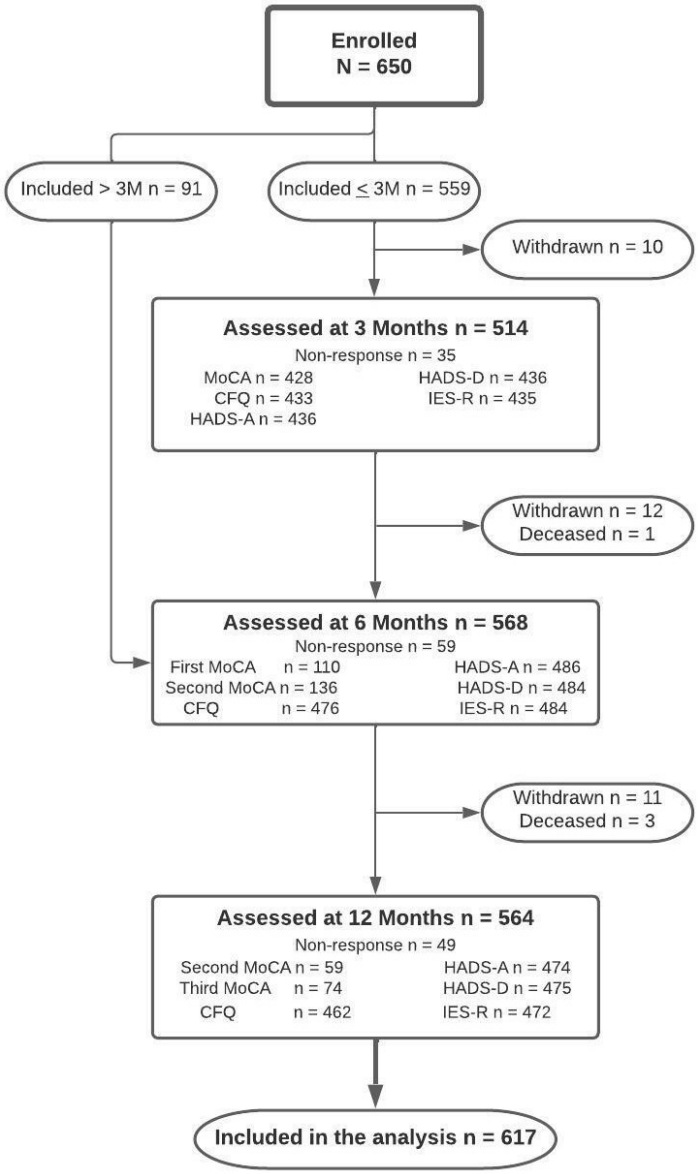


Figure 5.1 Flowchart of the CO-FLOW study recruitment and data gathering process.
In the current analysis, 617 participants who had at least one outcome of interest were included and were assessed at 3, 6, and 12 months after hospitalization for COVID-19.
>3M, participants included after 3 months after hospital discharge; ≤3M, participants included within 3 months of hospital discharge; CFQ, Cognitive Failure Questionnaire; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale, IES-R, Impact of Event Scale-Revised; MoCA, Montreal Cognitive Assessment; M, months.

Among participants with cognitive deficits, we observed significant improvement from 3 to 12 months in the No-rehab (MD 2.32, 95% CI 1.47 to 3.17; p<0.001); Com-rehab (MD 1.27, 95% CI 0.77 to 1.78; p<0.001); and Med-rehab (MD 1.63, 95% CI 0.17 to 3.10; p=0.029) groups; but not in the SNF-rehab group (MD 0.18, 95% CI −0.97 to 1.33; p=0.094) (Fig. 5.3B; Supplementary Table 5.4). At 12 months, the SNF-rehab group had the highest prevalence of cognitive deficits (22/59, 37%); their MoCA scores were significantly worse than those of the No-rehab (MD −2.38, 95% CI −3.91 to −0.85; p=0.002), Com-rehab (MD −1.44, 95% CI −2.83 to −0.06; p=0.042), and Med-rehab (MD −1.98, 95% CI −3.70 to −0.27; p=0.024) groups.

Table 5.2 *Estimated mean scores of 2 cognitive and 3 psychological outcome measures that were administered to participants at 3, 6, and 12 months after hospitalization for COVID-19 as part of the CO-FLOW study.*

	3 months	6 months	12 months	p-value[a]	p-value[b]	p-value[c]
MoCA	22.8 (0.2)	23.6 (0.2)	24.1 (0.2)	<0.001	<0.001	0.004
CFQ	29.7 (0.8)	29.8 (0.8)	30.8 (0.8)	0.069	0.730	0.040
IES-R	14.7 (0.6)	12.7 (0.6)	12.3 (0.6)	<0.001	<0.001	0.333
HADS-A	5.4 (0.2)	4.9 (0.2)	4.9 (0.2)	<0.001	<0.001	0.997
HADS-D	5.1 (0.2)	4.6 (0.2)	4.6 (0.2)	<0.001	0.001	0.503

Data are presented as estimated mean (standard error) based on generalized estimating equations. CFQ, Cognitive Failure Questionnaire; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale - Depression wqasubscale; IES-R, Impact of Event Scale-Revised; MoCA, Montreal Cognitive Assessment. [a] p-value illustrates total trajectory from 3 to 12 months. [b] p-value illustrates trajectory from 3 to 6 months. [c] p-value illustrates trajectory from 6 to 12 months.

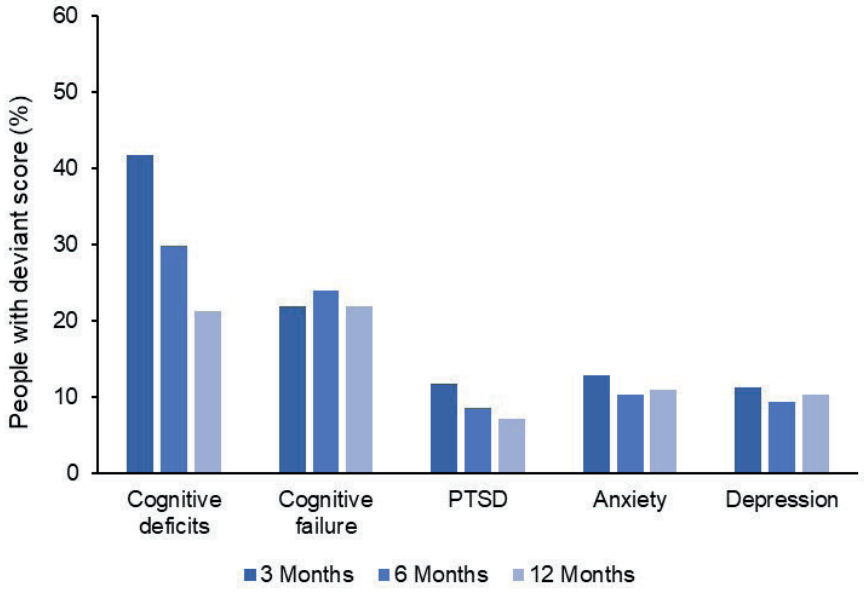


Figure 5.2 Graph showing the percentage (shown on the y-axis) of 617 participants from the CO-FLOW study with one or more deviant outcome scores (shown on the x-axis) at 3, 6, and 12 months after hospitalization for COVID-19. *CFQ, Cognitive Failure Questionnaire, a score >43 indicates cognitive failure; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale, a score ≥11 indicates anxiety; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale, a score ≥11 indicates depression; IES-R, Impact of Event Scale-Revised, a score IES-R ≥33 indicates a diagnosis of posttraumatic stress disorder (PTSD); MoCA, Montreal Cognitive Assessment, a score <26 indicates cognitive deficits.*

Cognitive failure

In the full cohort no significant changes occurred in cognitive failure over time (p=0.069*)* (Table 2). At 3 months, 22% (95/433) of participants experienced cognitive failure; at 6 months, 24% (114/476);) and at 12 months, 22% (101/462) (Fig. 5.2; Supplementary Table 5.1).

At 3 months, the No-rehab group had the lowest cognitive failure scores; significantly lower than the Com-rehab (MD −5.77, 95% CI −9.81 to −1.73; p=0.005) and SNF-rehab (MD −6.76, 95% CI −12.95 to −0.56; p=0.033) groups (Fig. 5.4A; Supplementary Table 5.4). At 3 months, 25% (61/246) of the Com-rehab group had cognitive failure, the highest incidence compared to the other groups (Supplementary Table 5.5). From 3 to 6 months, the cognitive failure score significantly increased only in the Med-rehab group (MD 4.24, 95% CI 1.63 to 6.84; p=0.001). From 6 to 12 months, the cognitive failure scores did not change significantly for any care pathway. At 12 months, the

Med-rehab group showed the highest cognitive failure score; significantly higher than the No-rehab (MD 11.84, 95% CI 4.95 to 18.72; p<0.001) and Com-rehab (MD 6.30, 95% CI 0.13 to 12.48; p=0.046) groups. The No-rehab group scored also significantly lower than Com-rehab (MD −5.53, 95% CI −9.47 to −1.59; p=0.006) and SNF-rehab (MD −6.84, 95% CI −12.49 to −1.20; p=0.018) groups. Of all care pathways, the Med-rehab group had the highest prevalence of cognitive failures (18/64, 27%) at 12 months.

Psychological outcomes

PTSD

In the full cohort, PTSD scores decreased significantly over time (MD −2.45, 95% −3.31 to −1.59; p<0.001), with a significant decrease from 3 to 6 months (MD −2.11 95% −2.91 to −1.31; p<0.001) (Table 5.2). At 3, 6, and 12 months the prevalence of PTSD was 12% (51/435), 9% (41/484), and 7% (34/472), respectively (Fig. 5.2; Supplementary Table 5.1).

At 3 months, No-rehab had the lowest prevalence (3/81, 4%) of PTSD of all groups (Fig. 5.4B, Supplementary Tables 5.4 and 5.5). Their PTSD score was significantly lower than the Com-rehab (MD −5.85, 95% CI −8.43 to −3.28; p<0.001), Med-rehab (MD −7.12, , 95% CI −12.73 to −1.51; p=0.013), and SNF-rehab (MD −8.81, 95% CI −13.58 to −4.03; p<0.001) groups. From 3 to 6 months, the PTSD scores for all participants reduced; this reduction was significant for the Com-rehab (MD −2.43, 95% CI −3.50 to −1.37; p<0.001) and SNF-rehab (MD −3.32, 95% CI −5.70 to −0.95; p=0.006) groups. At 12 months, the Com-rehab (MD 3.63, 95% CI 1.08 to 6.18; p=0.005), Med-rehab (MD 7.54, 95% CI 2.52 to 12.55; p=0.003), and SNF-rehab (MD 6.96, 95% CI 2.79 to 11.12; p=0.001) groups had a higher PTSD score than No-rehab. Participants in Med-rehab had the highest prevalence (11/73, 15%) of PTSD symptoms.

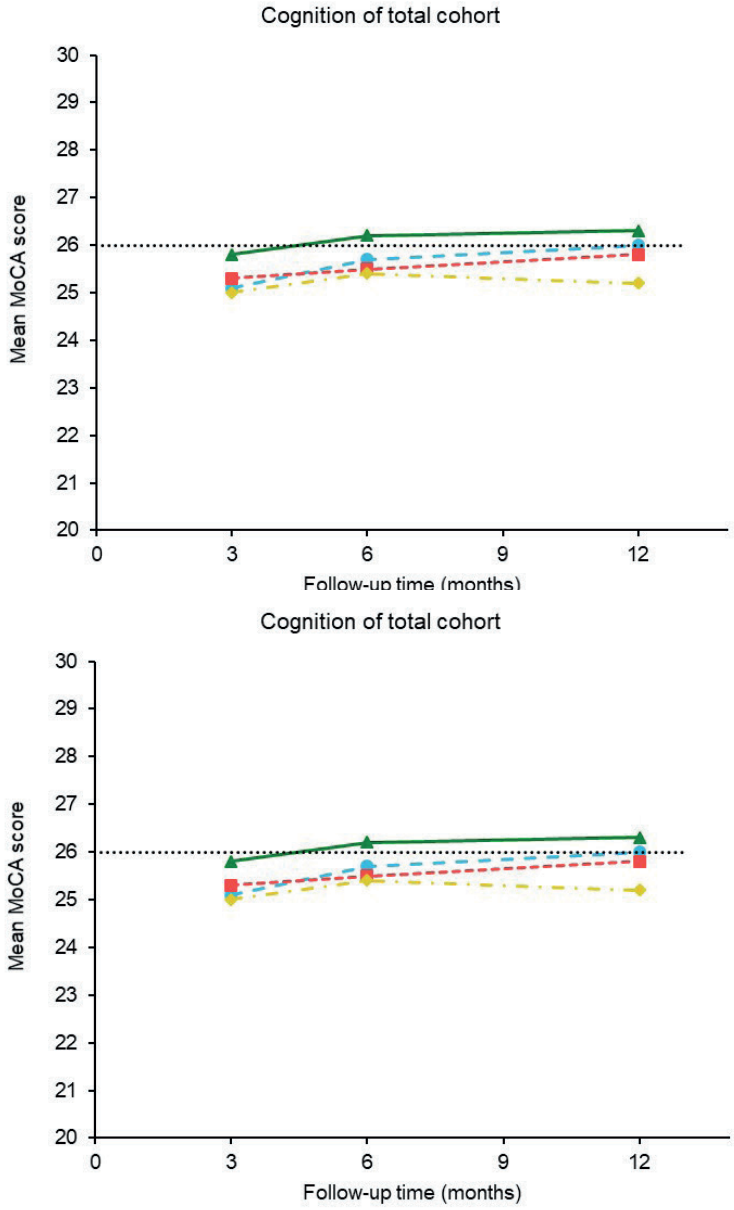


Figure 5.3 Graphs showing the estimated mean Montreal Cognitive Assessment (MoCA) scores of 617 participants scores at 3, 6, and 12 months (x-axis) after hospitalization for COVID-19.

Data were grouped by the 4 different care pathways as part of the CO-FLOW study. Participant MoCA score is shown along the y-axis; the dotted line at 26 refers to the MoCA score below which a cognitive deficit is indicated. In (A) the mean MoCA scores for all 617 participants in each care pathway group are shown; when participants had a MoCA score of ≥26, this score was re-used as their score for subsequent time points. The MoCA was only repeated at the next visit if the score was <26. In (B) the mean MoCA scores are presented only for those participants

in each care pathway group who scored <26 at 3 and/or 6 months, to show their improvement over time. Means are adjusted for age at admission, sex, body mass index at admission, pre-COVID employment status, and length of hospital stay. None of these covariables were found to have contributed significantly to the model.

Anxiety

In the full cohort, anxiety scores decreased significantly over time (MD −0.51, 95% CI −0.80 to −0.21; p<0.001), although the decrease was significant only from 3 to 6 months (MD −0.51, 95% CI −0.77 to −0.25; p<0.001) (Table 5.2). The prevalence of anxiety at 3 months was 13% (56/436); at 6 months, 10% (50/486); and at 12 months, 11% (52/474) (Fig. 5.2; Supplementary Table 5.1). Anxiolytic medication was taken by 8/380 (2%) participants at 3 months; 17/436 (4%) at 6 months; and 2/422 (1%) at 12 months; at the same time points, a psychologist saw, respectively, 49/380 (13%), 48/436 (11%), and 18/422 (4%) of participants who had scored below the cutoff. Of participants who scored above the cutoff, anxiolytic medication was taken by 3/56 (5%) participants at 3 months, and 2/50 (4%) at 6 months; 22/56 (39%) saw a psychologist at 3 months, 18/50 (36%) did so at 6 months, and 10/52 (19%) at 12 months.

At 3 months, the No-rehab group had a significantly lower anxiety score than Com-rehab (MD −1.68, 95% −2.52 to −0.84; p<0.001) and SNF-rehab (MD −1.77, 95% CI −3.16 to −0.38; p=0.013) groups; the No-rehab group also had the lowest prevalence (3/80; 4%) of anxiety among all groups (Fig. 5.4C; Supplementary Tables 5.4 and 5.5). From 3 to 6 months, anxiety scores decreased significantly in the Com-rehab (MD −0.67 95% CI −1.02 to −0.32; p<0.001) and SNF-rehab (MD −0.92, 95% CI −1.58 to −0.27; p=0.006) groups; it decreased non-significantly in the No-rehab (MD −0.37, 95% CI −0.92 to 0.19; p=0.2), and increased non-significantly Med-rehab (MD 0.57, 95% CI −0.27 to 1.41; p=0.182) groups. From 6 to 12 months, no significant changes occurred. At 12 months, the Med-rehab group had the highest prevalence of anxiety (12/73, 16%) while 5% (4/73) consulted a psychologist. This group had significantly higher anxiety scores than the No-rehab (MD 1.97, 95% CI 0.27 to 3.66; p=0.023) group.

Depression

In the full cohort, depression scores decreased significantly over time (MD −0.55, 95% CI −0.84 to −0.25; p<0.001); this change was only significant from 3 to 6 months (MD −0.46, 95% CI −0.73 to −0.18; p=0.001) (Table 5.2). At 3, 6, and 12 months, depression was reported in 11% (49/436), 9% (45/484), and 10% (49/475) of participants, respectively (Fig. 5.2; Supplementary Table 5.1). Among participants who scored below the cutoff, 20/387 (5%), 20/439 (5%), and

12/426 (3%) took antidepressant medication at 3, 6, and 12 months, respectively. In addition, at the same time points, 53/387 (14%), 52/439 (12%), and 20/426 (5%), respectively, consulted a psychologist. For those participants who scored above the cutoff, 3/49 (6%) took antidepressant medication at 3 months; 6/45 (13%) at 6 months, and 1/49 (2%) at 12 months. At the same time points, a psychologist was seen by 18/49 (37%), 13/45 (29%), and 9/49 (18%) participants, respectively.

At 3 months, the No-rehab group showed significantly lower depression scores than the Com-rehab (MD −1.52, 95% CI −2.36 to −0.68; p<0.001), Med-rehab (MD −1.94, 95% CI −3.76 to −0.12; p=0.037) and SNF-rehab (MD −2.19, 95% CI −3.58 to −0.80; p=0.002) groups. The No-rehab group also had the lowest prevalence of depression (2/80, 3%) compared to other groups (Fig. 5.4D; Supplementary Tables 5.4 and 5.5). From 3 to 6 months, depression scores decreased significantly in the Com-rehab (MD −0.60, 95% CI −0.96 to −0.25; p<0.001) and SNF-rehab (MD −0.80, 95% CI −1.47 to −0.13; p=0.019) groups, but not in the No-rehab (MD −0.17, 95% CI −0.81 to 0.47]; p=0.605) or Med-rehab (MD 0.15, 95% CI −0.85 to 1.16; p=0.764) groups. From 6 to 12 months, no significant changes were found. At 12 months, the Med-rehab group showed a higher depression score than No-rehab (MD 1.76, 95% CI 0.17 to 3.35; p=0.03. The highest prevalence of depression occurred in the Med-rehab and SNF-rehab groups (both 12/73, 16%): 6% (4/73) of Med-rehab participants and 1% (1/73) of SNF-rehab participants consulted a psychologist.

Correlation between cognitive and psychological outcomes

In the full cohort, cognitive deficits and/or cognitive failure were experienced by 48% (237/494) of participants at 3 months, 43% (230/530) at 6 months, and 38% (188/498) at 12 months. At least one clinically significant psychological impairment was experienced by 21% (91/440) of participants at 3 months; this decreased to 18% (87/494) at 6 months and 15% (74/482) at 12 months. At 12 months, cognitive failure, PTSD, anxiety, and depression were moderately associated; Spearman's correlation coefficients ranged from 0.559–0.728. Cognitive deficits were not associated with any of the self-reported cognitive and psychological outcomes (r≤0.2) (Supplementary Table 5.6).

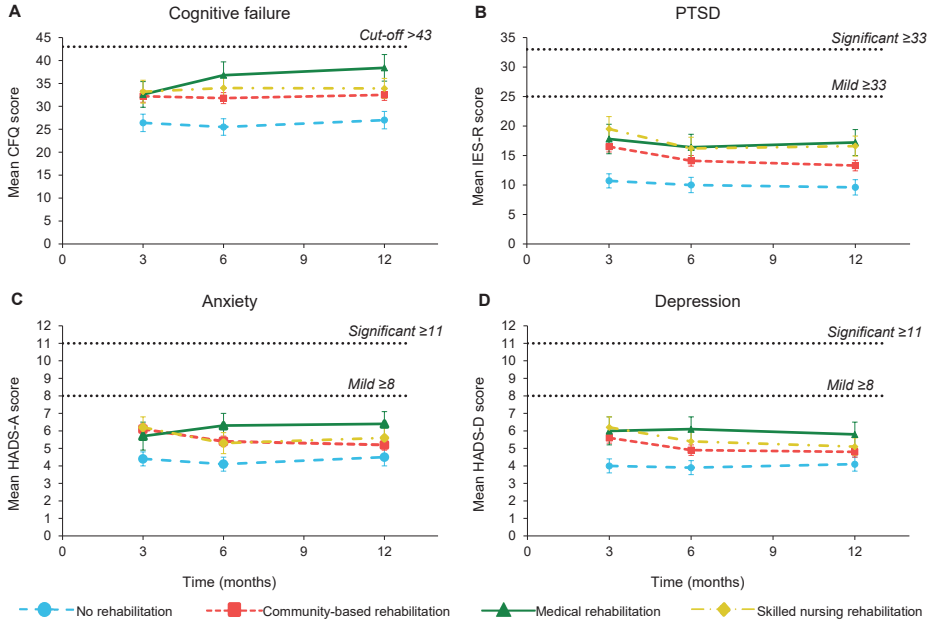


Figure 5.4 Graphs showing the estimated mean scores of the (A) Cognitive Failure Questionnaire (CFQ); (B) Impact of Event Scale-Revised (IES-R) for identification of posttraumatic stress disorder (PTSD); (C) Hospital Anxiety and Depression Scale - Anxiety subscale (HADS-A); and (D) Hospital Anxiety and Depression Scale - Depression subscale (HADS-D) in 617 participants at 3, 6, and 12 months after hospitalization for COVID-19.
Data were grouped by the 4 different care pathways as part of the CO-FLOW study. For each graph, scores above the dotted lines indicate either a mild (lower line) or significant (upper line) impairment for each outcome. CFQ, Cognitive Failure Questionnaire, a score >43 indicates cognitive failure; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale, a score ≥8 indicates mild, a score ≥11 indicates significant anxiety; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale, a score ≥8 indicates mild, a score ≥11 indicates significant depression; IES-R, Impact of Event Scale-Revised, a score ≥25 indicates mild, a score ≥33 indicates significant posttraumatic stress disorder (PTSD). Means were adjusted for participant age at admission, sex, body mass index at admission, pre-COVID employment status, and length of hospital stay. The following covariables contributed significantly to the models: for cognitive failure, age at admission (p=0.011), sex (p<0.001), and length of hospital stay (p<0.001); for anxiety, age at admission (p=0.042), and sex (p<0.001); for depression, sex (p=0.047); for PTSD, age at admission (p=0.004), and sex (p<0.001).

DISCUSSION

This is the first study to have longitudinally assessed outcomes across multiple rehabilitation settings in survivors of COVID-19 up to 12 months. The No-rehab group showed good cognitive recovery and reported the fewest psychological sequelae; possibly because participants were a priori the least severely injured. The SNF-rehab group had the most cognitive deficits and some self-reported cognitive failure. This group was composed of older people and more retirees; our findings thus agree with previous reports of COVID-19 recovery in older people.[11,37]

Objectively, Med-rehab participant data indicated that they made a good cognitive recovery, yet this group also had the most psychological sequelae at 12 months. The large improvement in cognitive deficits within 6 months therefore seems unexpected. This group was the most severely affected by COVID-19: they had the longest hospital stay, highest rates of ICU admission and most incidents of delirium and thrombosis. However, the Med-rehab participants were also the youngest people in the study with the highest employment rates pre-COVID. Thus, our findings may also be explained not only by younger age and cognitive therapy, but also the greater cognitive function challenges these people encountered on their return to work in areas such as attention, information processing, and working memory, all of which may have improved their recovery.[38,39]

The Med-rehab group experienced the most cognitive failures up to 12 months. This seems contradictory, as they showed improvements in cognitive deficit scores. However, objectively-measured and subjectively-reported cognitive difficulties are not necessarily correlated.[40] Voruz et al suggested this could be due to anosognosia, an impaired self-perception of cognitive deficiencies. Thus, people might have high, objectively-measured cognitive deficit scores, but not perceive their cognitive failure due to anosognosia.[41] Previous studies have shown that subjectively-reported cognitive difficulties are associated with psychological problems and fatigue in people hospitalized for COVID-19;[42-44] something we also observed. At 12 months, Med-rehab participants reported the most psychological symptoms associated with more cognitive failure. This group of people were initially referred for inpatient rehabilitation but could have experienced increased physical, cognitive, and psychological demands once discharged home, potentially leading to the higher rates of cognitive failure and psychological symptoms, such as depression.[45,46] Therefore, after

Med-rehab discharge such people might benefit from additional (vocational) rehabilitation programs and/or psychological coaching. A longer follow-up is needed to evaluate this pattern and long-term outcomes.

The largest care pathway group (Com-rehab) received monodisciplinary rehabilitation in the community; most often an outpatient physical therapy program. Surprisingly, one fifth of this group had cognitive deficits and a relatively high prevalence of self-reported cognitive failure over 12 months. Although their psychological status improved over time, anxiety and depression levels were not much lower than in the other rehabilitation groups. As described above, these psychological symptoms could explain the high prevalence of cognitive failure.[42,44] Persistent cognitive deficits should be further investigated to identify those people who would normally only be offered physical therapy who might instead require cognitive or psychological follow-up support.

Although overall cognitive deficits decreased over time, at 12 months after hospital discharge the incidence remained at 21% (101/474). Another similar study over 12 months reported cognitive deficits in 16% of people.[18] This is lower than our reported levels for the No-rehab (17/92, 19%), Com-rehab (54/259, 21%), and SNF-rehab (22/59, 37%) participants, but not for Med-rehab participants (8/70, 11%). The difference may be because 47% of the other study's participants were discharged to rehabilitation centers, compared to 14% of our cohort. We also observed fewer cognitive deficits in the Med-rehab group. Differences in cohort demographics might also be involved, as participants with a non-European background, a lower pre-COVID educational status, or who were pre-COVID unemployed or retired had a lower MoCA score. Furthermore, changes in brain structure associated with cognitive decline have been reported after comparing brain scans from individuals before and after COVID-19 to those from a well-matched control group, which may also explain cognitive deficits.[47] Follow-up is required to investigate such long-term effects.

Studies of post-COVID psychological outcomes report PTSD in 5–6% of people, anxiety in 9–26%, and depression in 6–11%, up to 15 months later.[5,18,19,26] These psychological sequelae after ICU treatment are described as the post-intensive care syndrome.[48] We found a higher prevalence of PTSD and depression in the Med-rehab and SNF-rehab groups, care pathways that were often provided after ICU treatment. However, the prevalence of psychological impairments

was low and comparable to the Dutch norm at 12 months, indicating good psychological recovery.[49,50]

Our study has some limitations. First, not all participants had a 3-month follow-up visit. Second, migration background might have influenced MoCA outcomes, as participants with a language barrier were excluded from the MoCA test. Third, the high prevalence of comorbidities like cardiovascular or pulmonary disease might have influenced MoCA outcomes as they also cause cognitive deficits. Fourth, by not repeating the MoCA after a score ≥26, we may have missed future deterioration in cognitive function. Fifth, the covariable adjustment might have strongly influenced the SNF-rehab results: this was the oldest population with the longest hospital stay. In addition, older age might also affect MoCA scores. Finally, we lacked information regarding participants' levels of cognitive and psychological functioning before COVID-19; therefore, we could only evaluate function relative to our first assessment.

A major strength of this study is the multicenter design with participation of hospitals and rehabilitation centers. This enabled recruitment of people from a large region of the Netherlands. Participants had a wide range of disease severity, migration backgrounds, treatment strategies, and care provision (both general ward and ICU). Second, the repeated measurements over time enabled analysis of recovery patterns up to 12 months and facilitates comparisons with other studies. Finally, the facilities where participants received treatment after hospitalization for COVID-19 were included. Thus, we can uniquely show cognitive and psychological recovery in people with COVID-19 across all main care pathways.

CONCLUSIONS

In conclusion, people hospitalized for COVID-19 showed cognitive and psychological recovery up to 12 months after discharge, with the largest improvement in the first 6 months. The No-rehab group had the fewest sequelae. People who received rehabilitation showed continued recovery in the first 6 months, although at 12 months, cognitive function problems persisted. Multidisciplinary rehabilitation comprising cognitive and psychological support should be considered in the management of people post-COVID since the condition seems to be multifactorial. Continued follow-up assessments will allow to monitor changes in cognitive and psychological outcomes.

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;324(8):782-93.
2. Rogers JP, Watson CJ, Badenoch J, et al. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. *J Neurol Neurosurg Psychiatry*. 2021;92(9):932-41.
3. Hellemons ME, Huijts S, Bek LM, et al. 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.
4. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-32.
5. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. 2021;398(10302):747-58.
6. Daroische R, Hemminghyth MS, Eilertsen TH, et al. Cognitive Impairment After COVID-19-A Review on Objective Test Data. *Front Neurol*. 2021;12:699582.
7. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open*. 2021;4(5):e2111417.
8. Ramakrishnan RK, Kashour T, Hamid Q, et al. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. *Front Immunol*. 2021;12:686029.
9. Seeßle J, Waterboer T, Hippchen T, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. *Clin Infect Dis*. 2022 Apr 9;74(7):1191-1198.
10. Beaud V, Crottaz-Herbette S, Dunet V, et al. Pattern of cognitive deficits in severe COVID-19. *J Neurol Neurosurg Psychiatry*. 2021;92(5):567-8.
11. Devita M, Di Rosa E, Iannizzi P, et al. Cognitive and Psychological Sequelae of COVID-19: Age Differences in Facing the Pandemic. *Front Psychiatry*. 2021;12:711461.
12. Negrini F, Ferrario I, Mazziotti D, et al. Neuropsychological Features of Severe Hospitalized Coronavirus Disease 2019 Patients at Clinical Stability and Clues for Postacute Rehabilitation. *Arch Phys Med Rehabil*. 2021;102(1):155-8.
13. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J Neurol Sci*. 2021;420:117271.
14. Alemanno F, Houdayer E, Parma A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. *PLoS One*. 2021;16(2):e0246590.
15. Jaywant A, Vanderlind WM, Alexopoulos GS, et al. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacology*. 2021;46(13):2235-40.
16. Frontera JA, Yang D, Lewis A, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci*. 2021;426:117486.
17. Poletti S, Palladini M, Mazza MG, et al. Long-term consequences of COVID-19 on cognitive functioning up to 6 months after discharge: role of depression and impact on quality of life. *Eur Arch Psychiatry Clin Neurosci*. 2021:1-10.
18. Latronico N, Peli E, Calza S, et al. Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax*. 2022;77(3):300-3.
19. Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. *JAMA*. 2022;327(6):559-65.
20. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med*. 2021;9(11):1275-87.
21. Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine*. 2021;39:101044.
22. Klaser K, Thompson EJ, Nguyen LH, et al. Anxiety and depression symptoms after COVID-19 infection: results from the COVID Symptom Study app. J Neurol Neurosurg Psychiatry. 2021 Dec;92(12):1254-1258.

23. Mazza MG, Palladini M, De Lorenzo R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun*. 2021;94:138-47.
24. Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. *Brain Behav Immun*. 2021;97:328-48.
25. Taquet M, Geddes JR, Husain M, et al. 6-month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416-27.
26. Sun L, Wang J, Wang Y-S, et al. 15-Month Health Outcomes of Hospitalized COVID-19 Patients from Onset: A Cohort Study. *Europe PMC [Preprint]*. Oktober 25, 2021; accessed January 28, 2022.
27. FMS: Langdurige klachten en revalidatie na COVID-19 Richtlijnendatabase [Internet]. The Netherlands. Federatie Medisch Specialisten; [updated 2022 March 21; cited 2024 Feb 27]. Available from:https://richtlijnendatabase.nl/richtlijn/covid-19/startpagina_-_langdurige_klachten_en_revalidatie_na_covid-19.html.
28. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med*. 2014;40(3):370-9.
29. Bek LM, Berentschot JC, Hellemons ME, et al. 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 2years after hospital discharge. *BMC Health Serv Res*. 2021;21(1):847.
30. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.
31. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-9.
32. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16.
33. Ponds R, Boxtel M, Jolles J. De 'Cognitive Failure Questionnaire' als maat voor subjectief cognitief functioneren. *Tijdschrift voor Neuropsychologie*. 2006;1:37-45.
34. Weiss DS, Marmar CR, Wilson JP, Keane TM. Assessing psychological trauma and PTSD. The Impact of Events Scale—Revised. 1997;19:399-411.
35. Zilberg NJ, Weiss DS, Horowitz MJ. Impact of Event Scale: a cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol*. 1982;50(3):407-14.
36. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.
37. Heyns A, Dupont J, Gielen E, et al. Impact of COVID-19: urging a need for multi-domain assessment of COVID-19 inpatients. *Eur Geriatr Med*. 2021;12(4):741-8.
38. Park DC, Bischof GN. The aging mind: neuroplasticity in response to cognitive training. *Dialogues Clin Neurosci*. 2013;15(1):109-19.
39. Nouchi R, Taki Y, Takeuchi H, et al. Brain training game boosts executive functions, working memory and processing speed in the young adults: a randomized controlled trial. *PLoS One*. 2013;8(2):e55518.
40. Demant KM, Vinberg M, Kessing LV, Miskowiak KW. Assessment of subjective and objective cognitive function in bipolar disorder: Correlations, predictors and the relation to psychosocial function. *Psychiatry Res*. 2015;229(1-2):565-71.
41. Voruz P, Cionca A, Jacot de Alcântara I, et al. Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome: is anosognosia a key determinant? *Brain Commun*. 2022;4(2):fcac057.
42. Brianna Sullivan BA, Tabitha W. Payne PD. Affective Disorders and Cognitive Failures: A Comparison of Seasonal and Nonseasonal Depression. *Am J Psychiatry*. 2007;164(11):1663-7.
43. Gouraud C, Bottemanne H, Lahlou-Laforêt K, et al. Association Between Psychological Distress, Cognitive Complaints, and Neuropsychological Status After a Severe COVID-19 Episode: A Cross-Sectional Study. *Front Psychiatry*. 2021;12:725861.
44. Torrente F, Yoris A, Low D, et al. Psychological symptoms, mental fatigue and behavioural adherence after 72 continuous days of strict lockdown during the COVID-19 pandemic in Argentina. *BJPsych Open*. 2022;8(1):e10.
45. Camicia M, Wang H, DiVita M, et al. Length of Stay at Inpatient Rehabilitation Facility and Stroke Patient Outcomes. *Rehabil Nurs*. 2016;41(2):78-90.

46. Boals A, Banks JB. Effects of traumatic stress and perceived stress on everyday cognitive functioning. *Cogn Emot*. 2012;26(7):1335-43.
47. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*. 2022;604(7907):697-707.
48. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-9.
49. de Graaf R, Ten Have M, van Gool C, van Dorsselaer S. [Prevalence of mental disorders, and trends from 1996 to 2009. Results from NEMESIS-2] Prevalentie van psychische aandoeningen en trends van 1996 tot 2009; resultaten van NEMESIS-2. *Tijdschr Psychiatr*. 2012;54(1):27-38.
50. de Vries GJ, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *J Trauma Stress*. 2009;22(4):259-67.



CHAPTER 6

Return to work and health-related quality of life up to 1 year in patients hospitalized for COVID-19: the CO-FLOW study

L. Martine Bek
Julia C. Berentschot
Merel E. Hellemons
Sylvia C. Remerie
Jasper van Bommel
Joachim G.J.V. Aerts
Gerard M. Ribbers
Rita J.G. van den Berg-Emons*
Majanka H. Heijenbrok-Kal*
On behalf of the CO-FLOW collaboration Group**

* Authors share senior authorship
** Listed in Appendix

BMC Medicine. 2023;21(1):380

ABSTRACT

Background Currently, evidence about the long-term consequences of COVID-19 on return to work and health-related quality of life (HRQoL) is limited. We evaluated return to work and its associations with baseline characteristics and physical and mental recovery over time in patients up to 1 year after hospitalization for COVID-19. Secondary, we aimed to evaluate the association between return to work and health-related quality of life (HRQoL).

Methods CO-FLOW, a multicenter prospective cohort study, enrolled adult participants hospitalized for COVID-19, aged ≥18 years within 6 months after hospital discharge. Return to work and HRQoL were collected at 3, 6, and 12 months after hospital discharge using the iMTA Productivity Cost Questionnaire and the 36-Item Short Form Health Survey, respectively. Data were collected between July 1, 2020, and September 1, 2022. Generalized estimating equations with repeated measurements were used to assess outcomes over time.

Results In the CO-FLOW study, 371 participants were employed pre-hospitalization. At 3, 6, and 12 months post-discharge, 50% (170/342), 29% (92/317), and 15% (44/295) of participants had not returned to work, and 21% (71/342), 21% (65/317), and 16% (48/295) only partially, respectively. ICU admission (adjusted odds ratio (95% confidence interval): 0.17 (0.10 to 0.30), p<0.001), persistent fatigue (0.93 (0.90 to 0.97), p<0.001), female sex (0.57 (0.36 to 0.90), p=0.017), and older age (0.96 (0.93 to 0.98), p<0.001) were independently associated with no return to work. ICU patients required a longer time to return to work than non-ICU patients. Patients who did not return or partially returned to work reported lower scores on all domains of HRQoL than those who fully returned.

Conclusions One year after hospitalization for COVID-19, only 69% of patients fully returned to work, whereas 15% did not return and 16% partially returned to work. No or partial return to work was associated with reduced HRQoL. This study suggests that long-term vocational support might be needed to facilitate return to work.

Trial registration World Health Organization International Clinical Trials Registry Platform NL8710.

BACKGROUND

More than 3 years after the outbreak of coronavirus disease 2019 (COVID-19), reports show that up to 90% of the patients hospitalized for COVID-19 experience a wide range of physical, cognitive, and mental health consequences up to 1 year after COVID-19.[1-4] These consequences could largely impact patients' participation in society, including return to work. While studies have shown long-lasting problems with return to work, the proportion of patients not able to return to work varies widely, ranging from 6 to 43% at 6 months and 11 to 88% at 1 year after hospitalization for COVID-19.[5-8,4]

A small cohort study showed that patients admitted to the intensive care unit (ICU) report a four times longer time to return to work compared with those treated at the general ward at 7 months after hospital discharge.[9] However, the longitudinal pattern of return to work and other factors beyond ICU admission that may impact the ability to return to work are currently poorly understood.

Long-term sick leave not only impacts society's productivity costs, but also largely affects patients and their families in their social life, finances, and overall well-being.[10,11] Up to 1 year post-COVID-19, patients report a reduced HRQoL.[12] Small cohort studies showed that patients who did not return to work report a worse HRQoL than those who did.[13,7] Moreover, ICU admission, female sex, and presence of post-COVID-19 symptoms, including fatigue, depression, and muscle weakness are associated with a reduced HRQoL.[14-16]

The current literature lacks large prospective cohort studies that repeatedly evaluate return to work over time, its risk factors, and its association with HRQoL up to 1 year post-COVID-19. However, as numerous patients experience long-term problems, understanding these aspects is crucial to optimize treatment. We sought to investigate the following aims within the CO-FLOW study, a large multicenter cohort study (N=650) following patients hospitalized for COVID-19 up to 2 years after hospital discharge with a large proportion of patients who have been admitted to the ICU. First, we aimed to evaluate return to work over time and its associations with baseline characteristics and physical and mental recovery over time in patients up to 1 year after hospitalization for COVID-19. Second, we evaluated the association between return to work and HRQoL. We hypothesized that returning to work improves over time, but takes longer for patients admitted to the ICU compared with

those who are not. Second, we expected that patients unable to return to work experience a worse HRQoL.

METHODS

Study design and participants

Participants of the COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system (CO-FLOW) study who were employed prior to hospitalization for COVID-19 were selected for this study. The design of the CO-FLOW study has been described previously.[17] In short, individuals hospitalized because of COVID-19 are followed up at 3, 6, 12, and 24 months after discharge within the southwest of the Netherlands. The current analysis focuses on measurements up to 12 months. Data were collected between July 1, 2020, and September 1, 2022. We included adult patients (≥18 years) with a confirmed COVID-19 diagnosis within 6 months after hospital discharge who were fluent in Dutch or English. Incapacitated patients were not included because of the study procedure. All participants provided written informed consent. The Medical Ethics Committee of the Erasmus Medical Center approved this study (MEC-2020-0487). The study is registered on the World Health Organization International Clinical Trials Registry Platform (NL8710) and reported in accordance with the STROBE guidelines.[18]

Measurements

Personal and clinical characteristics were obtained at study visits at 3, 6, and 12 months, and retrospectively from electronic patient records. Alongside each study visit, patient-reported outcome measures (PROMs) were collected using standardized questionnaires via email or postal mail.[17]

Primary outcome

Return to work was evaluated with the iMTA Productivity Cost Questionnaire (iPCQ).[19] The iPCQ enquires information regarding occupation, paid or unpaid work, number of workdays, hours per week of paid work, and short-term (≤ 4 weeks) and long-term (> 4 weeks) absence from paid work. Occupation was categorized into 3 categories: 1] white collar, including executive, administrative, and managerial (technical) occupations; 2] manual labor; and 3] service, including healthcare support, education, protective service, and personal care occupations.[20] In case iPCQ was missing, return to work was evaluated via the first item of the Utrecht Scale for Evaluation of Rehabilitation - Participation

that asks hours per week of paid work.[21] If both were missing, information regarding return to work was collected via a telephone interview.

Secondary outcome

HRQoL was assessed with the 36-Item Short Form Health Survey (SF-36). The SF-36 contains eight domains: Physical Functioning (PF), Role limitations due to Physical health (RP), Role limitations due to Emotional problems (RE), Vitality (VT), Mental Health (MH), Social Functioning (SF), Bodily Pain (BP), and General Health (GH).[22,23] Each domain is transformed to a scale ranging from 0 (worst health) to 100 (best health). Two higher-order summary scores are calculated: Physical Component Summary (PCS) by positively weighing the PF, RP, BP, VT and GH, and negatively weighing RE, MH, and SF; and the Mental Component Summary (MCS) by positively weighing RE, VT, MH, and SF, and negatively weighing PF, RP, BP, and GH.[24] The PCS and MCS are T-scores, having a normal mean score of 50 and SD of 10. The SF-36 has been extensively validated in the Dutch population.[22]

Baseline characteristics and recovery status

Personal characteristics included age at admission, sex, body mass index (BMI) at admission, migration background (European/non-European), and pre-hospitalization educational (low [primary or secondary education]; middle [high school]; high [postsecondary education or university]) status. Clinical characteristics included comorbidities, length of stay (LOS) in hospital in days, type of COVID-19-directed treatment during hospitalization (no treatment/steroids/antivirals/anti-inflammatory/(hydroxy)chloroquine/convalescent plasma), oxygen support, ICU admission, and LOS in ICU in days.

Recovery status was assessed at 3, 6, and 12 months after hospitalization. We assessed physical fitness by the 6-min walk test (6MWT) and 1-min sit-to-stand test (1MSTST) to assess cardiorespiratory fitness, and maximum isometric handgrip strength (HGS) to assess overall muscle strength, resulting in the following outcomes that were all normalized to percentage of normative values (%pred): 6-min walking distance in meters (6MWD),[25] number of sit-to-stand (STS) repetitions,[26] and maximum HGS in kg.[27] At 3, 6, and 12 months follow-up, we also collected PROMs on cognitive failures (Cognitive Failures Questionnaire, scoring range 0-100),[28] fatigue (Fatigue Assessment Scale, scoring range 10-50),[29] anxiety and depression (Hospital Anxiety and Depression Scale; Anxiety subscale and Depression subscale, scoring range

0-21),[30] and posttraumatic stress disorder (PTSD) (Impact of Event Scale-Revised, scoring range 0-88)[31]

Data analysis

Continuous variables are presented as mean (SD) and/or median (IQR); categorical variables as n (%). Descriptive statistics were used to check statistical assumptions. Generalized Estimating Equations (GEE) analyses with repeated measurements for binary logistic models using an unstructured working correlation matrix were performed to evaluate return to work over time and to identify variables associated with return to work via univariable and subsequent multivariable analyses. We categorized return to work into no, partial, i.e., working less hours than pre-hospitalization due to COVID consequences, or full, i.e., equal hours as pre-hospitalization. Primary analysis concerned patients who did not return to work versus those who partially or fully returned to work. Secondary analysis included patients who did not return or partially returned to work versus those who fully returned. In addition, we used GEE for linear models with repeated measurements to evaluate HRQoL over time and the independent association between return to work and HRQoL adjusted for covariables. In the univariable models, time together with the most prevalent comorbidities (>20%, history of obesity, cardiovascular disease, and pulmonary disease), ICU admission, and LOS hospital, and the time-varying variables occupational category, 6MWD %pred, STS %pred, HGS %pred, cognitive failures, fatigue, anxiety, depression, and PTSD were entered. To assess whether ICU patients required longer time to return to work than non-ICU patients, we entered an interaction term for ICU admission with follow-up time. Significant variables ($p<0.05$) were entered into the multivariable models, however, if multicollinearity (Spearman's rho ≥ 0.6) was present, ICU was preferred over LOS hospital, depression over anxiety and PTSD, and STS %pred over 6MWD %pred in the multivariable models, based on our aim, literature, and univariable significance level.[32,2] Little's missing completely at random test was performed for variables with missing values (BMI at admission, occupational category, 6MWT, HGS, STS, fatigue, cognitive failures, anxiety, depression, and PTSD) showing patterns in missing data ($p\leq 0.001$). We addressed missing data with multiple imputation under the missing-at-random assumption (one hundred datasets, hundred iterations, predictive mean matching (K=5), final models aggregated using Rubin's Rules). Model parameters are presented by forest plots showing the estimated adjusted odds ratios (AOR) for return to work or estimated mean differences for PCS and MCS with corresponding 95% confidence intervals

(CI), and p-values, using p<0.05 as significance level. Statistical analyses were carried out using SPSS version 28 (IBM SPSS statistics, SPSS Inc, Chicago, IL, USA) and R version 4.2.1 (R-Foundation) were used for graphs.

RESULTS

Study population

Of the 650 patients enrolled in the CO-FLOW study, 371/650 (57.1%) patients were employed pre-hospitalization and included in the study sample (Fig. 6.1). Of these, 359 (96.8%), 336 (90.6%), and 319 (86.0%) patients responded at 3, 6, and 12 months, respectively. At 12 months, responders did not differ significantly from non-responders regarding sex and LOS hospital (p=0.3; p=0.5), however responders were significantly older (55.7 [8.8] vs 48.4 [10.6], p<0.001) and less frequently admitted to the ICU (41.4% vs 61.5%, p=0.017). At hospital admission, the median age was 57.0 (50.0-61.0) years, median BMI was 28.4 (25.8-32.2), 104 (28.0%) patients were female, and 295/371 (79.5%) patients had ≥1 comorbidities (Table 6.1). Median LOS in the hospital was 11.0 (6.0-29.0) days, and 161 (43.4%) patients were admitted to the ICU with a median LOS in ICU of 18.0 (9.0-31.0) days.

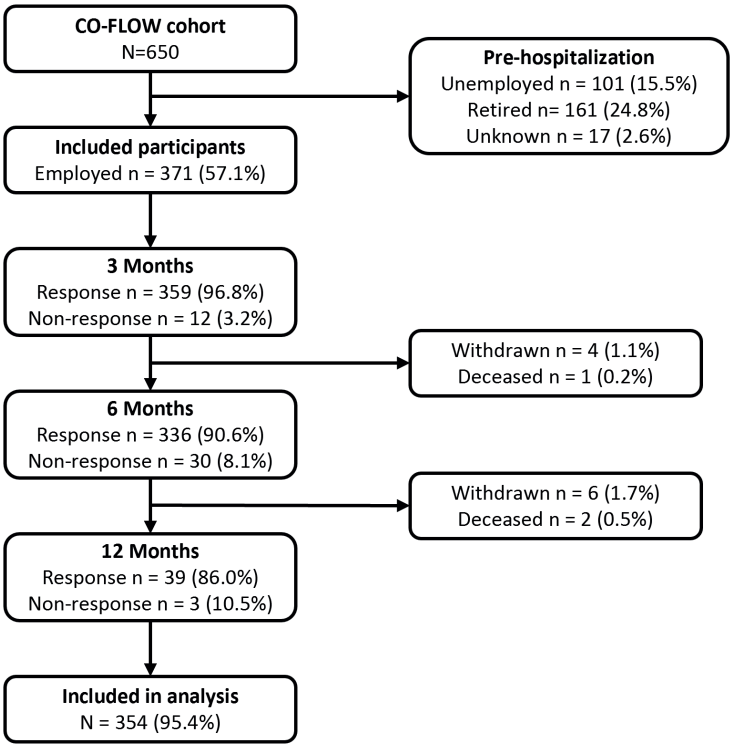


Figure 6.1 Flowchart of inclusion procedure for study sample.
Of the 650 patients, 371 were employed prior to hospitalization for COVID-19 and were included in the study sample. The final generalized estimating equations analyses with full model specification included 354 (95.4%) patients.

Table 6.1 *Demographics and clinical characteristics of the study population.*

	Study population (N = 371)
Demographics	
Age at admission, *years*	
mean (SD)	55.0 (9.4)
median (IQR)	57.0 (50.0-61.0)
Sex, *female*	104 (28.0)
BMI at admission, *kg/m²* [a]	
mean (SD)	29.5 (5.3)
median (IQR)	28.4 (25.8-32.2)
Migration background	
European	258 (69.5)
Dutch Caribbean	56 (15.1)
Asian	24 (6.5)
Turkish	17 (4.6)
(North) African	16 (1.3)

	Study population (N = 371)
Educational level	
Low	106 (28.6)
Middle	137 (36.9)
High	128 (34.5)
Clinical characteristics	
Comorbidities	
≥1	295 (79.5)
Obesity (BMI≥30)	160 (43.1)
Cardiovascular disease	122 (32.9)
Pulmonary disease	81 (21.8)
Diabetes	71 (19.1)
Malignancy	29 (7.8)
Neurological disease	28 (7.5)
Renal disease	25 (6.7)
Gastrointestinal disease	23 (6.2)
Autoimmune and/or inflammatory disease	33 (8.9)
Mental disorder	16 (4.3)
Treatment [a]	
No treatment	86 (23.2)
Steroids	259 (69.8)
Antivirals	54 (14.6)
Anti-inflammatory	50 (13.5)
(Hydroxy)chloroquine	9 (2.4)
Convalescent plasma	3 (0.8)
LOS hospital, *days*	
mean (SD)	19.7 (20.0)
median (IQR)	11.0 (6.0-29.0)
ICU admission	161 (43.4)
LOS ICU, *days* [a]	
mean (SD)	21.8 (16.3)
median (IQR)	18.0 (9.0-31.0)
Oxygen supplementation	362 (97.6)
High flow nasal cannula [a]	122 (34.9)
Invasive mechanical ventilation	136 (36.7)
Length of intubation, *days* [a]	
mean (SD)	20.3 (13.9)
median (IQR)	16.0 (9.0-29.8)
Tracheostomy [a]	56 (15.3)
Time interval between hospital discharge and follow-up visit	
3 Months visit, *days,* mean (SD)	95.5 (13.9)
6 Months visit, *days,* mean (SD)	187.0 (15.1)
12 Months visit, *days,* mean (SD)	368.8 (14.7)

Data are presented as n (%), unless indicated. BMI, Body Mass Index; ICU, Intensive Care Unit; LOS, Length Of Stay. [a] Missing values in BMI, n = 37; LOS in ICU, n = 1; Treatment, n = 29, High flow nasal cannula, n = 21; Length of intubation, n = 4, Tracheostomy, n = 4.

Return to work

At 3 months follow-up, 49.7% (170/342) of the study population had not returned to work, which decreased to 29.0% (92/317) at 6 months and 14.9% (44/295) at 12 months. Moreover, 20.8% (71/342) of the participants only partially returned to work at 3 months, 20.5% (65/317) at 6 months, and 16.3% (48/295) at 12 months (Fig. 6.2). Overall, 68.8% (203/295) of the patients fully returned to work after 12 months. Comparing patients who had and those who had not been admitted to the ICU, we found that 30.1% (46/153) of the ICU patients at 3 months, 57.3% (78/136) at 6 months, and 83.6% (102/122) at 12 months returned to work against 66.7% (126/189), 81.2% (147/181), and 86.1% (149/173) of the non-ICU patients, respectively (Fig. 6.3).

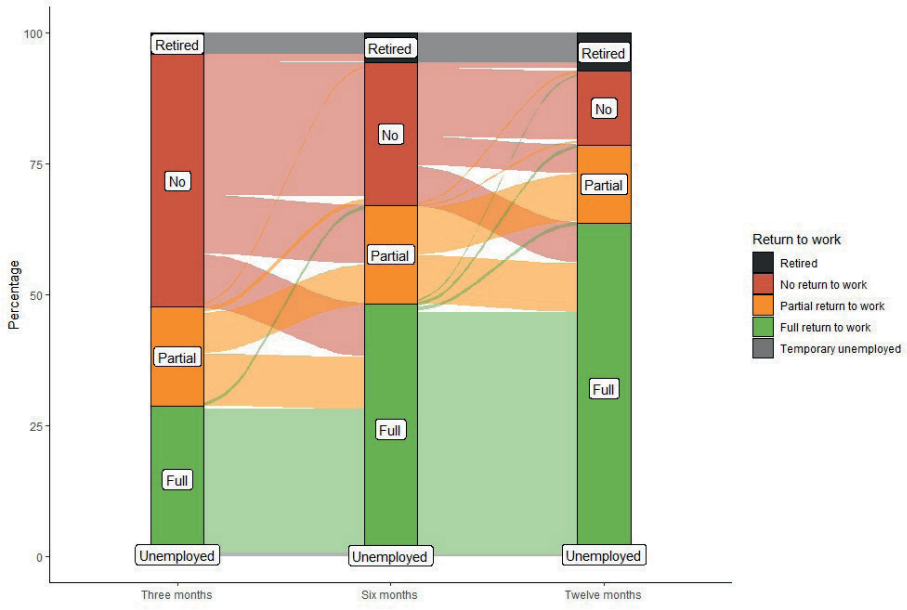


Figure 6.2 Alluvial plot showing changes in employment status (retired, no return to work, partial return to work, full return to work, or temporary unemployed) over follow-up time of patients employed prior to hospitalization for COVID-19.

Figure 6.3 Plots presenting the percentage of non-ICU patients compared to ICU patients who did not return, partially return, or fully returned to work at 3, 6, and 12 months after hospitalization for COVID-19. *ICU, Intensive Care Unit; OR, Odds Ratio; CI, Confidence Intervals.* [a] *Odds ratios are obtained from univariable Generalized Estimating Equations analysis with return to work (partial or full) as dependent variable.*

Results of univariable analyses for return to work (Fig. 6.1A) and full return to work (Supplementary Fig. 6.1B) are presented in the supplementary material.

The multivariable analysis showed that return to work significantly improved over time; patients were more likely to return to work at 6 months (OR (95%CI): 2.10 (1.40 to 3.15), p<0.001) and 12 months (3.13 (1.93 to 5.08), p<0.001) compared to 3 months after hospital discharge. ICU admission (0.17 (0.10 to 0.30), p<0.001), age (0.96 (0.93 to 0.98), p<0.001), sex (0.57 (0.36 to 0.91), p=0.017), and fatigue (0.93 (0.90 to 0.97), p<0.001) remained significantly associated with return to work (Fig. 6.4A). Overall, ICU patients were less likely to return to work (0.17 (0.10 to 0.30), p<0.001) compared with non-ICU patients.

Also, ICU patients required more time to return to work, as they were less likely to return at 3 months (0.17 (0.10 to 0.30), p<0.001), but changing from 3 to 12 months their change in relative odds ratio of return to work (4.04 (1.89 to 8.64), p<0.001)) was higher compared with non-ICU patients (Fig. 6.4A). This finding is also shown

in Fig. 6.3. The same associations were found for full return to work along with a history of cardiovascular disease (Fig. 6.4B).

Health-related quality of life

All domains of the SF-36 improved over time (all domains, $p<0.007$) (Fig. 6.5A, Supplementary Table 6.1 and 6.2). Most limitations were observed in RP, GH, VT, and RE at 1 year compared to the Dutch norm.

Patients who did not return to work reported significantly lower HRQoL on the SF-36 domains PH, RP, SF, BP, and PCS on all follow-up moments compared with patients who did partially or fully ($p<0.05$) (Supplementary Table 6.3). Patients who did not return or partially returned to work reported significantly lower HRQoL on all SF-36 domains, and both PCS and MCS at 3, 6, and 12 months compared with those who fully returned ($p<0.03$) (Fig. 6.5B–D, Supplementary Table 6.4 and 6.5).

Univariable associations for PCS and MCS are presented in Supplementary Fig. 6.2. In multivariable analysis, return to work remained significantly associated with PCS after adjustment for covariables. In addition, female sex, lower educational status, history of obesity, cardiovascular disease, and pulmonary disease, lower STS %pred, and persistent fatigue were negatively associated with PCS (Fig. 6.6A). Return to work was no longer significantly associated with MCS after adjustment for covariables, while persistent fatigue and depression were associated with a lower MCS (Fig. 6.6B).

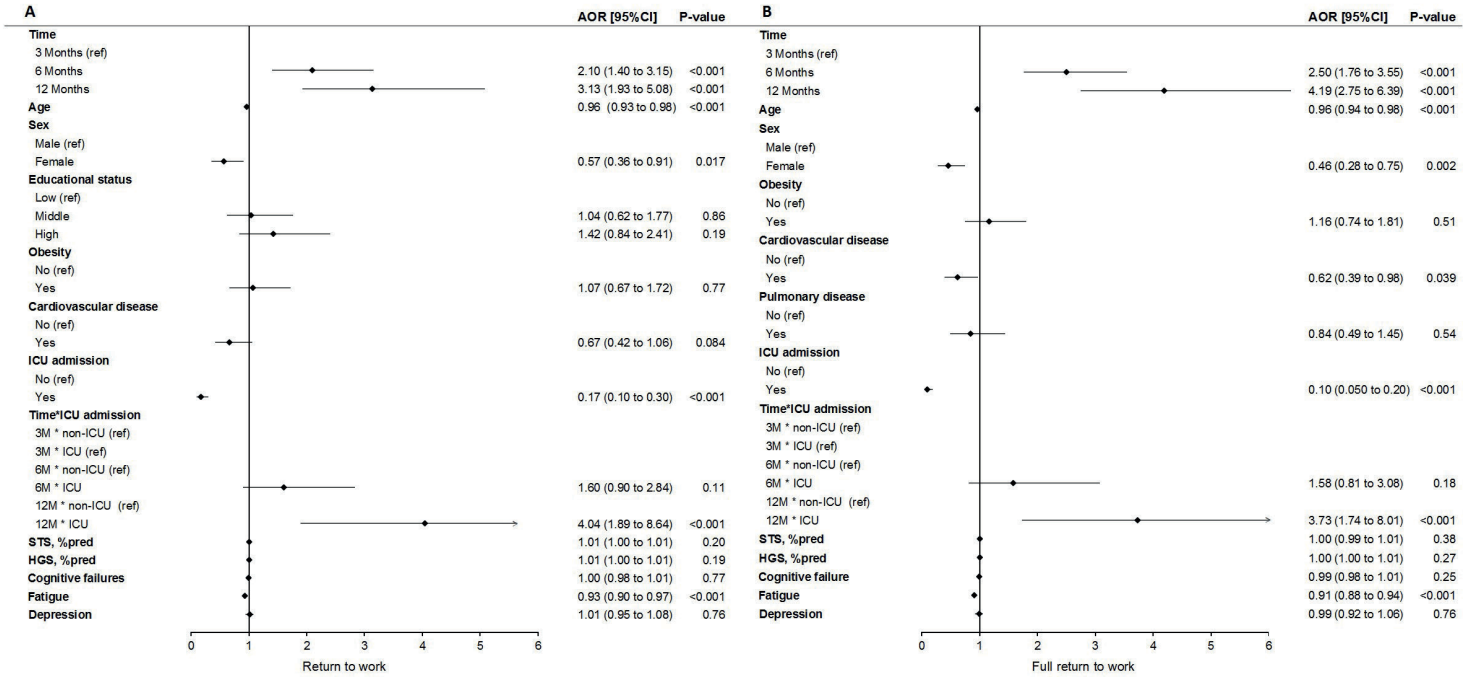


Figure 6.4 Forest plot showing adjusted odds ratios from multivariable analysis of **A** return to work (no versus partial/full) and **B** full return to work (no/partial versus full) up to 1 year after hospitalization for COVID-19. *ICU, Intensive Care Unit; M, Months; STS, Sit-To-Stand; %pred, percentage of normative values; HGS, Handgrip Strength.*

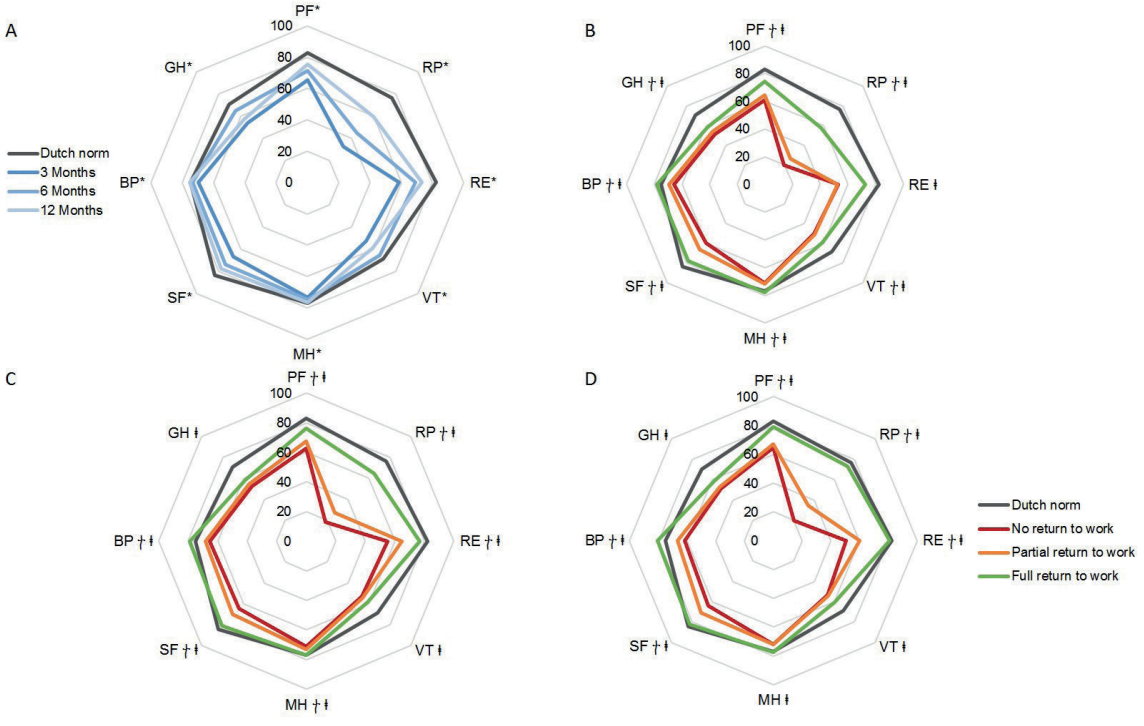


Figure 6.5 Radar plots representing HRQoL on the 8 domains of the SF-36 in the study population compared with the Dutch norm (grey line). **A** *HRQoL on SF-36 domains for the total cohort at 3, 6, and 12 months.* **B–D** *HRQoL on SF-36 domains for participants with no (red line), partial (orange line), or full (green) return to work. In* **B** *the results are shown for 3-month follow up; in* **C** *for 6-month follow-up; and in* **D** *for 12-month follow-up.*
** Significant improvement over time (p<0.007). † = Significant difference in HRQoL between no return to work and partial/full return to work (p<0.05). ǂ = Significant difference between no/partial return to work and full return to work (p<0.03). PF, Physical Functioning; RP, Role limitations due to Physical health; RE, Role limitations due to Emotional problems; VT, Vitality; MH, Mental Health; SF, Social Functioning; BP, Bodily Pain; GH, General Health.*

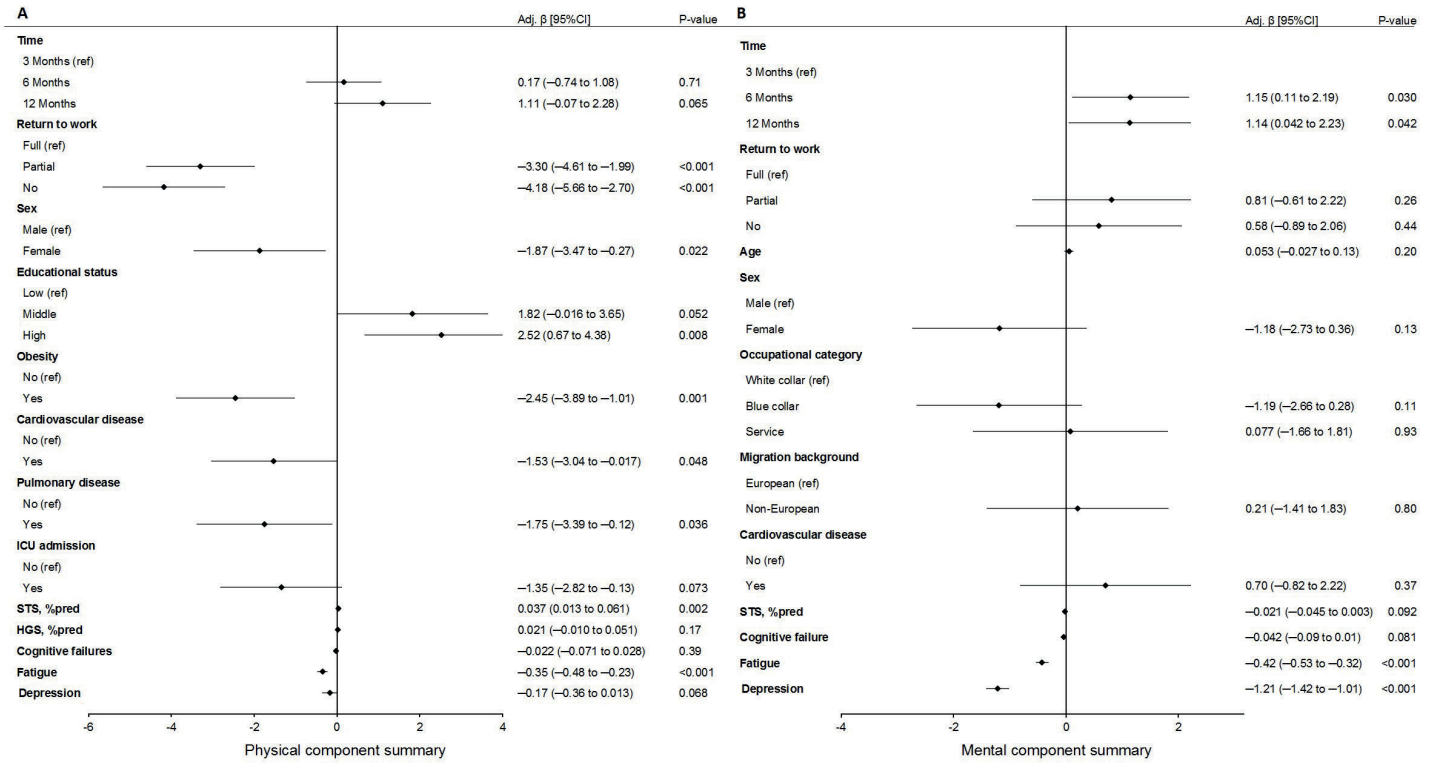


Figure 6.6 Forest plot showing adjusted odds ratios from multivariable analysis of **A** Physical Component Summary and **B** Mental Component Summary up to 1 year after hospitalization for COVID-19. *ICU, Intensive Care Unit; STS, Sit-To-Stand; %pred, percentage of normative values; HGS, Handgrip Strength.*

DISCUSSION

Our study contributes to the limited body of literature and demonstrates the extent of not returning to work up to 1 year post-COVID-19, its risk factors, and its association with HRQoL. Overall, 50% of patients had not yet returned to work at 3 months after hospital discharge, decreasing to 29% at 6 months, and 15% at 12 months. At 12 months, another 16% of patients partially returned to work, resulting in only 69% fully returning to work. We found that differences in percentage in return to work at 3 months were no longer observed at 12 months between ICU and non-ICU patients, indicating that ICU patients required a longer time to return to work compared with non-ICU patients. Besides patients treated in ICU, those with fatigue, female sex, and older age were less likely to return to work. In addition to these factors, patients with a history of cardiovascular disease were less likely to fully return to work. We also showed that patients who did not return or partially returned to work had worse HRQoL in all domains at all follow-up moments compared with those who fully returned. Return to work was independently associated with PCS, but not with MCS.

The proportions of patients without ICU admission not returning to work, i.e., 33% and 19% at 3 and 6 months, respectively, align with other studies in hospitalized patients.[33,9] Also, the proportions of those with ICU admission not returning to work at 3 and 6 months, 70% (107/153) and 43% (58/136), respectively, are similar to results of a Dutch post-ICU COVID-19 study (43%),[34] but somewhat higher than those of an Italian study (22%),[13] probably due to the small sample size of the latter or potential differences in ICU admission criteria, healthcare system, or labor market. Our study, along with others, has shown that ICU patients required more time to return to work compared with non-ICU patients.[9,5,33] Possibly, the post-intensive care syndrome (PICS), which refers to new or worsening physical, mental, and cognitive impairments in ICU survivors, complicates return to work.[35] A meta-analysis in PICS patients showed that 40% of patients did not return to work 12 months after ICU admission,[36] similar to our findings in patients with COVID-19 who were treated in the ICU. A potential intervention to prevent PICS is early mobilization with physical and occupational therapy during ICU admission, which has also been shown to reduce duration of delirium, length of ICU and hospital stay and mitigate long-term cognitive impairments.[37-39] To prevent PICS, which could in turn improve return to work and HRQoL, greater emphasis on rehabilitation during the early stages of ICU admission for COVID-19 could be recommended.[40,36]

Other effective interventions for improving return to work and HRQoL among individuals with chronic diseases and mental health conditions encompassed a multidisciplinary approach that addresses person-level components, such as symptom coping mechanisms, skills training, and goal establishment, and work-directed interventions involving adaption and evaluation of working task, schedule, and environment. These strategies, proven effective in previous contexts, hold promise for potential applicability among patients recovering from COVID-19.[41-44]

Other studies on patients hospitalized for COVID-19 and on non-COVID-19 severe acute respiratory syndrome survivors showed that 12–18% and 17%, respectively, of patients did not return to work at 12 months comparable to our findings.[45,4,46] We also found that 19% (48/251) of patients who returned to work at 12 months worked less hours than pre-hospitalization; Huang et al. reported an even higher proportion of 24%.[4] These findings suggest that COVID-19 could hinder patients' ability to perform at pre-hospitalization levels for up to 12 months after discharge.

People who did not return or partially returned to work reported a significantly lower HRQoL compared with those who fully returned, which is in agreement with the literature,[13,7] although the direction of this association is unknown. Return to work was independently associated with PCS, but not with MCS. This could be due to the emphasis on work performance in the physical domains of the SF-36, which are more heavily weighed in PCS. Other factors independently associated with PCS were a history of obesity, cardiovascular and pulmonary disease, female sex, persistent fatigue, and lower physical fitness. MCS was associated with depression and persistent fatigue.

Persistent fatigue was independently associated with return to work and HRQoL, consistent with other studies,[47,9,48] and reflecting the most common post-COVID-19 symptom.[2,49] Post-COVID-19 fatigue is a multidimensional construct, affecting patients' physical and mental health, and remains poorly understood.[50,51] Post-COVID-19 fatigue is associated with shortness of breath, psychological distress, cognitive impairment, depression, and anxiety.[52-54] Treatment options, e.g., vocational rehabilitation programs that focus on energy management and pacing could be beneficial to manage fatigue.[55-57] Moreover, physical rehabilitation could help improve physical fitness, and cognitive and psychological support could provide symptom relief. These interventions could promote successful return to work and improve HRQoL. Overall, further research into post-COVID-19 fatigue is essential to develop effective treatment options.

Our study has some limitations. Isolation measures while recovering from COVID-19 and the anxiety for the consequences of COVID-19 could have had a negative impact on HRQoL. The data collection period coincided with two national lockdowns, which may have influenced HRQoL due to restrictions on social contact, travel, and leisure independent of previous infection; thus, comparing with the Dutch norm of the SF-36 might not be appropriate. We did not collect data on changes in job responsibilities, limitations in work performance upon return to work, or the main reason for not returning to work. Job changes were not observed within 1 year, except for one patient. Moreover, we studied occupational categories, but did not find an effect on return to work. Lastly, although non-responders were younger, they were more frequently admitted to the ICU; therefore, it is hard to discern the effect on our results.

Strengths of our study include the recruitment of participants from academic and regional hospitals. This enabled us to include individuals with varying degrees of disease severity, which increases the external validity of the findings. Given the significant proportion of ICU patients, we were able to compare the ICU versus non-ICU patients within our cohort and with other ICU cohorts. Our findings may guide the development of rehabilitation programs tailored to the needs required for return to work. Additionally, the prospective design of our study with multiple follow-up time points enabled us to evaluate recovery up to 1 year. Finally, we used validated questionnaires to assess fatigue, cognitive, and psychological symptoms and objectively assessed the physical status. To our knowledge, this is the first comprehensive prospective cohort study to investigate the association between return to work and baseline characteristics and physical and mental recovery up to 1 year.

CONCLUSIONS

All in all, 15% of patients did not return and 16% partially returned to work, leaving only 69% who fully returned to work 1 year after hospitalization for COVID-19. ICU admission, persistent fatigue, female sex, and older age were independently associated with return to work. Patients who did not return or partially returned to work reported lower HRQoL. More research is required to identify effective therapies for the long-term consequences of COVID-19, including vocational support and support for fatigue and physical, cognitive, and psychological symptoms.

REFERENCES

1. Comelli A, Viero G, Bettini G, et al. Patient-Reported Symptoms and Sequelae 12 Months After COVID-19 in Hospitalized Adults: A Multicenter Long-Term Follow-Up Study. *Front Med (Lausanne)*. 2022;9:834354.
2. Bek LM, Berentschot JC, Heijenbrok-Kal MH, et al. Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *ERJ Open Res*. 2022:00355-2022.
3. Evans RA, Leavy OC, Richardson M, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022;10(8):761-75.
4. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. 2021;398(10302):747-58.
5. Jacobsen PA, Andersen MP, Gislason G, et al. Return to work after COVID-19 infection - A Danish nationwide registry study. *Public Health*. 2022;203:116-22.
6. Gualano MR, Rossi MF, Borrelli I, et al. Returning to work and the impact of post COVID-19 condition: A systematic review. *Work*. 2022.
7. O'Brien K, Townsend L, Dowds J, et al. 1-year quality of life and health-outcomes in patients hospitalised with COVID-19: a longitudinal cohort study. *Respir Res*. 2022;23(1):115.
8. Latronico N, Peli E, Calza S, et al. Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax*. 2022;77(3):300-3.
9. Hürlimann O, Decavel P, Annoni JM, Mancinetti M. Return to work after hospitalisation for COVID-19 infection. *Eur J Intern Med*. 2022;97:110-2.
10. Floderus B, Göransson S, Alexanderson K, Aronsson G. Self-estimated life situation in patients on long-term sick leave. *J Rehabil Med*. 2005;37(5):291-9.
11. Henderson M, Glozier N, Elliott KH. Long term sickness absence. *BMJ*. 2005;330(7495):802-3.
12. Verveen A, Wynberg E, van Willigen HDG, et al. Health-related quality of life among persons with initial mild, moderate, and severe or critical COVID-19 at 1 and 12 months after infection: a prospective cohort study. *BMC Med*. 2022;20(1):422.
13. Carenzo L, Dalla Corte F, Haines RW, et al. Return to Work After Coronavirus Disease 2019 Acute Respiratory Distress Syndrome and Intensive Care Admission: Prospective, Case Series at 6 Months From Hospital Discharge. *Crit Care Med*. 2021;49(11):e1157-e62.
14. Ma Y, Deng J, Liu Q, et al. Long-Term Consequences of COVID-19 at 6 Months and Above: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2022;19(11).
15. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol*. 2022;94(1):253-62.
16. Noujaim PJ, Jolly D, Coutureau C, Kanagaratnam L. Fatigue and quality-of-life in the year following SARS-Cov2 infection. *BMC Infect Dis*. 2022;22(1):541.
17. Bek LM, Berentschot JC, Hellemons ME, et al. 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 2years after hospital discharge. *BMC Health Serv Res*. 2021;21(1):847.
18. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-8.
19. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.
20. Pamuk E MD, Heck K, Reuben C, Lochner K. Socioeconomic Status and Health Chartbook. Health, 1998, United States. Hyattsville, Maryland: National Center for Health Statistics. 1998.
21. Post MW, van der Zee CH, Hennink J, et al. Validity of the utrecht scale for evaluation of rehabilitation-participation. *Disabil Rehabil*. 2012;34(6):478-85.
22. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055-68.
23. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.
24. Ware JE, New England Medical Center Hospital Health I. SF-36 physical and mental health summary scales : a user's manual. Boston: Health Institute, New England Medical Center Boston; 1994.

25. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158(5):1384-7.
26. Strassmann A, Steurer-Stey C, Dalla Lana K, et al. Population-based reference values for the 1-min sit-to-stand test. *Int J Public Health*. 2013;58(6):949-53.
27. Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: normative data from twelve British studies. *PloS One*. 2014;9(12):e113637.
28. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16.
29. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. *J Psychosom Res*. 2003;54(4):345-52.
30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-70.
31. Wilson JP, Keane TM, Weiss DS, Marmar CR. Assessing psychological trauma and PTSD: The Guilford Press.; 1997. 399-411 p.
32. Berentschot JC, Heijenbrok-Kal MH, Bek LM, et al. Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW). *Lancet Reg Health Eur*. 2022;22:100485.
33. Sanchez-Ramirez DC, Normand K, Zhaoyun Y, Torres-Castro R. Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. *Biomedicines*. 2021;9(8).
34. van Veenendaal N, van der Meulen IC, Onrust M, et al. Six-Month Outcomes in COVID-19 ICU Patients and Their Family Members: A Prospective Cohort Study. *Healthcare (Basel)*. 2021;9(7).
35. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-9.
36. Kamdar BB, Suri R, Suchyta MR, et al. Return to work after critical illness: a systematic review and meta-analysis. *Thorax*. 2020;75(1):17-27.
37. Fuke R, Hifumi T, Kondo Y, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ Open*. 2018;8(5):e019998.
38. Patel BK, Wolfe KS, Patel SB, et al. Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial. *Lancet Respir Med*. 2023.
39. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *The Lancet*. 2009;373(9678):1874-82.
40. Hsieh SJ, Otusanya O, Gershengorn HB, et al. Staged Implementation of Awakening and Breathing, Coordination, Delirium Monitoring and Management, and Early Mobilization Bundle Improves Patient Outcomes and Reduces Hospital Costs. *Crit Care Med*. 2019;47(7):885-93.
41. Edgelow M, Harrison L, Miceli M, Cramm H. Occupational therapy return to work interventions for persons with trauma and stress-related mental health conditions: A scoping review. *Work*. 2020;65(4):821-36.
42. Nazarov S, Manuwald U, Leonardi M, et al. Chronic Diseases and Employment: Which Interventions Support the Maintenance of Work and Return to Work among Workers with Chronic Illnesses? A Systematic Review. *Int J Environ Res Public Health*. 2019;16(10).
43. Vooijs M, Leensen MC, Hoving JL, et al. Interventions to enhance work participation of workers with a chronic disease: a systematic review of reviews. *Occup Environ Med*. 2015;72(11):820-6.
44. Wegrzynek PA, Wainwright E, Ravalier J. Return to work interventions for chronic pain: a systematic review. *Occup Med (Lond)*. 2020;70(4):268-77.
45. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med*. 2021;9(11):1275-87.
46. Tansey CM, Louie M, Loeb M, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Arch Intern Med*. 2007;167(12):1312-20.
47. Heightman M, Prashar J, Hillman TE, et al. Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. *BMJ Open Respir Res*. 2021;8(1).

48. Seeßle J, Waterboer T, Hippchen T, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. *Clin Infect Dis*. 2021;74(7):1191-8.
49. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863-76.
50. Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and Post-infective Fatigue Syndrome: A Review. *Open Forum Infect Dis*. 2021;8(10):ofab440.
51. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784.
52. Carfì A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020;324(6):603-5.
53. Gaber T. Assessment and management of post-COVID fatigue. *Prog Neurol Psychiatry*. 2021;25(1):36-9.
54. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol*. 2021;93(2):1013-22.
55. Fowler-Davis S, Platts K, Thelwell M, et al. A mixed-methods systematic review of post-viral fatigue interventions: Are there lessons for long Covid? *PLoS One*. 2021;16(11):e0259533.
56. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. 2006;333(7568):575.
57. O'Boyle S, Nacul L, Nacul FE, et al. A Natural History of Disease Framework for Improving the Prevention, Management, and Research on Post-viral Fatigue Syndrome and Other Forms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Med (Lausanne)*. 2021;8:688159.



CHAPTER 7

Not disease severity but other risk factors more consistently predict long-term multidimensional patient-centered outcomes after hospitalization for COVID-19

L. Martine Bek
Yasemin Türk
Matthijs L. Janssen
Gemma Weijsters
Julia C. Berentschot
Rita J.G. van den Berg-Emons
Majanka H. Heijenbrok-Kal
Gerard M. Ribbers
Joachim G.J.V. Aerts
Wessel E.J.J. Hanselaar
Henrik Endeman
Merel E. Hellemons
Evert-Jan Wils
on behalf of the CO-FLOW Collaboration group*** and Dutch HFNO COVID-19 study group****

*** Listed in Appendix
****Study group listed at the end of this chapter

BMJ Open Respiratory Research. (under review)

ABSTRACT

Objectives To investigate the association between COVID-19 disease severity during hospitalization for COVID-19, and long-term multidimensional patient-centered outcomes up to 12 months post-hospitalization. Secondary objective was to identify other risk factors for these long-term outcomes.

Methods In this multicenter prospective cohort study we categorized COVID-19 disease severity using the maximal level of respiratory support as proxy into 1] conventional oxygen therapy (COT), 2] high-flow nasal oxygen (HFNO), and 3] invasive mechanical ventilation (IMV). The primary outcome health-related quality of life (HRQoL), and the secondary outcomes self-reported symptoms and recovery were collected at 6 and 12 months post-hospitalization.

Results Data from 777 patients were analyzed, with 226(29%) receiving COT, 273(35%) HFNO, and 278 (36%) IMV. Patients reported impaired HRQoL, persistence of symptoms, and poor recovery. Multivariable generalized estimating equations analysis showed that COVID-19 disease severity was not associated with HRQoL and inconsistently with symptoms; HFNO group reported poorer recovery. Overall, female sex, younger age, and pulmonary history were independent risk factors for outcomes.

Conclusions COVID-19 disease severity was associated with self-perceived recovery, but not with HRQoL and inconsistently with symptoms. Our findings suggest that age, sex, and pulmonary history are more consistent risk factors for long-term multidimensional outcomes and offer better guidance for aftercare strategies.

INTRODUCTION

Hypoxemia and respiratory failure are the primary reasons for hospitalization in patients with COVID-19.[1] Depending on the severity of hypoxemia, oxygen therapy can range from low-flow nasal oxygen or oxygen masks to non-invasive respiratory support modalities (high-flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIV)), or even invasive mechanical ventilation (IMV).[2]

After hospitalization, patients frequently report long-term health problems,[3,4] known as post-COVID-19 condition (PCC) or "Long COVID".[5] These problems include a reduced health-related quality of life (HRQoL), persistence of symptoms, and incomplete self-perceived recovery.[4,6,7] Half of the patients with mild disease and up to 90% of people with moderate and severe disease continue to experience at least one ongoing symptom 1 year after disease onset.[4,7-10] Hospitalized patients requiring oxygen more frequently suffer from a reduced HRQoL and from symptoms compared to those with milder disease severity and those without hospitalization.[4,6,7,11-13] However, the association between COVID-19 disease severity and long-term outcomes in hospitalized patients requiring oxygen is uncertain. A more granular understanding of this association may help to guide, prioritize, and optimize treatment and aftercare strategies.

We hypothesized that long-term patient-centered outcomes are related to disease severity. Therefore, we assessed the association between the maximal level of respiratory support received during hospitalization, as a proxy for COVID-19 disease severity, and long-term multidimensional patient-centered outcomes (HRQoL, symptoms, and recovery) up to 12 months in patients hospitalized for COVID-19 requiring oxygen therapy. We further aimed to identify other risk factors for these long-term outcomes.

MATERIAL AND METHODS

Study design

Data from two multicenter prospective cohort studies conducted at 13 healthcare institutions in the Netherlands were combined: The Dutch HFNO COVID-19 study with trial register no. NL9067 and the COvid-19 Follow-up care paths and Long-term Outcomes Within the Dutch healthcare system (CO-FLOW) study with trial register no. NL8710 (both registered on the WHO ICTRP).

The study has been carried out in accordance with the Helsinki Declaration for medical research involving humans. Both studies were approved by the local Institutional Review Board (MEC-U AW21.015/W20.283 on Nov 25, 2020 (HFNO COVID-19 study) and 2020-098, MEC-2020-0487 on June 23, 2020 (CO-FLOW study). Details of the HFNO COVID-19 study and the CO-FLOW study have been described previously.[14,15] We reported this observational study according to STROBE guidelines; the STROBE checklist is provided in the supplemental material.

Participants

Eligible participants were hospitalized adults with confirmed COVID-19 infection who received treatment with conventional oxygen therapy (COT), high-flow nasal oxygen (HFNO), and/or invasive mechanical ventilation (IMV), and survived to hospital discharge. We excluded patients treated with NIV (n=18) as maximal level of respiratory support, as NIV was rarely applied in participating centers. All participants provided informed consent before data collection.

Data collection

Demographics and clinical characteristics were collected in both cohorts according to their respective study protocols previously (Supplementary Table 7.1).[14,15] Data were collected during study visits, from medical records, and via patient-reported outcomes measures sent via mail or postal mail.

Participants of the HFNO COVID-19 study admitted between 1 December 2020 and 31 March 2021 received questionnaires 12 months after discharge and participants admitted between 1 April 2021 and 30 June 2021 received questionnaires 6 months after discharge. Participants of the CO-FLOW study included between 1 July 2020 until 1 September 2021 received questionnaires at 6 and 12 months after hospital discharge. Data were stored in Castor Electronic Data Capture System (Castor EDC, Amsterdam, The Netherlands).

Outcomes

The primary outcome was health-related quality of life (HRQoL) as measured with the EuroQol Group five level, five-dimension descriptive system (EQ-5D-5L), consisting of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).[16] The EQ-5D-5L utility score was calculated according to the Dutch tariff for the EQ-5D-5L ranging from 0 (death) to 1 (best health possible). The mean (standard deviation, SD) Dutch references value for the general

population is 0.87 (0.17) and median value (interquartile ranges, IQR) is 0.89 (0.82-1.00).[17] The EQ-VAS records the participant self-rated health through a visual analogue scale ranging from 0 (worst imaginable health) to 100 (best health), to assess subjective general health. The mean (SD) Dutch reference value is 80.6 (14.7) and median value (IQR) is 81.0 (72.0-90.0).

Secondary outcomes were self-reported COVID-19 symptoms and self-reported recovery status. Symptoms were measured with the Corona Symptom Checklist that has been developed within the CO-FLOW study to assess newly developed or worsened symptoms since the onset of COVID-19 with "yes" or "no" as answer options.[14,18] Recovery status was assessed via the Core Outcome Measure for Recovery of COVID-19 using a 5-point Likert scale ranging from "not recovery at all" to "completely recovered".[19]

Data analysis

Data were analyzed from participants from whom data on the primary outcome of interest was available at one of the follow-up moments. Data were presented as mean (SD) and/or median (IQR), as applicable, for continuous variables and as number with percentage (%) for categorical variables. Participants were categorized into three groups according to their maximal level of respiratory support received during hospitalization, in line with the WHO clinical progression scale: ≤15 L/minute of conventional oxygen therapy (COT group, WHO score 5); high-flow nasal oxygen (HFNO group, WHO score 6), and invasive mechanical ventilation (IMV group, WHO score 7-9). We used the Kruskal-Wallis test and Chi-square test for group comparisons.

We used univariable linear generalized estimating equations (GEE) to investigate the association between maximal level of respiratory support and HRQoL, i.e., EQ-5D-5L utility and EQ-VAS score at 6 and 12 months, respectively. Second, we used multivariable linear GEE analysis with clinically important characteristics[4,20] (Supplementary Table 7.1) to identify additional risk factors for HRQoL. A priori, we had determined that the maximal level of respiratory support should be kept in all models irrespective of statistical significance.

We categorized self-reported symptoms into four clusters: physical, respiratory, fatigue, and cognitive symptom cluster as done previously.[18] Self-reported recovery was classified into good recovery (mostly and completely recovered) and poor recovery (not, somewhat, and half recovered).

Similarly, binary GEE analyses were performed for persistence of symptoms and recovery. We did an exploratory analysis with duration of HFNO treatment and respiratory and fatigue symptoms and recovery. A P-value <0.05 was considered statistically significant. Models are presented as forest plots with adjusted β or adjusted odds ratios (AORs), 95% CI, and P-values. Analyses were performed using SPSS Statistics 28, version 28 (IBM SPSS Statistics, SPSS Inc., Chicago, IL, USA).

RESULTS

Cohort characteristics

A total of 1036 participants were invited for long-term follow-up evaluation between January 2021 and April 2022, 725 patients at 6 months and 854 at 12 months; 555 participants from the CO-FLOW study and 481 of the HFNO COVID-19 study (Supplementary Fig. 7.1). At 6 months, 497 (68.6%) participants completed the EQ-5D-5L questionnaire and 620 (72.6%) participants at 12 months. Patient characteristics (BMI, respiratory support, ICU admission, and hospital LOS) differed between non-responders and responders at 6 months, but not at 12 months (Supplementary Table 7.2). Clinically relevant differences in baseline characteristics were not present between the participants evaluated at 6 and 12 months (Supplementary Table 7.3). The current analysis included 777 participants in whom the primary outcome was available at one of the follow-up moments. Of those, 226 (29.1%) received COT, 273 (35.1%) HFNO, and 278 (35.8%) IMV as maximal level of respiratory support. Detailed characteristics of participants are shown in Table 7.1.

Table 7.1 *Baseline characteristics of the full cohort and split by the maximal level of respiratory support.*

	Full cohort	COT	HFNO	IMV	P-value
N	777	226 (29.1)	273 (35.1)	278 (35.8)	
Demographics					
Sex, *female*	241 (31.0)	80 (35.4)	92 (33.7)	69 (24.8)	0.019
Age at admission, *years*	60.0 (53.0-67.0)	61.0 (54.0-68.0)	60.0 (53.0-67.0)	60.0 (54.0-67.3)	0.601
BMI at admission, *kg/m²*[a]	28.5 (25.9-32.3)	27.5 (25.2-31.0)	28.5 (25.8-32.2)	29.4 (26.6-33.5)	<0.001
Physical activity level[a]					0.109
Physically inactive	119 (15.5)	32 (14.3)	51 (18.8)	36 (13.1)	
Light physical activity	410 (53.3)	115 (51.6)	136 (50.0)	159 (58.0)	
Regular physical activity and training	203 (26.4)	60 (26.9)	77 (28.3)	66 (24.1)	
Regular hard physical training for competitive sports	37 (4.8)	16 (7.2)	8 (2.9)	13 (4.7)	
Smoking status, *ex-/current*[a]	355 (49.9)	126 (56.2)	97 (42.7)	132 (50.8)	0.015
Clinical characteristics					
Medical history					
≥1	589 (75.8)	163 (72.1)	202 (74.0)	224 (80.6)	0.059
Obesity (BMI≥30)	296 (39.7)	72 (31.9)	95 (39.3)	129 (46.6)	0.004
Cardiovascular disease	305 (39.3)	86 (38.1)	101 (37.0)	118 (42.4)	0.390
Pulmonary disease	181 (23.3)	52 (23.0)	68 (24.9)	61 (21.9)	0.712
Diabetes	156 (20.1)	40 (17.7)	59 (21.6)	57 (20.5)	0.550
CRP, *mg/L*[a]	103.0 (56.0-165.0)	69.0 (39.3-114.8)	112.0 (68.0-172.8)	125.0 (69.0-195.0)	<0.001
Creatinine, *umol/L*[a]	83.0 (69.0-100.0)	79.0 (65.0-94.5)	80.0 (66.5-94.0)	88.0 (75.0-110.5)	<0.001
Pharmaceutical treatment during admission[b]					
No specific treatment	93 (12.0)	48 (21.2)	3 (1.1)	42 (24.6)	0.003
Antivirals	74 (9.5)	47 (20.8)	14 (5.1)	13 (4.7)	<0.001[c]

Table 7.1 *Continued*

	Full cohort	COT	HFNO	IMV	P-value
Steroids	655 (84.3)	166 (73.5)	266 (97.4)	223 (80.2)	<0.001[c]
Anti-inflammatory	239 (30.8)	2 (0.9)	122 (44.7)	115 (41.4)	<0.001[c]
HFNO	470 (60.5)	0 (0)	273 (100)	197 (70.9)	<0.001
Duration of HFNO, *days*		NA	5.0 (3.0-7.0)	1.0 (1.0-3.0)	<0.001
ICU admission	380 (48.9)	6 (2.7)	96 (35.2)	278 (100)	<0.001
ICU LOS, *days*	11.0 (6.0-25.0)	2.0 (0.0-6.5)	3.5 (2.0-6.0)	16.0 (10.0-30.0)	<0.001
Length of IMV, *days*		NA	NA	12.0 (7.0-24.0)	NA
Post-discharge care[a]					<0.001
No or community-based rehabilitation	521 (72.9)	217 (96.0)	213 (88.4)	91 (36.7)	
Medical rehabilitation	97 (13.6)	1 (0.4)	7 (2.9)	89 (35.9)	
Skilled nursing rehabilitation	97 (13.6)	8 (3.5)	21 (8.7)	68 (27.4)	
Hospital LOS, *days*[a]	13.0 (8.0-26.0)	6.0 (4.0-10.3)	11.0 (11.0-15.0)	32.0 (20.0-46.0)	<0.001
Time interval between hospital discharge and follow-up visit					
6 Months visit, *months*	6.0 (6.0-7.0)	6.0 (6.0-6.0)	7.0 (6.0-8.0)	7.0 (6.0-7.0)	
12 Months visit, *months*	12.0 (12.0-13.0)	12.0 (12.0-12.0)	12.0 (11.0-12.0)	12.0 (12.0-13.0)	

Data are presented as median (interquartile range) or n (%). P-value is obtained using Kruskal-Wallis test, or Chi-squared test as appropriate. COT, Conservative Oxygen Therapy; HFNO, High Flow Nasal Oxygen; IMV, Invasive Mechanical Ventilation; BMI, Body Mass Index; CRP, C-Reactive Protein; ICU, Intensive Care Unit; LOS, Length of Stay; NA, Not Applicable.

[a]Missing values (n(%)) in BMI at admission, n=72 (9.3%); Pre-COVID smoking status, n=66 (8.5%); Pre-COVID physical activity level, n=8 (1.0%); Creatinine at admission, n=18 (2.3%); CRP at admission, n=19 (2.4%); LOS hospital, n=4 (0.5%); post-discharge care, n=62 (8.0).

[b]Treatment strategies during hospitalization varied between the CO-FLOW study and HFNO COVID-19 study related to the different inclusion periods. The distribution (n(%)) is as follows: CO-FLOW vs. HFNO COVID-19: No treatment: n=97 (21.1%) vs. n=3 (0.9%); Antivirals: n=64 (13.9%) vs. n=10 (3.2%); Steroids: n=341 (74.1%) vs. n=314 (99.1%); Anti-inflammatory: n=59 (12.8%) vs. n=180 (56.8%).

[c]COT groups received most often antiviral treatment, but less often anti-inflammatory treatment, HFNO group received most often treatment with steroids

Disease severity and HRQoL

We first assessed the association between the maximal level of respiratory support for HRQoL at 6- and 12-month follow-up (Fig. 7.1). The EQ-5D-5L utility score did not differ significantly between the COT, HFNO, and IMV groups at both 6 and 12 months. Similarly, EQ-VAS did not differ significantly between respiratory support groups at 6 and 12 months. The median EQ-5D-5L utility score was 0.85 (0.70-0.92) at 6 months and 0.85 (0.72-1.00) at 12 months (Supplementary Table 7.4). The median EQ-VAS for the total cohort was 75.0 (61.0-86.5) at 6 months and 75.0 (63.0-85.0) at 12 months (Supplementary Table 7.4). Both median EQ-5D-5L utility and EQ-VAS score were at 6 and 12 months significantly lower than the Dutch reference value ($p<0.001$). EQ-5D domains split by respiratory support group are shown in Supplementary Table 7.5 and Supplementary Table 7.6.

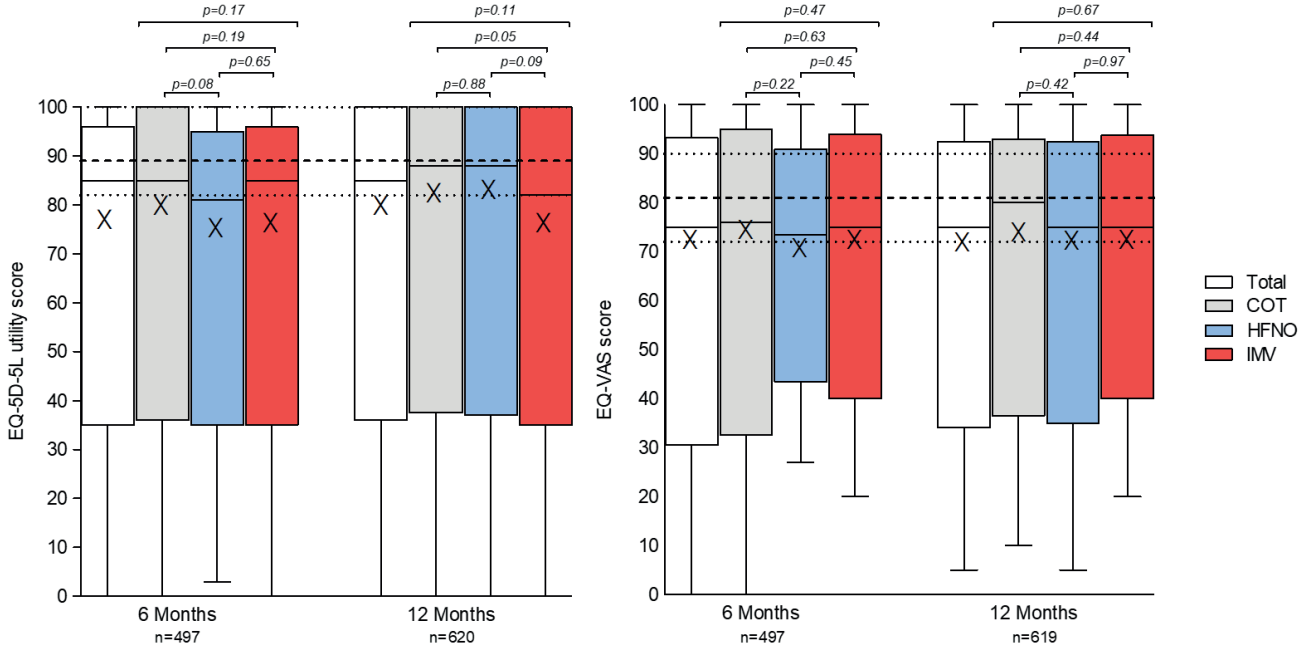


Figure 7.1 Health-related quality of life for different maximum level of respiratory support at 6 and 12 months after hospital discharge.
Boxplots showing distribution of health-related quality of life; A] EQ-5D-5L utility score and B] EQ-VAS at 6 and 12 months for the total cohort and for each level of respiratory support (COT, HFNO, or IMV). Boxplots displaying mean, median, interquartile range, and range. A box shows the upper and lower quartiles with the inside of the box indicating the interquartile range; the midline signifies the median; the whisker indicates the range with minimum and maximum values. The symbol X represents the mean. Dotted lines indicate the references value of the Dutch population as median with interquartile ranges. EQ-5D-5L, EuroQol Group five level, five-dimension descriptive system; EQ-VAS, EQ visual analogue scale; COT, Conventional Oxygen Therapy; HFNO, High Flow Nasal Oxygen; IMV, Invasive Mechanical Ventilation.

Risk factors of HRQoL

Using multivariable GEE analysis we identified female sex, physical inactivity prior to infection, pulmonary history as risk factors for lower EQ-5D-5L utility score at 6 months (Fig. 7.2). Participants who were female, were younger, had a cardiovascular history, and pulmonary history had a lower EQ-5D-5L utility score at 12 months.

Participants who were female, were younger, and were physically inactive prior to infection had a lower EQ-VAS score at 6 months. These risk factors together with an ex-/current smoking status, cardiovascular history, and pulmonary history were associated with a lower EQ-VAS score at 12 months.

Disease severity and symptoms

At 6 months, 503 participants (64.7%) experienced symptoms in ≥1 of the symptom clusters and at 12 months 587 (75.5%) participants. Of all symptom clusters, symptoms from the physical cluster were most prevalent at 6 and 12 months (91.0% and 87.7%, respectively) (Supplementary Table 7.7).

We assessed the role of maximal level of respiratory support on the persistence of symptoms. The HFNO group was more likely to experience respiratory symptoms compared with the COT (AOR: 2.6 (95%CI: 1.6 to 4.2), p<0.001) and IMV group (2.3 (1.4 to 3.6), p<0.001) at 6 months, but not at 12 months. At 12 months, the IMV group was at increased risk for physical symptoms compared with the COT group (2.5 (1.4 to 4.7), p=0.003), and the HFNO group had a higher risk for fatigue symptoms compared with the COT group (1.9 (1.3 to 2.8), p=0.002).

Risk factors of symptoms

We further identified potential risk factors for persistence of symptom using multivariable GEE analysis (Fig. 7.3 and Supplementary Fig. 7.2). Female sex was the only risk factor for physical symptoms at 6 months (Fig. 7.3A). The HFNO group was more likely to experience respiratory symptoms compared with the COT (AOR: 2.4 (95% CI: 1.3 to 4.2), p=0.003) and IMV groups (1.8 (1.0 to 3.1), p=0.04) (Fig. 7.3C). Other risk factors for respiratory symptoms were female sex and receiving steroid or anti-inflammatory treatment. Risk factors for fatigue symptoms were female sex, pulmonary history, and receiving steroid or anti-inflammatory treatment (Supplementary Fig. 7.2A). Cognitive symptoms were associated with female sex, younger age, and pulmonary history (Supplementary Fig. 7.2C).

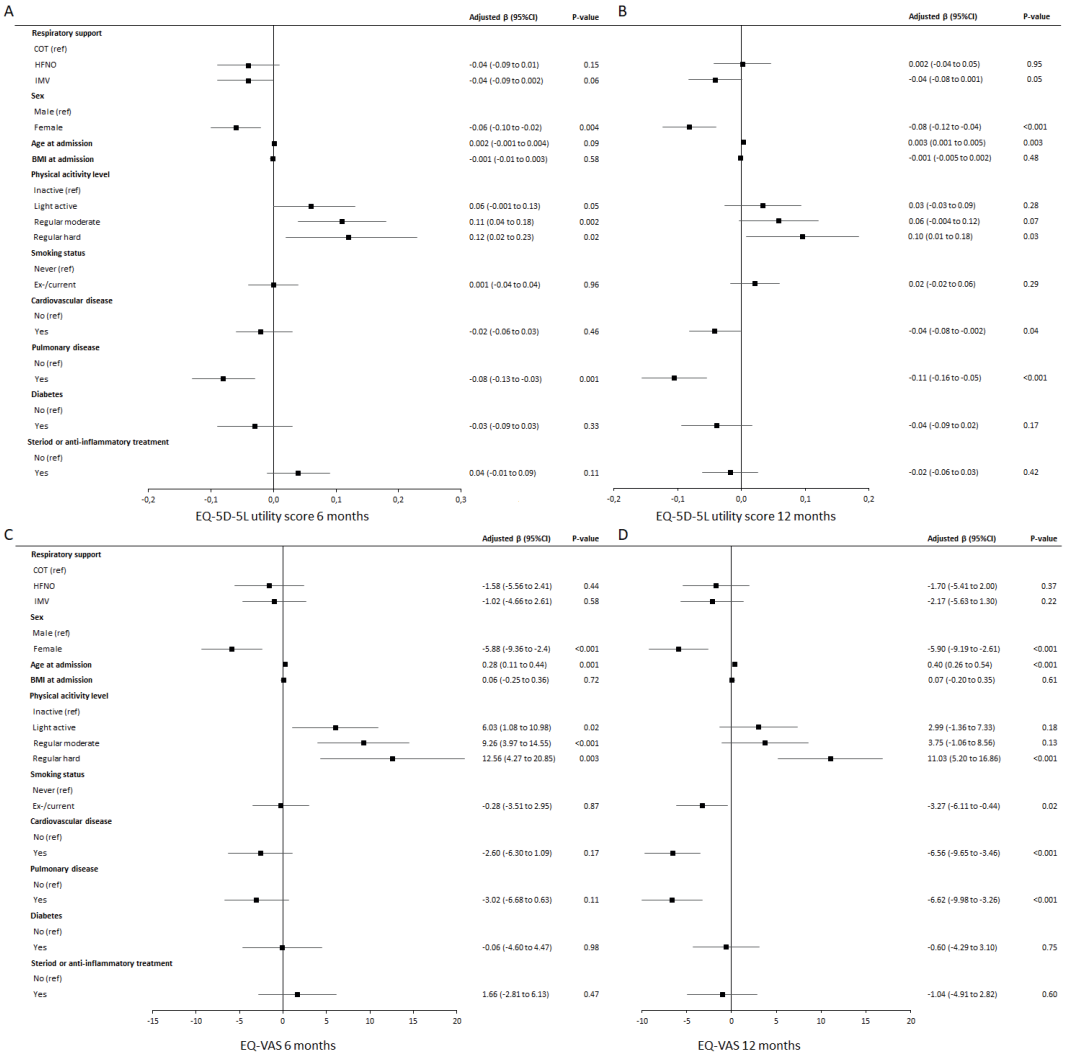


Figure 7.2 Health-related quality of life and its risk factors at 6 and 12 months after hospital discharge.
Forest plots presenting risk factors for health-related quality of life A] EQ-5D-5L utility score and B] EQ-VAS at 6 and 12 months after hospitalization for COVID-19. Data are obtained using multivariable linear Generalized Estimating Equations analysis. The EQ-5D-5L utility score was calculated according to the Dutch tariff for the EQ-5D-5L ranging from 0 (death) to 1 (best health possible).[17] The EQ-VAS ranges from 0 (worst imaginable health) to 100 (best health), to assess subjective general health β, Beta/Estimated Mean; CI, Confidence Interval; COT, Conventional Oxygen Therapy; HFNO, High Flow Nasal Oxygen; IMV, Invasive Mechanical Ventilation; BMI, Body Mass Index; VAS, Visual Analogue Scale.

By exploring the univariable association between HFNO treatment duration and respiratory symptoms we observed an association in patients with HFNO as maximal level of respiratory support (n=114) (1.0 (1.0 to 1.2), p=0.04) as well

as in patients treated with HFNO and subsequent IMV (n=198) (1.1 (1.1 to 1.2), p=0.002), at 6 months, but not at 12 months.

At 12 months, the IMV group was more likely to experience physical symptoms compared with the COT group. Other risk factors were female sex, ex-/current smoking status, and pulmonary history (Fig. 7.3B). Risk factors for respiratory symptoms were female sex, ex-/current smoking status, pulmonary history, and receiving steroid or anti-inflammatory treatment (Fig. 7.3D). The HFNO and IMV groups were more likely to experience fatigue symptoms compared with the COT group, but there was no association with duration of HFNO therapy (Supplementary Fig. 7.2B). Other risk factors for respiratory symptoms were female sex, younger age, and pulmonary history. Female sex was the only risk factor for cognitive symptoms (Supplementary Fig. 7.2D).

Disease severity and recovery

At 6 months, 29% of the participants had a poor self-reported recovery and 25% at 12 months (Supplementary Table 7.8). A higher level of maximal respiratory support was univariably associated with poorer recovery (HFNO vs. COT: 2.4 (1.3 to 4.3), p=0.004; IMV vs. COT: 2.3 (1.3 to 4.1), p=0.005) at 6 months, but not at 12 months.

Risk factors of recovery

Poor recovery at 6 months was more likely in participants receiving HFNO or IMV compared with COT (Fig. 7.4A). At 12 months, in the multivariable analysis, the HFNO group was more likely to report poor recovery compared to the COT group, but duration of HFNO treatment was not associated with recovery. Other risk factors for poor recovery were female sex and pulmonary history (Fig. 7.4B).

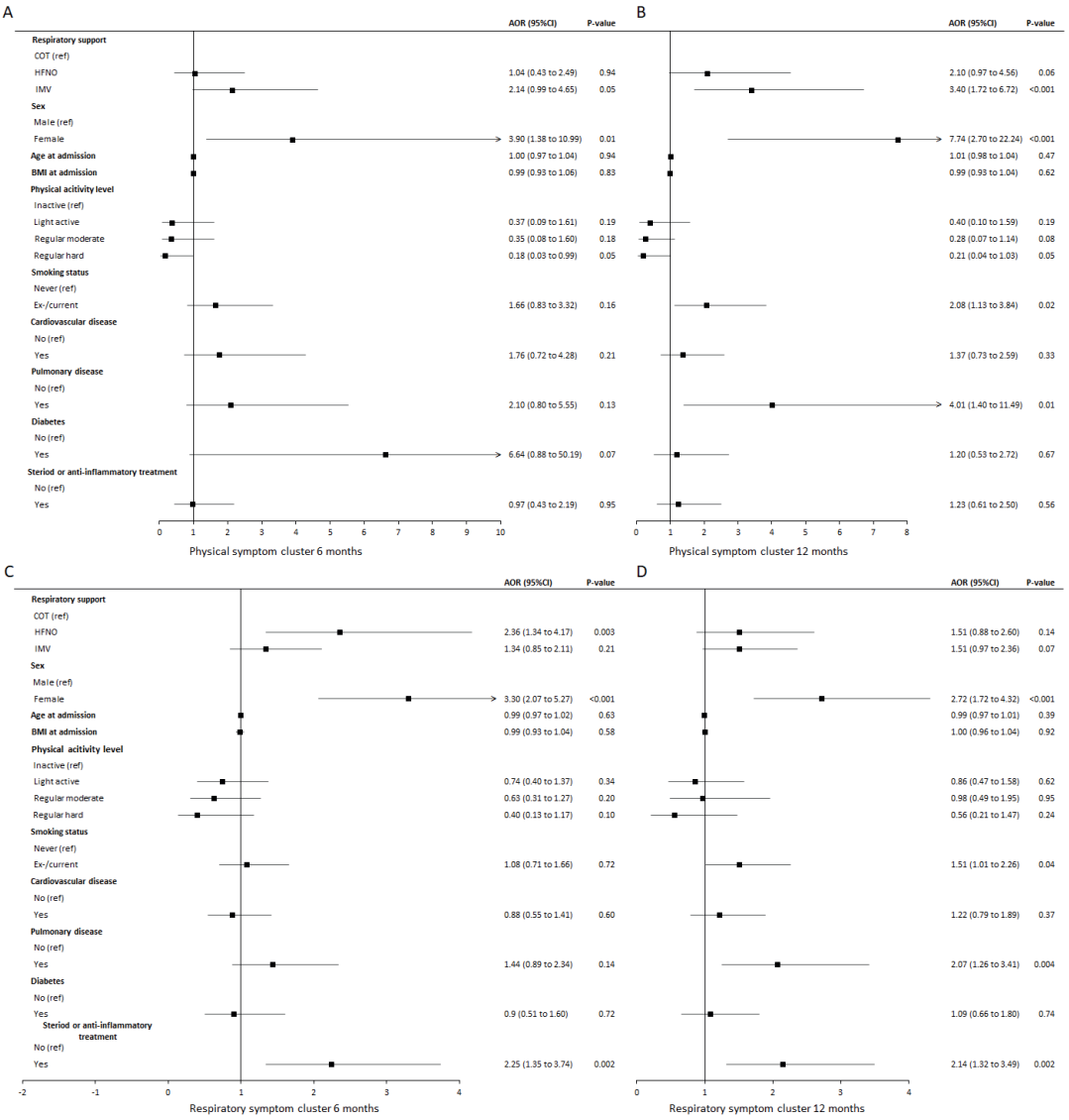


Figure 7.3 Physical and respiratory symptom cluster and their risk factors at 6 and 12 months after hospital discharge.
Forest plots present risk factors of A: physical symptom cluster at 6 months, B: physical symptom cluster at 12 months, C: respiratory symptom cluster at 6 months, and D: respiratory symptom cluster at 12 months post-discharge. Data are obtained using multivariable binary Generalized Estimating Equations analysis. Symptoms were assessed with the Corona Symptom Checklist.[18] AOR, Adjusted Odds Ratio; CI, Confidence Interval; COT, Conventional Oxygen Therapy; HFNO, High Flow Nasal Oxygen; IMV, Invasive Mechanical Ventilation; BMI, Body Mass Index.

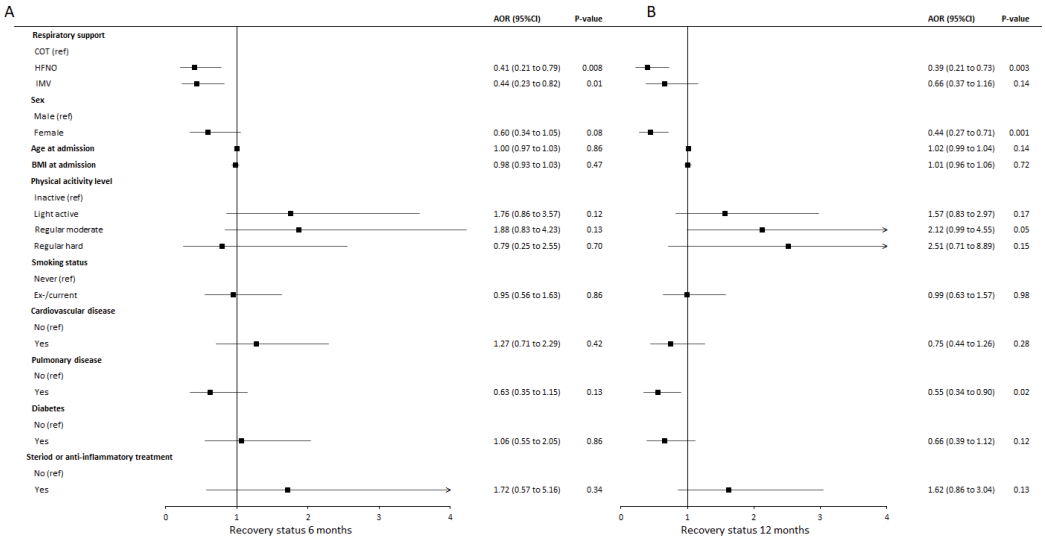


Figure 7.4 Recovery status and its risk factors at 6 and 12 months after hospital discharge. *Forest plots present risk factors for self-reported recovery status from COVID-19. Data are obtained using multivariable Generalized Estimating Equations analysis. Recovery status from COVID-19 was assessed with the Core Outcome Measure for Recovery. Recovery was dichotomized into good recovery (complete or mostly recovered) and poor recovery (not recovered at all, somewhat recovered, or half recovered). AOR, Adjusted Odds Ratio; CI, Confidence Interval; COT, Conventional Oxygen Therapy; HFNO, High Flow Nasal Oxygen; IMV, Invasive Mechanical Ventilation; BMI, Body Mass Index.*

DISCUSSION

In this study, we used data from two large prospective multicenter cohorts of patients hospitalized for COVID-19 to investigate the role of COVID-19 disease severity and other risk factors on long-term multidimensional endpoints. Our key findings include: 1] 6 and 12 months after hospitalization for COVID-19, HRQoL was still impaired, symptoms persisted, and self-perceived recovery was often poor, 2] COVID-19 disease severity was not associated with HRQoL, 3] patients treated with HFNO more frequently experienced respiratory symptoms and reported poorer recovery, 4] in contrast to COVID-19 disease severity, female sex, younger age, and a pulmonary history were more consistent risk factors across long-term multidimensional outcomes.

Hospitalized COVID-19 patients typically require monitored oxygen therapy due to their high disease burden, increasing their susceptibility to long-term health problems compared to those not hospitalized.[6,7] Our study provided further

data supporting that hospitalized patients experience multidimensional impairments up to 12 months post-discharge.[8] The relation between COVID-19 disease severity and long-term outcomes in hospitalized patients is less clear.[4,10-13,21-23] Studies suggest that hospitalized patients with more severe initial disease may be at higher risk.[4,11-13] However, COVID-19 disease severity was not a consistent risk factor across our multidimensional outcomes.[10,21-23] Moreover, the large sample of hospitalized patients receiving various respiratory support modalities enabled us to conduct a comprehensive multivariable analysis of COVID-19 disease severity and other risk factors on long-term multidimensional outcomes. This contrasts previous studies that were in part hampered by their single center design, limited sample size (especially NIV/HFNO treatment; WHO score 4),[4,12,22] often single long-term outcome measure,[6,7,12,22] and comparison to patients not requiring oxygen at all.[4,12] To differentiate between disease severity, several studies dichotomized between ICU and non-ICU admission.[13,23] The three levels of respiratory support are plausible a more valid proxy for disease severity as the true disease severity of ICU admitted patients may vary considerably between centers and countries.[24]

Some notable associations between maximal level of respiratory support and outcomes were however observed. IMV treatment especially impacted the persistence of physical symptoms, while HFNO treatment posed a risk for persistent respiratory symptoms, particularly dyspnea and cough, at 6 months and poor recovery up to 12 months. Moreover, the duration of HFNO therapy was associated with respiratory symptoms at 6 months, but not at 12 months. While these findings are exploratory and require confirmation, they provide a signal of caution for the use of HFNO, especially when employed for a prolonged period. Aligning our findings, previous studies showed that patients with severe COVID-19 (HFNO, NIV or IMV therapy) experienced delayed pulmonary recovery, yet only one study differentiated between HFNO/NIV and IMV.[22,25] Possible explanations for why patients on (prolonged) HFNO more frequently experience late respiratory symptoms remain hypothetical but may be related to the potential damaging effect of prolonged vigorous efforts during HFNO in severely hypoxemic patients.[26]

Ideally, risk factors should be easily collected within the standard of care, guiding early identification of patients at risk for relevant outcomes. However, due to the multifaceted nature and lack of definitive and validated outcome measures, let alone a golden standard,[27] assessing Long COVID is challenging. Various metrics, including symptomatology, HRQoL, pulmonary

function or exercise testing, are used to 'define' and evaluate Long COVID, resulting in clinical risk factors that are variably related to different post-COVID outcomes.[25,28] Ideally, selected risk factors should either directly relate to the gold standard or align with multiple relevant endpoints recognized by stakeholders. Due to inconsistent findings and lack of gold standard diagnostics for Long COVID, we identified alternative risk factors with consistent associations across multiple outcomes. In multivariable GEE analyses, we observed that sex, age, and pulmonary history were independent risk factors across long-term multidimensional outcomes. These risk factors have indeed surfaced repeatedly[11,18,20,22] and could be used to guide aftercare strategies. In our cohort, we observed that a greater proportion of patients treated with IMV, indicating more severe disease, received medical or skilled nursing rehabilitation. More intensive rehabilitation might have a positive effect on long-term outcomes,[29,30] potentially preventing even more severe outcomes.

Our study indicates that COVID-19 disease severity as measured by the maximal level of respiratory support is not a consistent risk factor for long-term outcomes in hypoxemic patients hospitalized for COVID-19. Instead, sex, age, and pulmonary history are more consistently associated with multiple domains of outcomes. Given the expected large number of patients with Long COVID, the strain on healthcare systems could become overwhelming.[31] Screening could help prioritize limited societal resources by directing post-hospital aftercare therapy to those most in need. Factors relevant for multiple long-term outcomes may well serve as relevant screening criteria. These screening criteria can be further explored for their applicability in other post-infectious disease syndromes and the post-IC syndrome, given the evident similarities with long COVID.

The major strengths of our study are its prospective multicenter design, its significant sample size covering a wide variety of in-hospital COVID-19 disease severities, and its relatively high response rate. Also, we collected a comprehensive set of long-term multidimensional patient-centered outcomes and patient-related variables enabling us to perform an in-depth analysis and adjust for a multitude of relevant confounders.

Our study also comes with several limitations. First, we collected data during the first and second pandemic wave, while the virus, treatments, and patients at risk changed over time. We could partly address this by adjusting for treatment

differences in our multivariable analyses. Second, non-Dutch-speaking patients were excluded due to study procedures, potentially overlooking individuals with a migration background known to be prone to impaired HRQoL recovery. Also, at 6 months outcomes might be underestimated as non-responders showed more severe disease characteristics than responders. However, at 12 months this difference was not observed. Given the consistent outcomes at 6 and 12 months, overall underestimation is unlikely to play a major role. Further, the participants' pre-COVID HRQoL may well impact the evolution of HRQoL after the disease episode of interest. Although pre-COVID HRQoL data were not collected, data on physical activity prior to infection was and was included in the multivariable GEE analyses. Additionally, dichotomized scoring of symptoms may have led to missing nuances in symptoms severity. By using symptom clusters, we aimed to capture broader symptom severity. Also, our GEE analysis may have suffered from not including all relevant confounders, despite our efforts to include those deemed relevant at the time.

In conclusion, up to 12 months after hospitalization for COVID-19 HRQoL remained reduced compared to general population, symptoms persisted, and a substantial number of patients reported incomplete recovery. COVID-19 disease severity was not consistently associated across an array of long-term multidimensional outcomes. Patients treated with HFNO reported more respiratory symptoms and poor recovery. Female sex, younger age, and pulmonary history were more consistently associated with outcomes. Our findings collectively suggest that factors other than COVID-19 disease severity are possibly better factors to guide and prioritize aftercare therapy for long-term problems.

DUTCH HFNO COVID-19 STUDY GROUP[***]:

(listed in alphabetical order)

Yaar Aga[1], PhD, MD, Sefanja Achterberg[2], PhD, Laura Cox[3], MD, Alain V.F. Dubois[4], MD, Jan H. Elderman[5,6], MD, Henrik Endeman[5], PhD, Shailin Gajadin[7], MD, Wessel E.J.J. Hanselaar[8], PhD, Roxane Heller-Baan[9], MD, Rogier A.S. Hoek[10], PhD, Jürgen Holters[11], PhD, Oscar Hoiting[12], PhD, Wouter Jacobs[13], MD, Matthijs L. Janssen[1,5,10], MD, Julien van Oosten[5], MD, Susanne Stads[14], PhD, Mariëlle J.M.M. van der Steen-Dieperink[5], MD, Yasemin Türk[8], PhD, Vera J. Versluijs[13], MD, Imro N. Vlasveld[15], MD, Folkert J. van der Wal[16], MD, Evert-Jan Wils[1,5], PhD.

Affiliations

[1]Department of Intensive Care, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands. [2]Department of Intensive Care, Haaglanden Medisch Centrum, Den Haag, The Netherlands. [3]Department of Intensive Care Medicine, Admiraal de Ruyter Hospital, Goes, The Netherlands. [4]Department of Respiratory Medicine, Admiraal de Ruyter, Hospital, Goes, The Netherlands. [5]Department of Intensive Care, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [6]Department of Intensive Care, IJsselland Hospital, Capelle aan den IJssel, The Netherlands. [7]Department of Respiratory Medicine, IJsselland Hospital, Capelle aan den IJssel, The Netherlands. [8]Department of Respiratory Medicine, Franciscus Gasthuis and Vlietland, Rotterdam, The Netherlands. [9]Department of Respiratory Medicine, Ikazia Hospital, Rotterdam, The Netherlands. [10]Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands. [11]Department of Respiratory Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands. [12]Department of Intensive Care, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands. [13]Department of Respiratory Medicine, Martini Hospital, Groningen, The Netherlands. [14]Department of Intensive Care, Ikazia Hospital, Rotterdam, The Netherlands.[15]Department of internal medicine, Martini Hospital, Groningen, The Netherlands. [16]Department of Intensive Care, Martini Hospital, Groningen, The Netherlands.

REFERENCES

1. Docherty AB, Mulholland RH, Lone NI, et al. Changes in in-hospital mortality in the first wave of COVID-19: a multicentre prospective observational cohort study using the WHO Clinical Characterisation Protocol UK. *Lancet Respir Med*. 2021;9(7):773-85.
2. Covid-ICU group. Benefits and risks of noninvasive oxygenation strategy in COVID-19: a multicenter, prospective cohort study (COVID-ICU) in 137 hospitals. *Crit Care*. 2021;25(1):421.
3. Hellemons ME, Huijts S, Bek LM, et al. 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.
4. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863-76.
5. WHO. World Health Organistation. A clinical case definition of post COVID-19 condition by a Delphi consensus. 2021. [updated 2021 October 6; accessed 2022 January 02]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
6. Verveen A, Wynberg E, van Willigen HDG, et al. Health-related quality of life among persons with initial mild, moderate, and severe or critical COVID-19 at 1 and 12 months after infection: a prospective cohort study. *BMC Med*. 2022;20(1):422.
7. Wynberg E, van Willigen HDG, Dijkstra M, et al. Evolution of Coronavirus Disease 2019 (COVID-19) Symptoms During the First 12 Months After Illness Onset. *Clin Infect Dis*. 2022;75(1):e482-e90.
8. Comelli A, Viero G, Bettini G, et al. Patient-Reported Symptoms and Sequelae 12 Months After COVID-19 in Hospitalized Adults: A Multicenter Long-Term Follow-Up Study. *Front Med (Lausanne)*. 2022;9:834354.
9. Evans RA, Leavy OC, Richardson M, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *The Lancet Resp Med*. 2022;10(8):761-75.
10. Demoule A, Morawiec E, Decavele M, et al. Health-related quality of life of COVID-19 two and 12 months after intensive care unit admission. *Ann Intensive Care*. 2022;12(1):16.
11. Legrand M, Fong N, Laouénan C, et al. Risk factors of long term symptoms and outcomes among patients discharged after covid-19: prospective, multicentre observational study. *BMJ Med*. 2022;1(1):e000093.
12. Rosa RG, Cavalcanti AB, Azevedo LCP, et al. Association between acute disease severity and one-year quality of life among post-hospitalisation COVID-19 patients: Coalition VII prospective cohort study. *Intensive Care Med*. 2023;49(2):166-77.
13. Musheyev B, Boparai MS, Kimura R, et al. Longitudinal medical subspecialty follow-up of critically and non-critically ill hospitalized COVID-19 survivors up to 24 months after discharge. *Intern Emerg Med*. 2023;18(2):477-86.
14. Bek LM, Berentschot JC, Hellemons ME, et al. 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 2years after hospital discharge. *BMC Health Serv Res*. 2021;21(1):847.
15. Janssen ML, Türk Y, Baart SJ, et al. Safety and Outcome of High-Flow Nasal Oxygen Therapy Outside ICU Setting in Hypoxemic Patients With COVID-19. *Crit Care Med*. 2024;52(1):31-43.
16. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
17. Versteegh MM, Vermeulen KM, Evers SMAA, et al. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health*. 2016;19(4):343-52.

18. Bek LM, Berentschot JC, Heijenbrok-Kal MH, et al. Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *ERJ Open Research*. 2022:00355-2022.
19. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med*. 2021;49(3):503-16.
20. Nandasena H, Pathirathna ML, Atapattu A, Prasanga PTS. Quality of life of COVID 19 patients after discharge: Systematic review. *PLoS One*. 2022;17(2):e0263941.
21. Darcis G, Bouquegneau A, Maes N, et al. Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: a monocentric prospective observational cohort study. *Int J Infect Dis*. 2021;109:209-16.
22. Lorent N, Vande Weygaerde Y, Claeys E, et al. Prospective longitudinal evaluation of hospitalised COVID-19 survivors 3 and 12 months after discharge. *ERJ Open Res*. 2022;8(2).
23. Wahlgren C, Forsberg G, Divanoglou A, et al. Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. *Lancet Reg Health Eur*. 2023;28:100595.
24. Mukherjee V, Maves RC. Critical Care Is a Concept, Not a Location. *Crit Care Med*. 2024;52(1):145-7.
25. Schlemmer F, Valentin S, Boyer L, et al. Respiratory recovery trajectories after severe-to-critical COVID-19: a 1-year prospective multicentre study. *Eur Respir J*. 2023;61(4).
26. Tonelli R, Busani S, Tabbì L, et al. Inspiratory Effort and Lung Mechanics in Spontaneously Breathing Patients with Acute Respiratory Failure due to COVID-19: A Matched Control Study. *Am J Respir Crit Care Med*. 2021;204(6):725-8.
27. Munblit D, Nicholson T, Akrami A, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med*. 2022;10(7):715-24.
28. Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22(4):e102-e7.
29. Bek LM, Hellemons ME, Berentschot JC, et al. Cognitive and psychological recovery patterns across different care pathways 12 months after hospitalization for COVID-19: A multicenter cohort study (CO-FLOW). *Ann Phys Rehabil Med*. 2023;66(5):101737.
30. Berentschot JC, Heijenbrok-Kal MH, Bek LM, et al. Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW). *Lancet Reg Health Eur*. 2022;22:100485.
31. Soriano JB, González J, Torres A. Panta rhei (Πάντα ῥεῖ), or everything flows with long COVID. *Eur Respir J*. 2023;61(4).



CHAPTER 8

Healthcare Professionals' perspective on the organization of COVID-19 post-hospital aftercare: perspective, barriers and facilitators

L. Martine Bek
Erwin Ista
Julia C. Berentschot
Merel E. Hellemons
Joachim G.J.V. Aerts
Gerard M. Ribbers
Majanka H. Heijenbrok-Kal
Rita J.G. van den Berg-Emons
On behalf of the CO-FLOW Collaboration Group***

*** Listed in Appendix

International Journal of Healthcare Management. 2024:1-16.

ABSTRACT

Background After the outbreak of COVID-19, new post-hospital aftercare for patients with COVID-19 had to be established which healthcare professionals (HCPs) had to implement in their healthcare settings.

Purpose This study aimed to evaluate HCPs' perspective on the organization of COVID-19 post-hospital aftercare and identify barriers and facilitators regarding this aftercare in the Netherlands.

Methods In this mixed-methods study we sent out a survey 1 and 2 years after the COVID-19 outbreak in the Netherlands to healthcare institutions (HCIs) and asked HCPs across multiple disciplines involved in the COVID-19 post-hospital aftercare to participate. The survey comprised three parts: 1] demographics; 2] the Care Process Self-Evaluation Tool as quantitative measure (CPSET; five domains; scoring range 0-100) to assess HCPs' perspective on COVID-19 post-hospital aftercare; and 3] barriers and facilitators regarding this aftercare as a qualitative measure. Descriptive statistics and thematic analysis were performed.

Results At 1 year, 82 HCPs from 48 HCIs, and at 2 years, 29 HCPs from 24 HCIs participated in the survey. Overall, HCPs had a favorable perspective on COVID-19 aftercare in both assessments. The CPSET domain 'patient-focused organization' scored highest (median 81.7 [Interquartile range 75.0-90.0] and 85.0 [78.3-96.7]) and 'monitoring of follow-up care' lowest (67.1 [55.7-75.7] and 70.0 [52.0-86.7]) at 1 and 2 years, respectively. According to HCPs the COVID-19 post-hospital aftercare solutions to overcome the identified barriers include a clear follow-up and referral procedures with emphasis on multidisciplinary treatment, employment of more HCPs, and extension of treatment duration.

Conclusion We concluded that HCPs generally held a positive perspective on COVID-19 aftercare, despite its rapid development and reliance on expert opinion. Key steps in improving COVID-19 aftercare include using quality indicators for monitoring of follow-up care, establishing a well-defined aftercare pathway, addressing resource constraints, and enhancing multidisciplinary collaboration and communication. These insights obtained from HCPs are crucial for policymakers and national healthcare authorities to further improve COVID-19 post-hospital aftercare and for pandemic preparedness.

INTRODUCTION

With the outbreak of coronavirus disease 2019 (COVID-19) in March 2020 in the Netherlands, hospitals were flooded by critically ill patients suffering from COVID-19 associated viral pneumonia and respiratory insufficiency,[1,2] leading to prolonged hospitalization with or without intensive care unit (ICU) treatment. Severely affected patients required inpatient rehabilitation in a medical rehabilitation center or skilled nursing facility, while others could be discharged home, with or without rehabilitation in the community. Healthcare institutions (HCIs), such as hospitals, medical rehabilitation centers, skilled nursing facilities, and community-based rehabilitation centers, including physical and occupational therapy and general practices, had to face a surge of patients who required post-hospital aftercare for COVID-19. However, structured aftercare for these patients did not yet exist, prompting rapid organization of aftercare. Thus, within a short period of time the first COVID-19 aftercare was established,[3,4] crucial to provide structured and comprehensive post-hospital aftercare.

Initially, suggested guidance for COVID-19 aftercare was established with limited knowledge of rehabilitation needs after hospitalization.[5] However, as knowledge increased, this aftercare evolved. Globally, guidelines for management of long-term effects of COVID-19 were established.[6-8] In March 2022, Dutch healthcare societies published a guideline for management of long-term sequelae and rehabilitation after COVID-19; this guideline focused on indication and on treatment programs for different types of rehabilitation, follow-up, diagnostics, and multidisciplinary involvement in primary and secondary care.[9]

The dynamic organization of COVID-19 aftercare likely posed large challenges to healthcare professionals (HCPs), given the unique nature of the disease that demanded the implementation of new treatment protocols and constantly evolving practices as knowledge increased. Literature from previous pandemics, e.g., Ebola and SARS, underscore the challenges HCPs may encounter in implementing new protocols, emphasizing the importance of consistent knowledge and information distribution, ongoing training, and access to adequate resources.[10,11] Existing literature of COVID-19 predominantly focuses on specific healthcare settings, such as primary care, where studies have identified rapidly changing circumstances and resource constraints as barriers to effective care delivery.[12-15] However, literature to

guide the development of COVID-19 aftercare is scarce and studies that evaluate the newly established post-COVID-19 aftercare services across a broad healthcare setting, including primary, secondary, and tertiary care, are limited.[16] This highlights a crucial gap in our understanding of how HCPs perceived the organization of COVID-19 aftercare, while understanding their experiences and perspectives is vital to improve the organization of post-hospital aftercare for COVID-19, and comparable infectious diseases, and for pandemic preparedness. Therefore, we focused on the organization of aftercare throughout the healthcare system provided to patients post-hospitalization for COVID-19 in HCIs across the western region of the Netherlands at 1 and 2 years after the COVID-19 outbreak. Our objectives were to: (1) Evaluate HCPs' perspective on the organization of post-hospital COVID-19 aftercare; (2) Identify barriers and facilitators experienced by HCPs in delivering this aftercare; and (3) Identify strategies to overcome these barriers.

METHODS

Study design

This study had a mixed-methods design using a convenience sampling method to perform a survey study among HCPs in the Rotterdam-Rijnmond-Delft region in the Netherlands; this region is in the western part of the Netherlands that covers a large urban area. This study is part of the CO-FLOW study,[17] which is a study that evaluates long-term outcomes in patients up to 2 years after hospitalization for COVID-19. The CO-FLOW study was approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2020-0487). We used the Care Process Self-Evaluation Tool (CPSET) as a quantitative measure to evaluate the HCPs' perspective on the organization of their care provided for patients after hospitalization for COVID-19. Further, we qualitatively evaluated the barriers and facilitators as perceived by HCPs regarding the COVID-19 aftercare. This study was conducted in March 2021 and in May 2022, which was about 1 and 2 years after the COVID-19 outbreak in the Netherlands, respectively. In March 2022, a formal guideline on COVID-19 aftercare was implemented, which was evidence-based and in accordance with implementation guidelines.[9] The study adheres to the consensus-based checklist for reporting of survey studies (CROSS) (supplementary materials).[18]

Measurement

The survey comprised three sections. For the first round, around 1 year after the COVID-19 outbreak in the Netherlands (March 2021) the first section focused on demographics: type of HCI, profession of respondent, sex, and age. The second section contained the Care Process Self-Evaluation Tool (CPSET), which is a validated questionnaire to quantitatively evaluate the organization of care processes in HCIs from an interprofessional team perspective.[19] In this study, we used the CPSET to specifically evaluate the HCPs' perspective on the care processes within the COVID-19 post-hospital aftercare. The CPSET has 29 items divided in 5 domains (patient-focused organization [6 items], coordination of follow-up care [7 items], communication with patient and family [4 items], collaboration with HCIs [3 items], and monitoring of follow-up care [9 items]) (Supplementary appendix 8.1). Items are scored on a 10-point Likert scale, ranging from 1 (totally disagree) to 10 (totally agree). This tool has good validity (confirmatory factor analysis) and reliability (Cronbach's alpha for subscale 0.869—0.950).[19,20] The original CPSET only includes the domain 'collaboration with primary care'. However, considering the extensive collaboration between multiple HCIs involved in COVID-19 aftercare in the Netherlands, we renamed this domain to 'collaboration with HCIs'. We kept the original question format and answer options, but added questions to evaluate for each HCI separately the collaboration with other HCIs. This extension maintains consistency in answer options, while aligning more closely with the unique dynamics of COVID-19 aftercare in the Netherlands.

The third section, which we added to each CPSET domain for the purpose of our study, aimed at qualitatively identifying barriers and facilitators as perceived by HCPs regarding the COVID-19 aftercare. For each CPSET domain, HCPs were asked to report barriers and facilitators they encountered while providing COVID-19 aftercare via open questions; 'Could you mention a factor(s) that hindered/facilitated the COVID-19 aftercare for [CPSET domain]?'.

For the second round, around 2 years after the COVID-19 outbreak in the Netherlands (May 2022), the first and second section were similar to the 1-year survey. The third section focused on the barriers identified in the 1-year survey and HCPs were asked to provide potential solutions to overcome these barriers. For each domain, we listed the most frequently mentioned barriers and asked HCPs to indicate whether they had never experienced, still experienced, or had seen improvement over the last year. Subsequently, if a barrier persisted, HCPs were asked to suggest ways to address it, while if it had improved, they were

asked to identify contributing factors. We pre-formulated solutions, based on the facilitators mentioned in the 1-year survey. HCPs could select multiple suggestions and offer additional input via free text boxes.

Data collection

For the first round in March 2021, via convenience sampling method we contacted 7 hospitals (1 academic and 6 community hospitals), 4 medical rehabilitation centers, 2 skilled nursing facilities, 1 nursing home, 1 sheltered care facility, and 52 community-based rehabilitation centers. The inclusion criteria were that these HCIs participated in the CO-FLOW study and/or had treated patients that participated in that study.[17] Consequently, these HCIs had to implemented COVID-19 aftercare into their routine practice. HCPs in these HCIs received an email with an open invitation to fill in the survey, and we encouraged distribution of the survey among HCPs in various disciplines involved in the COVID-19 post-hospital aftercare, including pulmonology, intensive care, internal medicine, rehabilitation medicine, physical and occupational therapy, dietetics, and general practice.

For the second round, we again sent an open invitation to the HCIs mentioned previously and encouraged distribution of the survey among colleagues. Consequently, HCPs participating in the second round might differ from those who participated in the first round. Data were collected online using LimeSurvey software (LimeSurvey GmbH).[21]

Analyses

Descriptive statistical methods (median with interquartile range (IQR)) are used to present CPSET domain scores and total CPSET score. Categorical outcomes are presented as number (n) and percentage (%). An average score per domain (sum of domain item scores/number of domain items) and a total score (sum of domain scores/number of domains) were calculated resulting in a scale ranging from 0 to 100. Median scores are presented to enable comparison and interpretation of scores using a cut-off scoring table based on percentiles (P), which was developed by Seys et al. (Supplementary Table 8.1).[20] This table was created using CPSET data collected between 2007 and 2011 in 114 healthcare organizations in Belgium and The Netherlands, allowing for comparisons of how different teams and hospitals perceived the organization of their care process relative to others in different settings. For instance, a domain score of 75.00 for 'patient-focused organization' equals the P50, indicating that in different settings 50% of HCPs assign the same score to this domain.

The Kruskal—Wallis test was used to compare median domain scores among the HCIs. A p-value of 0.05 was considered statistically significant. Full text of barriers and facilitators was categorized into broad themes within the CPSET domains. Upon reading and re-reading, categories became more explicit and were refined, resulting in themes that transcended the CPSET domains. After discussing the themes within the research team, we established seven main themes for both barriers and facilitators which seemed a proper fit for interpreting the data. Provided solutions and full text of solutions were grouped and reported for the concerning barrier.

RESULTS

Characteristics of participating HCIs and HCPs

At 1 year, 48 HCIs participated which represented six different types of HCIs; 6 hospitals, 4 medical rehabilitation centers, 2 skilled nursing facilities, 1 nursing home, 1 sheltered care facility, and 34 community-based rehabilitation centers (Supplementary Table 8.2). The survey was completed by 82 HCPs representing 12 different disciplines; 35.4% was male and the median (IQR) age was 43.0 (33.0—53.0) years. At 2 years, 24 HCIs participated which represented four different types of HCIs; 5 hospitals, 2 medical rehabilitation centers, 2 skilled nursing facilities, and 14 community-based rehabilitation centers (Supplementary Table 8.2). The survey was completed by 29 HCPs representing six different disciplines; 32.1% was male and the median (IQR) age was 39.0 (31.5—48.5) years. Nursing homes and sheltered care facilities were not represented at 2 years as these were no longer involved in COVID-19 post-hospital aftercare.

HCPs' perspective on COVID-19 aftercare

Over all HCIs, the median total CPSET score was 76.3 (72.6—81.0) at 1 year and 75.1 (68.0—81.4) at 2 years (Table 8.1). The median domain scores were situated within the P70-80, except for 'monitoring of follow-up care' which scored P50 at 1 year and P60 at 2 years.

Across HCIs, the median total CPSET scores were situated within P60-P80 and P50-P90 at 1 and 2 years, respectively. Community-based rehabilitation centers had a higher median total CPSET score, while medical rehabilitation centers and skilled nursing facilities had a lower score at 2 years compared to 1 year. The median domain scores varied across HCIs; more specifically, at 1

year, the median domain scores for 'patient-focused organization' of hospitals, medical rehabilitation centers, and community-based rehabilitation centers were situated within P70-80, while for skilled nursing facilities, nursing homes, and sheltered care facilities scores were within lower percentiles (P30-P40); skilled nursing facilities (P40) scored significantly lower for 'patient-focused organization' than community-based rehabilitation centers (P80) (p=0.048). Sheltered care facilities had the lowest median score for 'monitoring of follow-up care' (P20), which was significantly lower than the score of community-based rehabilitation centers (P60) (p=0.019).

At 2 years, the median domain score for 'patient-focused organization' of skilled nursing facilities was lowest (P20) of all HCIs (P70-80) and was significantly lower than that of community-based rehabilitation centers (P80) (p=0.030). In addition, hospitals, medical rehabilitation centers, and skilled nursing facilities had lower median domain scores for 'monitoring of follow-up care', while community-based rehabilitation centers had a higher score compared to 1 year. Hospitals had the lowest median domain score for 'monitoring of follow-up care' (P10), which was significantly lower than that of community-based rehabilitation centers (P90) (p=0.018). These results are visualized in Fig. 8.1.

Table 8.1 *Healthcare professionals' perspective on the quality of the organization of the COVID-19 aftercare as measured with the CPSET.*

	Patient-focused organization	Coordination of follow-up care	Communication with patient and family	Collaboration with institutions	Monitoring of follow-up care	Total CPSET score
1-year outcomes						
All healthcare institutions						
HCPs, n	82	67	69	53	64	46
Median (IQR)	81.67 (75.00—90.00)	80.00 (70.00—84.29)	77.50 (66.25—82.50)	80.00 (73.33—85.50)	67.14 (55.71—75.71)	76.32 (72.59—80.98)
Percentile [a]	P70	P70	P80	P80	P50	P70
Hospital						
HCPs, n	12	11	10	8	10	8
Median (IQR)	81.67 (70.00—90.42)	80.00 (78.57—82.56)	75.00 (56.88—80.63)	79.08 (75.50—88.17)	56.43 (37.14—73.57)	76.78 (69.28—82.14)
Percentile [a]	P70	P70	P70	P70	P30	P70
Medical rehabilitation center						
HCPs, n	18	15	15	14	14	13
Median (IQR)	81.67 (74.17—87.08)	81.43 (78.57—85.71)	82.50 (77.50—87.50)	80.00 (75.21—84.17)	65.71 (55.54—70.00)	76.36 (74.21-79.55)
Percentile [a]	P70	P80	P80	P80	P50	P70
Skilled nursing facility						
HCPs, n	9	7	6	6	5	5
Median (IQR)	73.33 (68.33—81.67)[†]	75.71 (64.29—78.57)	76.25 (68.13—83.13)	75.00 (67.50—83.00)	68.57 (65.71—77.14)	73.30 (67.58-80.06)
Percentile [a]	P40	P60	P70	P60	P60	P60
Nursing home						
HCPs, n	4	3	2	2	2	2

Table 8.1 *Continued*

	Patient-focused organization	Coordination of follow-up care	Communication with patient and family	Collaboration with institutions	Monitoring of follow-up care	Total CPSET score
Median (IQR)	70.83 (47.92—82.50)	80.00 (61.43—80.00)	67.50 (55.00—80.00)*	71.67 (66.70—76.67)*	67.14 (64.30—70.00)*	69.60 (63.90-75.30)*
Percentile [a]	P30	P70				
Sheltered care facility						
HCPs, n	5	2	4	4	4	2
Median (IQR)	70.00 (57.50—90.83)	70.71 (67.10—74.30)*	65.00 (44.38—95.00)	79.67 (65.83—86.50)	50.00 (23.21—51.07)[†]	68.64 (62.10-75.2)*
Percentile [a]	P30		P50	P70	P20	
Community-based rehabilitation center						
HCPs, n	34	29	31	19	28	16
Median (IQR)	85.83 (78.33—95.42)[†]	78.57 (69.29—85.00)	75.00 (62.50—82.50)	80.00 (70.00—85.00)	70.71 (61.43—84.64)[†]	77.23 (73.17—85.92)
Percentile [a]	P80	P70	P70	P80	P60	P80
2-year outcomes						
All healthcare institutions						
HCPs, n	29	29	28	17	27	17
Median (IQR)	85.00 (78.33—96.67)	77.14 (71.43—86.43)	77.50 (72.50—90.00)	80.00 (69.11—90.00)	70.00 (52.00—86.67)	75.09 (68.02—81.37)
Percentile [a]	P80	P70	P80	P80	P60	P70
Hospital						
HCPs, n	8	8	7	7	7	7
Median (IQR)	82.50 (68.75—91.25)	77.86 (62.50—87.50)	75.00 (60.00—77.50)	87.33 (80.00—100.00)	41.11 (34.44—78.89)[c]	75.09 (60.49—80.44)
Percentile [a]	P70	P70	P70	P90	P10	P70

	Patient-focused organization	Coordination of follow-up care	Communication with patient and family	Collaboration with institutions	Monitoring of follow-up care	Total CPSET score
Medical rehabilitation center						
HCPs, n	3	3	3	3	3	3
Median (IQR)	83.33 (80.00—91.70)	81.43 (75.71—82.86)	77.50 (67.50—85.00)	80.00 (65.70—83.33)	54.40 (52.22—61.11)	73.75 (68.01—80.79)
Percentile [a]	P70	P80	P80	P80	P20	P70
Skilled nursing facility						
HCPs, n	3	3	3	3	3	3
Median (IQR)	65.00 (63.33—78.33) [b]	71.43 (68.57—77.14)	67.50 (65.00—75.00)	76.00 (59.17—90.00)	58.89 (41.11—65.55)	68.07 (64.44—71.90)
Percentile [a]	P20	P50	P60	P60	P30	P50
Community-based rehabilitation center						
HCPs, n	15	15	15	4	14	4
Median (IQR)	95.00 (81.67—100.00) [b]	81.43 (71.43—94.29)	87.50 (77.50—97.50)	69.44 (56.81—86.67)	85.56 (74.17—92.78)[c]	83.46 (77.64—92.74)
Percentile [a]	P80	P80	P90	P40	P90	P90

The CPSET results are presented for all healthcare institutions and across healthcare institutions at 1 and 2 years after the COVID-19 outbreak in the Netherlands.
Data are presented as median with interquartile ranges with corresponding percentiles from the cutoff table developed by Seys et al.[14] CPSET, Care Process Self-Evaluation Tool; HCPs, Healthcare Professionals; P, Percentile.
[a] Percentiles correspond to the cutoff table developed by Seys et al.[14]
[†] Skilled nursing facilities scored significantly lower than community-based rehabilitation centers (p=0.048).
** Data are presented as median (range) due to limited responses (n≤2).*
[ŧ] Sheltered care facilities scored significantly lower than community-based rehabilitation centers (p=0.019).
[b] Skilled nursing facilities scored significantly lower than community-based rehabilitation centers (p=0.030).
[c] Hospitals scored significantly lower than community-based rehabilitation centers (p=0.018).

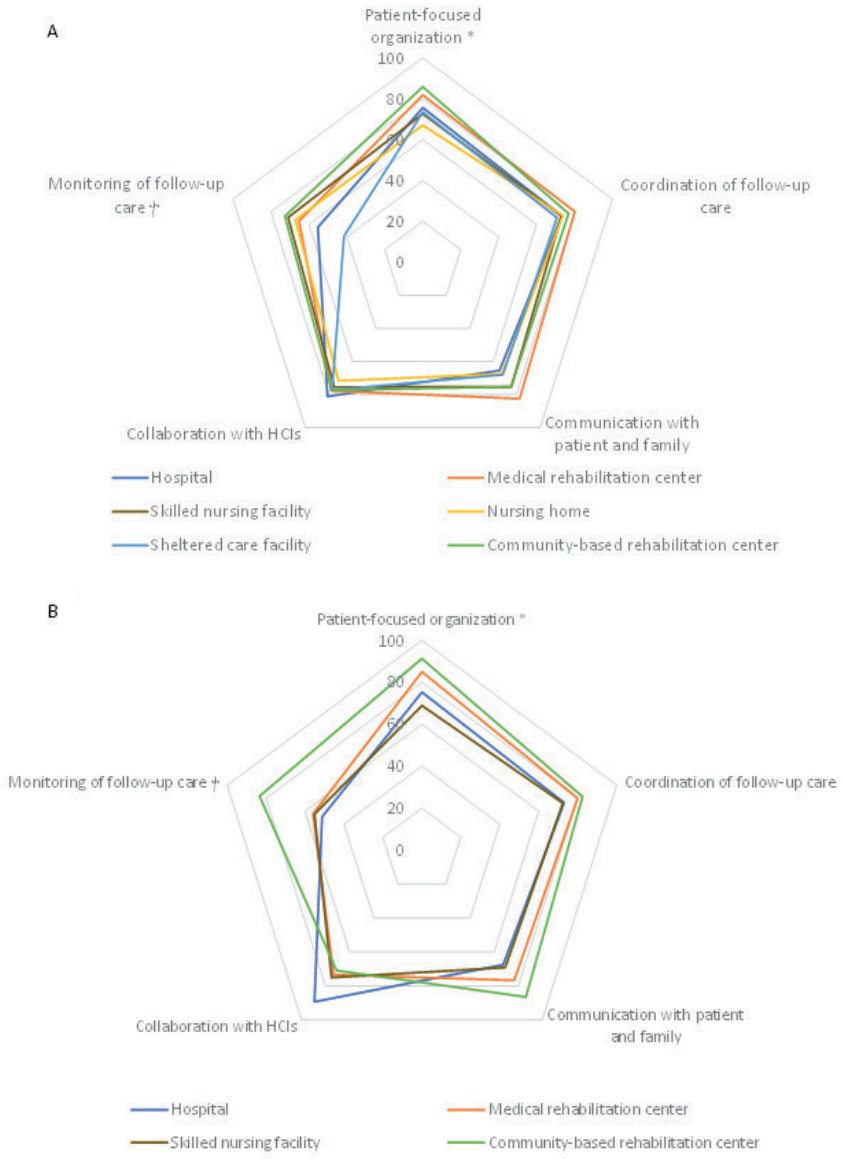


Figure 8.1 Median CPSET scores of all healthcare institutions are presented as a radar chart.
The domains of the care process self-evaluation tool are presented at the five corners (13). The colored lines represent the median scores of the different healthcare institutions.
A] *Median scores at 1 year after initial COVID-19 outbreak.* Skilled nursing facilities scored significantly lower than community-based rehabilitation centers (p=0.048). † Sheltered care facilities scored significantly lower than community-based rehabilitation centers (p=0.019).*
B] *Median scores at 2 years after initial COVID-19 outbreak. * Skilled nursing facilities scored significantly lower than community-based rehabilitation centers CBR (p=0.030). † Hospitals scored significantly lower than community-based rehabilitation centers (p=0.018).*
HCIs, healthcare institutions

Barriers and facilitators of COVID-19 aftercare at 1 year

Barriers and facilitators were asked for each CPSET domain, and some were reported across multiple CPSET domains (Table 8.2). Depending on the extent to which a COVID-19 aftercare pathway was already implemented within HCIs, some HCPs could perceive certain factors as barriers, while others could perceive them as facilitators for the same domain.

Across CPSET domains, and especially regarding 'patient-focused organization', HCPs were most often hindered by capacity and resource constraints (Table 8.2). HCPs mentioned a high workload, absence of required healthcare infrastructure, and time constraints in treatment and consultations.

> *HCPs described: 'Not all patients are followed up in the outpatient clinic due to capacity constraints' and 'There is not enough time to treat patients and answer their questions.'*

Consequently, HCPs mentioned sufficient capacity and resources as facilitator, especially for 'patient-focused organization' and 'communication with patient and family'. A healthcare infrastructure that suffices demands, such as sufficient staff, knowledge, materials, and communication tools, including devices to provide eHealth, and adequate treatment time and provision of home care were noticed as facilitators.

> *A HCP mentioned: 'We are a very broad team, being able to provide knowledge from all disciplines about fatigue and pulmonary and neurological problems.'*

The missing or unclear COVID-19 aftercare pathway was another major barrier, especially for optimal 'coordination of follow-up care'. Issues addressed concerned absence of treatment protocols, unclear referral or follow-up procedures, non-functional measures to evaluate patient recovery, and varying aftercare pathways among HCIs.

> *HCPs mentioned: 'After transfer to another healthcare institution or discipline, patient follow-up stops' and 'Procedures for patient follow-up or referral are not specified within an aftercare pathway or an aftercare pathway is absent.'*

On the other hand, a well-defined COVID-19 aftercare pathway, in which accurate testing for patient recovery is documented, and treatment and referral procedures and protocols for aftercare are defined, was frequently mentioned as a facilitator.

> *HCPs commented: 'A clearly specified policy for aftercare' and 'Patients are referred to another discipline, if necessary, based on their symptoms.'*

HCPs also reported insufficient knowledge of COVID-19 as a barrier across all domains, except 'collaboration with HCIs'. The diversity and complexity of COVID-19 symptoms and the lack of knowledge of long-term consequences and consistent information were experienced as barriers.

> *A HCP stated: 'Due to diversity and complexity of COVID-19, it is difficult to provide optimal treatment to patients as standard protocols won't apply.'*

Another barrier identified across 3 out of 5 domains was collaboration and communication problems. There was limited collaboration and communication among disciplines and HCIs, multidisciplinary treatments were not used to their full potential, and aftercare options in other HCIs were often unknown.

> *A HCP said: 'There is a lack of multidisciplinary use and communication among network partners. This causes unfamiliarity with treatment options.'*

Indeed, HCPs emphasized the importance of collaboration and communication among disciplines and HCIs, in which multidisciplinary treatment and multidisciplinary consultations play a major role as well as accessibility and involvement of all HCIs providing COVID-19 aftercare.

> *A HCP commented: 'Multidisciplinary teams for inpatient and outpatient treatment.'*

The ability to provide patient-centered care was identified as facilitator, in which HCPs pointed out the importance of the patient's request for help as starting point in therapy, actively involved HCPs, and the ability to provide individualized treatment.

> *HCPs mentioned: 'Patient's request for help is the starting point in therapy.' and 'Individual approach leads to tailor-made care.'*

Finally, less frequently mentioned barriers were limited reimbursement or unclear reimbursement policies in all domains, except 'monitoring of follow-up care', and insufficient involvement of patient support systems and language barriers, especially for 'communication with patient and family'.

For facilitators, HCPs reported an increased knowledge of COVID-19, including an increased experience with treatment of COVID-19 patients and the training or education of HCPs. Moreover, the ability to provide information to patients and the involvement of a patient support system, e.g., via telecommunication/video calls with family or relatives during consultation, and improvement of reimbursement policies would facilitate the COVID-19 aftercare according to HCPs.

Table 8.2 *Barriers and facilitators per CPSET domain reported by healthcare professionals at 1 year after the COVID-19 outbreak.*

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Patient-focused organization	**Capacity and resources**	**High workload and time constraints** 'Not all patients are followed up in the outpatient clinic due to capacity constraints' 'The high workload at the referring discipline hinders follow-up'	9 (15.0)
		Problems with planning and administration of aftercare 'Planning of appointments and connecting appointments is difficult'	8 (13.3)
		Absence of required healthcare infrastructure 'The maximum time to provide care and the structure of care make it impossible to provide patient-centered care; care can't be started when needed'	7 (11.7)
		Time constraints in treatment duration 'There is too little treatment time'	6 (10.0)
		COVID-19 measures complicated optimal patient aftercare 'Practical problems, such as the maximum number of persons allowed in the room for group treatment, complicate follow-up' 'Follow-up needed to be given via telephone, while physical outpatient follow-up is preferred'	5 (8.3)
		Missing or unclear COVID-19 aftercare pathway 'It was unclear in the beginning what the best strategy is for treatment of COVID-19 patients' 'A care pathway or protocol is missing'	9 (15.0)
		Lack of patient follow-up 'Patients themselves have to take initiative for aftercare if they are not diagnosed as someone with post-COVID symptoms'	5 (8.3)
Patient-focused organization	**Knowledge of COVID-19**	**Insufficient knowledge of long-term COVID-19 consequences** 'Knowledge lacks on long-term consequences'	16 (26.7)
		Diversity and complexity of COVID-19 symptoms 'Due to diversity and complexity of COVID-19, it is difficult to provide optimal treatment to patients as standard protocols won't apply'	4 (6.7)
		Disease-centered instead of patient-centered care 'There is a lot of attention for the disease, but little for the person as a whole'	2 (3.3)

Table 8.2 *Continued*

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Patient-focused organization	**Collaboration and communication**	**Limited collaboration and communication (among disciplines and healthcare institutions)** 'There is a lack of multidisciplinary use and communication among network partners. This causes unfamiliarity with treatment options' 'Insufficient consultations with other disciplines, especially the general practitioner is hard to consult'	12 (20.0)
	Reimbursement	**Limited reimbursement or unclear reimbursement policies** 'Reimbursement lasts only for half a year, which is most often insufficient'	12 (20.0)
	Language barriers	**Language barriers**	3 (5.0)
Coordination of follow-up care	**Capacity and resources**	**Difficulties in scheduling of treatment** 'There are too few therapists to plan all required treatments'	12 (24.5)
		High demand for healthcare service due to influx of COVID-19 patients	6 (12.2)
	COVID-19 aftercare pathway	**Missing or unclear COVID-19 aftercare pathway** 'After transfer to another healthcare institution or discipline, patient follow-up stops; Procedures for patient follow-up or referral are not specified within an aftercare pathway or an aftercare pathway is absent' 'Healthcare institutions implement different aftercare pathways' 'There are too many questionnaires and tests within the aftercare pathway'	25 (51.0)
	Knowledge on COVID-19	**Insufficient knowledge of long-term COVID-19 symptoms or aftercare options for patients** 'Due to the unknown/unpredictable nature of COVID-19, coordination of care is not always easy'	8 (16.3)
		Unforeseen rapid recovery leads to sudden discharge, complicating arrangements for optimal transition to home 'Sometimes patients are discharged so quickly, because they suddenly recover and then inpatient admission is no longer necessary. The home front still has to get used to the quick transition.' 'Patients may recover quickly, leading to discharge, however, may suddenly have a relapse; this is difficult to coordinate'	4 (8.2)

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Coordination of follow-up care	**Collaboration and communication**	**Limited collaboration and communication (among disciplines and healthcare institutions)** 'There is a lack of multidisciplinary consultations' 'There is insufficient interim evaluation as a team' 'Patients are informed at the aftercare appointment what happened during hospital admission'	8 (16.3)
	Reimbursement	**Limited reimbursement or unclear reimbursement policies** 'Some patients need more than 6 months of aftercare, for which reimbursement is lacking'	6 (12.2)
	Patient support system	**Lack of patient support system** 'The family is not sufficiently involved' 'Patients don't always have a support system'	4 (8.2)
Communication with patient and family	**Capacity and resources**	**Time constraints in treatment and consultation** 'There is not enough time to treat patients and answer their questions' 'A 30-minute physical therapy session is often too short to both provide care and answer all questions of the patient'	15 (41.7)
	COVID-19 aftercare pathway	**Missing or unclear COVID-19 aftercare pathway** 'The general practitioner is unfamiliar with aftercare options'	8 (22.2)
	Knowledge of COVID-19	**Insufficient knowledge of COVID-19 with large variety in information** 'Patients regularly ask for information about their physical condition' 'Information also included several inaccuracies'	2 (5.6)
		Unrealistic or divergent expectations about recovery from patients and/or their relatives 'The expectations are too high' 'The expectations of patients and family regarding rehabilitation'	3 (8.3)
	Reimbursement	**Limited reimbursement or unclear reimbursement policies** 'There are insufficient physical therapy sessions within the reimbursement policy'	2 (5.6)
	Patient support system	**Insufficient involvement of patient support system** 'Family or partner are often not present during consultations'	13 (36.1)
	Language barriers	**Language barriers**	5 (13.9)

Table 8.2 *Continued*

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Collaboration with healthcare institutions	**Capacity and resources**	**Time constraints for consultations and waiting list for referral to collaborating partners** 'There is insufficient time for interdisciplinary consultations' 'Collaborating partners have long waiting lists'	12 (44.4)
		High workload 'Administrative burden' 'Pulmonologists are extremely busy, general practitioners as well'	3 (11.1)
	COVID-19 aftercare pathway	**Missing or unclear COVID-19 aftercare pathway** 'Patients are often not referred and do not receive an extensive referral letter' 'Patient flow to other HCIs is challenging'	9 (33.3)
	Collaboration and communication	**Limited collaboration among primary and secondary/tertiary care (aftercare options are often unknown)** 'I believe that hospitals don't inform patients about rehabilitation options in primary care upon discharge' 'There is no active collaboration with hospitals, rehabilitation centers, and sheltered care facilities' 'There is minimal collaboration among primary care and hospitals'	7 (25.9)
	Reimbursement	**Limited reimbursement or unclear reimbursement policies** 'For physical therapy there is no possibility to reimburse consultations or collaborations'	3 (11.1)
Monitoring of follow-up care	**Capacity and resources**	**High demand for healthcare service due to influx of COVID-19 patients** 'Due to the high number of COVID-19 patients, we have waiting list and thus can't always help patients immediately'	2 (8.0)
	COVID-19 aftercare pathway	**Missing or unclear COVID-19 aftercare pathway** 'Unfamiliarity with aftercare pathways for patients with COVID-19' 'Despite referrals from pulmonologists, patients often lack follow-up and feedback is limited'	12 (48.0)
		Lack of active monitoring of COVID-19 aftercare pathway 'I don't have the impression that the functioning of the aftercare pathway is actively monitored' 'Patient satisfaction is not standardized'	8 (32.0)
	Knowledge of COVID-19	**Insufficient knowledge of COVID-19; a complex disease with an unpredictable course** 'Recovery is inconsistent, which sometimes causes unpredictable reactions'	5 (20.0)
CPSET domain	**Facilitators with quotes from healthcare professionals**		**N (%)**

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Patient-focused organization	**Capacity and resources**	**Healthcare infrastructure suffices care demands** 'We are a very broad team, being able to provide knowledge from all disciplines about fatigue and pulmonary and neurological problems'	14 (20.9)
		Sufficient treatment time to provide patient-centered care 'The extensive intake involving various disciplines ensures the proper identification of problems'	9 (13.4)
		Provision of home care and eHealth 'Measures are performed by patients themselves at home'	3 (4.5)
		Accessible care	2 (3.0)
	COVID-19 aftercare pathway	**Well-defined COVID-19 aftercare pathway** 'The treatment program is developed relatively quickly' 'The appropriate measures are applied to assess recovery' 'Patients are referred to another discipline if necessary, based on their symptoms'	16 (23.9)
Patient-focused organization	**Knowledge of COVID-19**	**Increased experience with COVID-19 treatment** 'All aftercare is performed by two pulmonologists who are also involved in ward care and thus have a lot of experience'	6 (9.0)
		Training or education of healthcare professionals 'We could follow extra training on COVID-19 and infection prevention'	4 (6.0)
		Patient education for post-treatment phase 'The patient is provided with tools to facilitate further recovery within primary care' 'Within a short time we learned a lot and all knowledge is shared with patients'	4 (6.0)
	Collaboration and communication	**Collaboration and communication (among disciplines and healthcare institutions)** 'Multidisciplinary teams for inpatient and outpatient treatment' 'Multidisciplinary consultations and communication'	27 (40.3)
	Patient support system	**Involvement of patient support system** 'Meetings with partners and/or family to facilitate peer contact'	4 (6.0)
Patient-focused organization	**Patient-centered care**	**Provision of patient-centered care (i.e., HCPs are actively involved and provide personal therapy, the request for help is the starting point in therapy)** 'Patient's request for help is the starting point in therapy' 'Individual approach leads to tailor-made care' 'Healthcare professionals have extra attention for and monitor patient recovery'	29 (43.3)

Table 8.2 *Continued*

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Coordination of follow-up care	**COVID-19 aftercare pathway**	**Well-defined COVID-19 aftercare pathway** 'Correct referral from hospitals and follow-up appointments' 'Well-defined protocol regarding COVID-19 aftercare'	20 (47.6)
	Knowledge of COVID-19	**Training or education of healthcare professionals** 'Healthcare professionals follow training by themselves'	3 (7.1)
Monitoring of follow-up care	**Collaboration and communication**	**Collaboration and communication (among disciplines and healthcare institutions)** 'Rehabilitation consultation with the whole team' 'Collaboration within multidisciplinary teams' 'Provide a report to the general practitioner upon completion of the rehabilitation program'	28 (66.7)
	Reimbursement	**Improvement of reimbursement** 'Reimbursement is very important' 'Reimbursement should be accessible'	2 (4.8)
	Patient-centered care	**Patient-centered care** 'There is an overall feeling of responsibility towards the patients'	13 (31.0)
Communication with patient and family	**Capacity and resources**	**Sufficient treatment time to provide patient-centered care (e.g., intake interview, via eHealth, group therapy)** 'During treatment much time is planned for communication among patients and healthcare professionals'	12 (38.7)
		Accessible care '24/7 accessibility' 'Low-key contact and the possibility to plan appointments'	6 (19.4)
		Required communication tools available (e.g., feedback provision to patient, digital communication) 'Evaluation of recovery measures can be shown in graphs and can be discussed' 'Digital communication is possible via an online portal'	5 (16.1)
	Patient support system	**Information provision and involvement of patient support system (e.g., video calls, taster days for support system)** 'We offer group sessions for partners' 'The family is included in consultations via video calls'	14 (45.2)
	COVID-19 aftercare pathway	**Well-defined COVID-19 aftercare pathway** 'The collaboration with hospitals improved' 'There is good collaboration with general practitioners'	10 (33.3)

CPSET domain	Barriers with quotes from healthcare professionals		N (%)
Collaboration with healthcare institutions	**Knowledge of COVID-19**	**Training or education of healthcare professionals** 'Some paramedic teams have contacted us and explained their approach, how they collaborated, and how patients could find them'	4 (13.3)
	Collaboration and communication	**Accessibility and involvement of partners through low-barrier communication** 'Quick and easy communication and referrals to other disciplines'	16 (53.3)
		Multidisciplinary treatment approach 'There are fast and convenient contact and referral options with speech therapists, occupational therapists, dieticians, and psychologists within the treatment team' 'Meetings with pulmonary primary care physical therapy network'	4 (13.3)
Monitoring of follow-up care	**COVID-19 aftercare pathway**	**Well-defined COVID-19 aftercare pathway** 'A clearly specified policy for aftercare' 'Applicable measures allow for evaluation of recovery, providing feedback to the patient'	8 (53.3)
	Collaboration and communication	**Collaboration and communication (among disciplines and healthcare institutions)** 'Multidisciplinary meetings to evaluate the course and result of rehabilitation'	7 (46.7)
	Patient-centered care	**Individualized patient treatment** 'Patients recover well after optimal rehabilitation' 'Intense rehabilitation treatment'	5 (33.3)

Per CPSET domain healthcare professionals (HCPs) mentioned barriers and facilitators which were categorized into broad themes of barriers and facilitators. Quotes per barrier/facilitator are listed. In addition, the number (%) of HCPs that mentioned a certain barrier/facilitator is shown, which is calculated as the number of HCPs mentioning the barrier/facilitator divided by the total number of HCPs responding per CPSET domain. CPSET, Care Process Self-Evaluation Tool.

Table 8.3 *Overview of the barriers reported at 1 year and the corresponding solutions assessed at 2 years after the COVID-19 outbreak.*

Barrier	What could contribute or what contributed to overcome the barrier?
Capacity and resource constraints	• Employment of more (trained) healthcare professionals or training of healthcare professionals • Extension of treatment period (especially in primary care) • Increase in resources (e.g. treatment space, equipment) • Information provision via leaflets and websites for patients • Structured aftercare pathways with scheduled multidisciplinary consultations for healthcare professionals • Increase in knowledge of COVID-19 on residual damage and treatment • Expiration of COVID-19 measures • Appointment of a permanent contact person to establish regular contact with partners
Missing or unclear COVID-19 aftercare pathway	• Development of a well-defined COVID-19 aftercare pathway ° This aftercare pathway should ideally incorporate the following items: • National and regional guidelines and/or protocols • Dynamic aftercare pathway • Clear follow-up procedures • Clear referral procedures • Possibility for referral to multiple disciplines • Establishment of multidisciplinary teams for COVID-19 treatment • Adequate recovery outcome measures • Measures to monitor aftercare • Description of specific goals for aftercare • Increased knowledge of COVID-19 improved alignment of recovery outcome measures • Familiarity of aftercare options by healthcare professionals • Reimbursement for extension of treatment period (especially in primary care)
Insufficient knowledge of COVID-19	• Information provision via courses, webinars, and scientific or professional literature • Performance of scientific research • Increase in knowledge and experience with COVID-19 in general

Barrier	What could contribute or what contributed to overcome the barrier?
Limited collaboration and communication (among disciplines and healthcare institutions)	• Structured aftercare pathways with scheduled multidisciplinary consultations for healthcare professionals • Familiarity of aftercare options by healthcare professionals • Development of clear referral and follow-up procedures • Improvement in referral procedures through experienced and established contact with partners • Improvement in referral to and reimbursement for multidisciplinary treatment • Possibility for referral to multiple disciplines
Limited reimbursement or unclear reimbursement policies	• Development of clear guidelines by the government • Provision of extra reimbursement for patients with persistent COVID-19 symptoms
Insufficient involvement of patient support system	• Involvement of patient support system via eHealth • Improvement of the understanding of the importance of the patient support system • Information provision via leaflets and websites for post-COVID-19 patient care support

Lack of active monitoring of the aftercare pathway	• Development of a well-defined COVID-19 aftercare pathway
	  ° Inclusion of measures to monitor aftercare
	  ° Description of specific goals for aftercare

The broad themes of barriers reported at 1 year after the COVID-19 outbreak are listed. Healthcare professionals were asked for solutions that could contribute or contributed to overcome each barrier.

Barriers and improvements in COVID-19 aftercare

At 2 years, HCPs (48%) indicated an improvement regarding insufficient knowledge of COVID-19, which concerned unknown long-term consequences and patient treatment (Fig. 8.2). This improvement was facilitated by information provision via courses, webinars, scientific literature, and by the increase in knowledge and experience with COVID-19 in general (Table 8.3).

Also, collaboration and communication among colleagues, disciplines, and HCIs from primary and secondary/tertiary care had improved according to HCPs (31%). Aspects that led to this improvement included the ability for HCPs to schedule multidisciplinary consultations within their regular planning, the fact that aftercare options were now familiar to HCPs, and the development of clear referral and follow-up procedures.

The absence of a clear COVID-19 aftercare pathway was still experienced as a barrier by 24% of the HCPs but had improved according to 22%. HCPs pointed out that a well-defined COVID-19 aftercare pathway should be established by national and regional guidelines, it should be dynamic, include clearly specified follow-up and referral procedures with the possibility to refer to multiple disciplines, it should emphasize multidisciplinary treatment and adequate recovery outcome measures, and specify goals for aftercare and measures to monitor the aftercare. In addition, familiarity with aftercare options by all HCPs and reimbursement for extension of the treatment period, especially in primary care, were mentioned as important aspects. A well-defined COVID-19 aftercare pathway was reported as an important solution to overcome barriers in all CPSET domains.

Many HCPs (45%) still experienced capacity and resources constraints. Elements that could contribute to improve this situation included employment of more (trained) HCPs, extension of the treatment period (especially in primary care), increase in resources (treatment space and equipment), information provision via leaflets and websites for patients, and the ability to schedule multidisciplinary consultations for HCPs within their regular planning.

The situation regarding reimbursement policies improved according to 32% of HCPs. Insufficient involvement of patient support system and lack of active monitoring of the aftercare pathway were still reported by 28% and 41%, respectively.

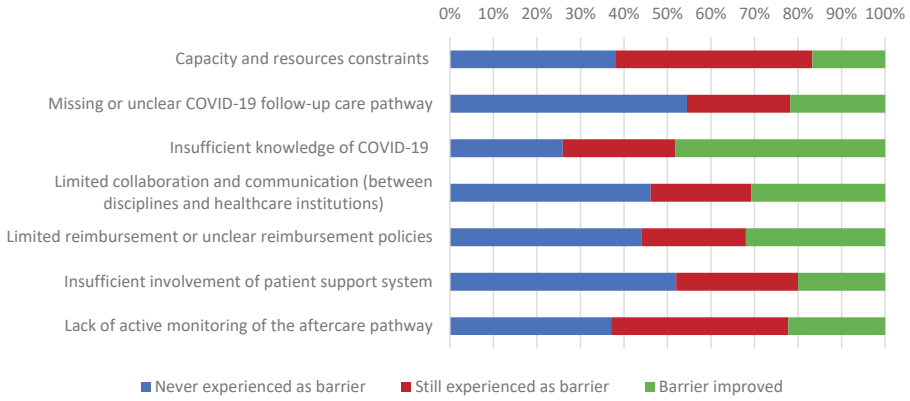


Figure 8.2 Healthcare professionals' perspective on barriers at 2 years.
Healthcare professionals were asked to indicate whether the barrier was never experienced, still experienced, or improved during the last year. Barriers were identified by healthcare professionals in the 1-year survey. In the 2-year survey their perspective on the barriers was assessed again and is displayed in the figure.

DISCUSSION

The implementation of newly established COVID-19 aftercare with its dynamic organization due to evolving knowledge, posed large challenges to HCPs to implement this aftercare into their healthcare services. Therefore, we aimed to evaluate HCPs perspective on this aftercare and identify its barriers and facilitators to enhance the aftercare for COVID-19 and comparable infectious diseases, and for pandemic preparedness.

In general, HCPs across all HCIs had a favorable perspective on the organization of COVID-19 aftercare at both 1 and 2 years. Median domain scores, ranging from P50-80, reflected a positive assessment, especially considering the novel nature of COVID-19 and the short timeframe for aftercare implementation. HCPs from skilled nursing facilities had the least favorable perspective on the organization of COVID-19 aftercare, especially regarding the domain 'patient-focused organization'. Furthermore, the domain 'monitoring of follow-up care' was scored in the lower percentiles, except for community-based rehabilitation centers. Finally, it seemed that HCPs from community-based rehabilitation centers perceived improvements on 'monitoring of follow-up care' from 1 to 2 years, but HCPs from hospitals, medical rehabilitation centers, and skilled

nursing facilities perceived deteriorations in this domain. It is essential to emphasize the heterogeneity in care processes across different HCIs and the varying importance of different domains within each HCI. Consequently, the relevance of specific care processes may vary depending on the type of HCIs. Additionally, over time, it became increasingly evident that community-based rehabilitation centers played a crucial role in the long-term recovery of COVID-19 patients. Consequently, the follow-up care, especially vital in this HCI, was likely to be well-established at the 2-year measurement, which could explain the improved perspective of HCPs on 'monitoring of follow-up care'. However, the represented HCIs at 1 year differ from those at 2 years, complicating direct comparison. Nonetheless, placing greater emphasis on 'monitoring of follow-up care' may potentially enhance quality of COVID-19 aftercare.

Integrated care pathways are a way to standardize care processes, reducing variation in given care, improving continuity and transparency of care, and ensuring long-term patient monitoring.[22,23] Furthermore, they help multidisciplinary teams to coordinate and reorganize their work and to facilitate collaboration among HCIs.[22,23] Care pathways are important for optimizing physician-patient communication and patient satisfaction, reducing in-hospital complications and costs, while improving quality and quantity of documentation in medical records.[23,24] In addition, within integrated care pathways, routine outcome monitoring could be implemented to improve quality of care, assist in long-term follow-up of chronically ill patients, and evaluate healthcare services.[25-27] HCPs indeed emphasized the importance of a well-defined COVID-19 post-hospital aftercare pathway, which should include a dynamic aftercare pathway supported by national and regional guidelines outlining follow-up and referral procedures. Especially multidisciplinary treatment, and thus the possibility for multidisciplinary referral, was deemed crucial, achievable through clarifying HCPs' roles and responsibilities within the guidelines. Also, regional or national (online) platforms for HCPs could facilitate multidisciplinary collaboration. These facets of aftercare pathways were also identified in a study by Brus et al. in patients with Q-fever.[28] The introduction of the Dutch guideline on long-term rehabilitation of COVID-19 in March 2022[9] marked a significant step forward. While this guideline offered a framework for aftercare provision, it is important to acknowledge its limitations due to a lack of solid scientific evidence regarding aftercare and still limited guidance. Apparently, at the 2-year survey, the guideline was not fully implemented yet, as some HCPs still reported the absence of a COVID-19 aftercare pathway. The added value of integrated care pathways is well-

recognized and considered essential to deliver efficient and patient-focused care. However, their uptake is hampered by policy barriers, financial flaws, and challenges in data management.[28,29] Therefore, it is important to involve policy makers of representing HCP associations, healthcare insurance companies and national healthcare authorities, particularly the ministry of Health and national health institutions, as the core responsibility for developing and implementing care pathways for COVID-19 aftercare on a national level primarily falls on them.[30]

A failure to establish adequate care pathways could result in a *'hidden epidemic'* and unmet needs where individuals with chronic conditions remain unidentified and may not receive the appropriate care. Therefore, it would be desirable to have integrated care pathways engaging HCPs from primary and secondary care, with a critical role for the general practitioner.

Resource constraints are an increasing challenge in healthcare worldwide. Simple interventions, such as providing comprehensive information through leaflets and websites which ease the burden on HCPs during patient consultations, or offering (online) educational programs for HCPs, can be relatively easy to implement.[31-34] However, establishing regular multidisciplinary consultations among HCPs collaborating within an integrated chain requires careful planning and coordination involving multiple stakeholders and may require organizational changes and collaboration among different healthcare disciplines. Disruptive innovations become imperative when considering structural aspects of COVID-19 aftercare. Addressing resource constraints requires a multifaceted approach, which may involve increasing the number of HCPs involved in aftercare, extending treatment periods to accommodate the patients' needs, and enhancing overall healthcare capacity and implementing e-health interventions.[35,36] These measures require additional resources, workforce allocation, and strategic planning, thereby making their implementation more complex.

This study demonstrates notable strengths. First, anonymity in the survey ensured that respondents could provide honest feedback regarding the organization of the COVID-19 post-hospital aftercare, contributing to an accurate representation of their experiences and perspectives. Second, despite the relatively small sample size within certain HCIs, HCPs encompassed a diverse range of disciplines and experiences. This diversity enabled us to identify critical areas for improvement in the COVID-19 aftercare. Therefore,

our study provided valuable insights into the strengths and weaknesses of the COVID-19 aftercare.

Our study has some limitations. First, the CPSET is a self-evaluation tool that provides subjective scores.[19] Nonetheless, it remains useful in evaluating the perceptions of individuals. Second, HCPs' perspective might be susceptible to the influence of patients who have received care within HCIs, but were not necessarily hospitalized for COVID-19. Third, the extension of the CPSET tool has not been validated yet, which we believe should be prioritized in future research. Moreover, we should be cautious about generalizing the results, as we sent an open invitation to participate. This may have introduced selection bias, as individuals who chose to respond could differ from those who did not. Also, the HCPs of the 1-year survey differed from those of the 2-years survey, complicating comparisons between these time points. Moreover, fewer types of HCIs participated in the 2-years survey. However, 2 years after the initial COVID-19 outbreak these were the most important HCIs involved in the COVID-19 aftercare. Similarly, the relatively low response rate from HCPs of some HCIs, thereby potentially overlooking disciplines involved in the COVID-19 aftercare, could result in a more positive or negative perspective, further complicating the generalizability of the results. Nevertheless, obtaining insights from a single representative can still provide a reasonable informative understanding of the HCI's operational dynamics. In addition, this research was conducted with a small sample size in a specific urban region, which may restrict the transferability of the findings to other healthcare settings. However, the insights gathered from this region could still be applicable to other regions in the Netherlands, as healthcare delivery is constructed rather similarly across the country. Thus, to enhance the generalizability, future investigations should explore diverse healthcare settings, wider geographical regions, and larger sample sizes.

CONCLUSION

Overall, HCPs held a favorable perspective on the organization of COVD-19 post-hospital aftercare at both 1 and 2 years, despite its rapid development and limited available knowledge.

Directions to improve COVID-19 aftercare involve implementing quality indicators for monitoring follow-up care, establishing a well-defined COVID-

19 aftercare pathway, addressing resource constraints, and improving multidisciplinary collaboration and communication among disciplines and HCIs. As new COVID-19 patients present themselves daily, these findings offer valuable insights for policymakers of representing HCP associations, healthcare insurance companies, and national healthcare authorities to further develop and improve the COVID-19 post-hospital aftercare and for pandemic preparedness.

We recommended that to enhance the effectiveness of COVID-19 post-hospital aftercare, it is crucial to prioritize the development and implementation of integrated care pathways at a national level. Policymakers, particularly those from HCP associations, healthcare insurance companies, and national health authorities, should take a leading role in overcoming barriers related to policy, financial resources, and data management. A coordinated approach between primary and secondary care, with a central role for general practitioners, is essential to ensure patient-centered and continuous care. Furthermore, resource constraints should be addressed through workforce expansion, extended treatment periods, and the integration of e-health interventions, which will require careful strategic planning. These might not only improve COVID-19 aftercare but also strengthen preparedness for future pandemics.

REFERENCES

1. Miners S, Kehoe PG, Love S. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther*. 2020;12(1):170.
2. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-15.
3. NHG-Richtlijnen: Langdurige klachten na COVID-19 [Internet]. The Netherlands. NHG-Richtlijnen: Nederlands Huisartsen Genootschap; [updated 2022 March; cited 2024 Feb 27]. Available from: https://richtlijnen.nhg.org/standaarden/langdurige-klachten-na-covid-19
4. VerenSo. COVID-19 / Coronavirus [Internet]. The Netherlands. Vereniging van specialisten ouderengeneeskunde; [updated 2022 Sep 07; cited 2024 Feb 27]. Available from: https://www.verenso.nl/kwaliteit/thema-s-en-projecten/infectieziekten/covid-19-coronavirus
5. Santhosh L, Block B, Kim SY, Raju S, Shah RJ, Thakur N, et al. Rapid Design and Implementation of Post-COVID-19 Clinics. *Chest*. 2021;160(2):671-7.
6. CDC: Post-COVID Conditions: Overview for Healthcare Providers [Internet]. Atlanta (GA). Centers for Disease Control and Prevention; [updated 2024 Feb 6; cited 2024 Feb 27]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html.
7. NICE: COVID-19 rapid guideline: managing the long-term effects of COVID-19 [Internet]. United Kingdom. National Institute for Health and Care Excellence; [updated 2024 Jan 25; cited 2024 Feb 27]. Available from: https://www.nice.org.uk/guidance/ng188
8. WHO: Clinical management of COVID-19: World Health Organization [Internet]. Geneva, Switserland. World Health Organisation; [updated 2023 Aug 18; cited 2024 Feb 27]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.1.
9. FMS: Langdurige klachten en revalidatie na COVID-19 Richtlijnendatabase [Internet]. The Netherlands. Federatie Medisch Specialisten; [updated 2022 March 21; cited 2024 Feb 27]. Available from:https://richtlijnendatabase.nl/richtlijn/covid-19/startpagina_-_langdurige_klachten_en_revalidatie_na_covid-19.html.
10. Belfroid E, van Steenbergen J, Timen A, Ellerbroek P, Huis A, Hulscher M. Preparedness and the importance of meeting the needs of healthcare workers: a qualitative study on Ebola. *J Hosp Infect*. 2018;98(2):212-8.
11. Billings J, Ching BCF, Gkofa V, Greene T, Bloomfield M. Experiences of frontline healthcare workers and their views about support during COVID-19 and previous pandemics: a systematic review and qualitative meta-synthesis. *BMC Health Serv Res*. 2021;21(1):923.
12. Marta W, Melanie H, Nina G, et al. Transformation of primary care during the COVID-19 pandemic: experiences of healthcare professionals in eight European countries. *Br J Gen Pract*. 2021;71(709):e634.
13. Rawaf S, Allen LN, Stigler FL, Kringos D, Quezada Yamamoto H, van Weel C. Lessons on the COVID-19 pandemic, for and by primary care professionals worldwide. *Eur J Gen Pract*. 2020;26(1):129-33.
14. Sterling MR, Tseng E, Poon A, et al. Experiences of Home Health Care Workers in New York City During the Coronavirus Disease 2019 Pandemic: A Qualitative Analysis. *JAMA Intern Med*. 2020;180(11):1453-9.
15. Van Poel E, van Loenen T, Collins C, Van Roy K, Van den Muijsenbergh M, Willems S. Barriers and Enablers Experienced by General Practitioners in Delivering Safe and Equitable Care during COVID-19: A Qualitative Investigation in Two Countries. *Healthcare*. 2023;11(23):3009.
16. Valenzuela C, Nigro M, Chalmers JD, et al. COVID-19 follow-up programs across Europe: an ERS END-COVID CRC survey. *Eur Respir J*. 2022:2200923.
17. Bek LM, Berentschot JC, Hellemons ME, et al. 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 2years after hospital discharge. *BMC Health Serv Res*. 2021;21(1):847.
18. Sharma A, Minh Duc NT, Luu Lam Thang T, et al. A Consensus-Based Checklist for Reporting of Survey Studies (CROSS). *J Gen Intern Med*. 2021;36(10):3179-87.
19. Vanhaecht K, De Witte K, Depreitere R, Van Zelm R, De Bleser L, Proost K, Sermeus W. Development and validation of a care process self-evaluation tool. *Health Serv Manage Res*. 2007;20(3):189-202.
20. Seys D, Deneckere S, Sermeus W, et al. The Care Process Self-Evaluation Tool: a valid and reliable instrument for measuring care process organization of health care teams. *BMC Health Serv Res*. 2013;13:325.

21. GmbH. L. LimeSurvey: An Open Source survey tool: LimeSurvey GmbH, Hamburg, Germany.; [Available from: http://www.limesurvey.org.
22. Vanhaecht K, De Witte K, Panella M, Sermeus W. Do pathways lead to better organized care processes? *J Eval Clin Pract*. 2009;15(5):782-8.
23. Bravi F, Ruscio ED, Frassoldati A, et al. Patient and Health Care Professional Perspectives: A Case Study of the Lung Cancer Integrated Care Pathway. *Int J Integr Care*. 2018;18(4):7.
24. Plishka CT, Rotter T, Penz ED, Hansia MR, Fraser SA, Marciniuk DD, Saskatchewan CCRG. Effects of Clinical Pathways for COPD on Patient, Professional, and Systems Outcomes: A Systematic Review. *Chest*. 2019;156(5):864-77.
25. Black N. Patient reported outcome measures could help transform healthcare. *BMJ*. 2013;346:f167.
26. Ahmed S, Berzon RA, Revicki DA, et al. The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. *Med Care*. 2012;50(12):1060-70.
27. Seys D, Coeckelberghs E, Sermeus W, Van Zelm R, Panella M, Babu Payedimarri A, Vanhaecht K. Overview on the target population and methods used in care pathway projects: A narrative review. *Int J Clin Pract*. 2021;75(10):e14565.
28. Brus IM, Spronk I, Haagsma JA, et al. Prerequisites, barriers and opportunities in care for Q-fever patients: a Delphi study among healthcare workers. *BMC Health Serv Res*. 2023;23(1):319.
29. Seckler E, Regauer V, Rotter T, Bauer P, Müller M. Barriers to and facilitators of the implementation of multi-disciplinary care pathways in primary care: a systematic review. *BMC Fam Pract*. 2020;21(1):113.
30. Walker SC, Baquero B, Bekemeier B, Parnes M, Arora K. Strategies for enacting health policy codesign: a scoping review and direction for research. *Implement Sci*. 2023;18(1):44.
31. Forsetlund L, Bjorndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*. 2009;2009(2):CD003030.
32. Hempel S, O'Hanlon C, Lim YW, Danz M, Larkin J, Rubenstein L. Spread tools: a systematic review of components, uptake, and effectiveness of quality improvement toolkits. Implement Sci. 2019;14(1):83.
33. Lalani M, Wytrykowski S, Hogan H. Approaches to improving patient safety in integrated care: a scoping review. *BMJ Open*. 2023;13(4):e067441.
34. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*. 2007;2007(4):CD000409.
35. Van Grootven B, Irusta LA, Christiaens W, et al. Experiences with the implementation of remote monitoring in patients with COVID-19: A qualitative study with patients and healthcare professionals. *J Nurs Scholarsh*. 2023;55(1):67-78.
36. Haleem A, Javaid M, Singh RP, Suman R. Telemedicine for healthcare: Capabilities, features, barriers, and applications. *Sens Int*. 2021;2:100117.



Chapter 9

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)

Julia C. Berentschot*
L. Martine Bek*
Majanka H. Heijenbrok-Kal
Jasper van Bommel
Gerard M. Ribbers
Joachim G.J.V. Aerts
Merel E. Hellemons**
Rita J.G. van den Berg-Emons**
On behalf of the CO-FLOW Collaboration Group***

* Authors share first authorship
** Authors share senior authorship
*** Listed in Appendix

Journal of Intensive Care.2024;12(1):47.

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;[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 (α=0.00185), validated PROMs (α=0.00417), objective study measurements (α=0.01), and routine follow-up data (α=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 (Fig. 9.1), 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 9.1 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.

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 9.2 and Supplementary Table 9.1). 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 9.2).

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 9.2). 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 9.1 *Baseline characteristics of study participants.*

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Patient characteristics					
Age, years					0.19
Mean		59.7 (11.4)	60.6 (11.4)	58.6 (11.5)	
Median		60.0 (53.0-67.0)	61.0 (53.0-68.0)	60.0 (53.0-67.0)	
Sex, male		449 (69%)	244 (65%)	205 (75%)	**0.005**
BMI, kg/m^2	589				**<0.001**
Mean		29.4 (5.4)	28.5 (5.1)	30.5 (5.5)	
Median		28.4 (25.7-32.2)	27.6 (25.3-31.0)	29.7 (26.3-33.3)	
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**

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
Diabetes		130 (20%)	78 (21%)	52 (19%)	0.61
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**

Table 9.1 *Continued*

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
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**
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**

	N[a]	All (N=650)	Non-ICU (n=377)	ICU (n=273)	P value
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%)	
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).

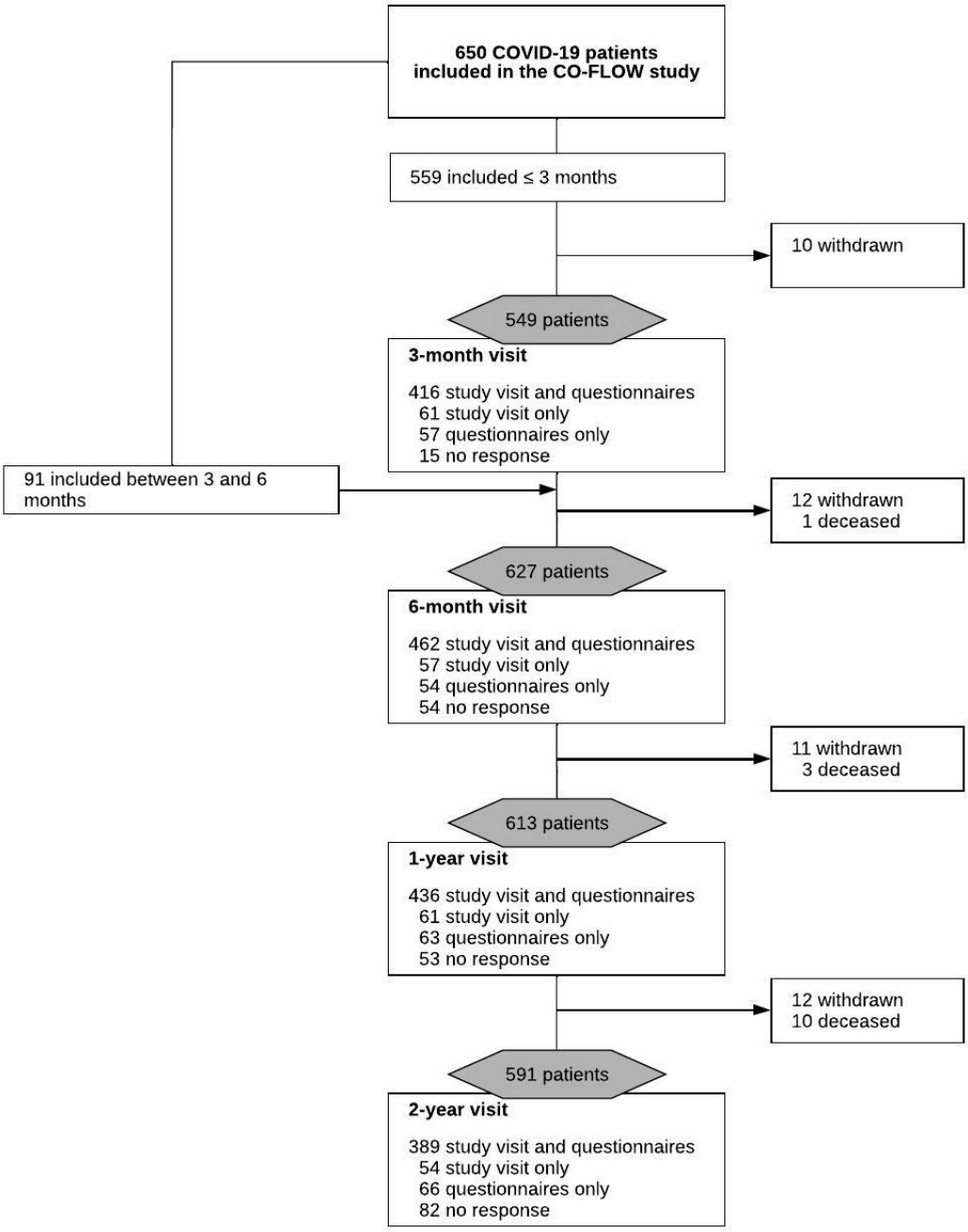


Figure 9.1 Flowchart of CO-FLOW study visits.

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 9.3). 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.

Table 9.2 *Trajectories of self-reported recovery and the ten most prevalent symptoms in*

	Total					**Non-ICU**		
	3 M	**6 M**	**1 Y**	**2 Y**	**P value**	**3 M**	**6 M**	**1 Y**
Recovery status, *n*	*159*	*300*	*418*	*443*		*90*	*184*	*225*
Not completely recovered	142 (89%)	248 (83%)	316 (77%)	322 (73%)	**<0.001**	78 (87%)	142 (77%)	159 (74%)
Symptoms, *n*	*441*	*528*	*532*	*503*		*275*	*311*	*310*
Impaired fitness	362 (83%)	379 (72%)*	346 (65%)*#	311 (62%)*ǂ	**<0.001**	217 (79%)	218 (70%)	196 (63%)
Fatigue	116/140 (83%)	162/241 (67%)*	237/380 (62%)#	302/493 (61%)	**<0.001**	74/84 (88%)	93/140 (66%)	146/235 (62%)
Dyspnea	87/128 (68)%	127/237 (54%)*	210/378 (56%)	251/493 (51%)	**0.001**	61/78 (78%)	74/135 (55%)	133/235 (56%)
Muscle weakness	253 (58%)	258 (49%)*	225 (42%)*#	189 (38%)ǂ	**<0.001**	143 (52%)	135 (43%)	116 (38%)
Memory problems	238 (54%)	302 (57%)	296 (56%)	274 (55%)	0.44	163 (59%)	190 (61%)	177 (57%)
Concentration problems	232 (53%)	273 (52%)	271 (51%)	259 (52%)	0.81	158 (58%)	166 (54%)	159 (51%)
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%)
Joint pain	187 (43%)	218 (41%)	217 (41%)	170 (34%)ǂ	**<0.001**	109 (40%)	113 (36%)	110 (36%)
Balance problems/ dizziness	184 (42%)	228 (44%)	223 (42%)	200 (40%)	0.53	118 (43%)	126 (41%)	123 (40%)
Sleep disturbances	160 (36%)	182 (35%)	185 (35%)	141 (28%)*	**0.002**	108 (39%)	119 (39%)	101 (33%)

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.

ICU- and *non-ICU-treated patients for COVID-19 up to 2 years after hospital discharge.*

Non-ICU	ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
2 Y	**3 M**	**6 M**	**1 Y**	**2 Y**	**P value**	**P value**
260	*69*	*116*	*193*	*183*		
180 (69%)	64 (93%)	106 (91%)	157 (81%)	142 (78%)	0.003	0.08
300	*166*	*218*	*222*	*203*		
165 (58%)	145 (88%)	161 (74%)	149 (67%)	138 (68%)	0.02	0.17
190/292 (58%)	42/56 (75%)	69/101 (68%)	91/145 (63%)	132/201 (66%)	0.99	0.16
139/292 (48%)	26/50 (52%)	53/102 (52%)	77/143 (54%)	112/201 (56%)	0.47	0.005
105 (35%)	110 (66%)	123 (57%)	108 (49%)	84 (41%)	**<0.001**	0.23
155 (52%)	75 (45%)	112 (52%)	119 (54%)	119 (59%)	0.11	**0.001**
150 (50%)	74 (45%)	107 (49%)	111 (50%)	109 (54%)	0.19	0.03
103/294 (35%)	17/48 (35%)	44/100 (44%)	55/145 (38%)	90/201 (46%)	0.65	0.09
92 (31%)	78 (48%)	105 (48%)	107 (48%)	78 (38%)	0.002	0.75
104 (35%)	66 (40%)	102 (47%)	99 (45%)	96 (48%)	0.09	0.09
73 (24%)	52 (31%)	63 (29%)	83 (37%)	68 (34%)	0.97	**<0.001**

*The trajectories of all the assessed symptoms are shown in Supplementary Table 9.1. 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 ŧ between the 6-month and 2-year study visits. † indicates significant difference between ICU and non-ICU group at 2 years.*

Table 9.3 *Trajectories of validated PROMs in COVID-19 patients up to 2 years*

	Total					Non-ICU	
	3 M	**6 M**	**1 Y**	**2 Y**	**P value**	**3 M**	**6 M**
Fatigue, *n*	*438*	*483*	*478*	*433*		*272*	*289*
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)
Fatigue (FAS ≥22)	258 (59%)	278 (58%)	266 (56%)	222 (51%)†	**0.004**	166 (61%)	170 (59%)
mMRC dyspnea scale, *n*	*433*	*484*	*473*	*466*		*270*	*289*
mMRC ≥1	175 (40%)	174 (36%)	163 (35%)	187 (40%)	0.08	117 (43%)	110 (38%)
Mental health, *n*	*436*	*486*	*483*	*446*		*274*	*294*
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)
Anxiety (HADS-A ≥11)	56 (13%)	50 (10%)	53 (11%)	43 (10%)	0.27	38 (14%)	31 (11%)
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)
Depression (HADS-D ≥11)	49 (11%)	45 (9%)	50 (10%)	45 (10%)	0.84	34 (13%)	33 (11%)
IES-R, total score	14.1 (13.9)	12.2 (12.6)*	12.0 (12.5) #	10.9 (12.5)*†	**<0.001**	13.4 (13.2)	11.7 (12.2)
PTSD (IES-R ≥33)	51 (12%)	41 (9%)	35 (7%)#	31 (7%)	**0.004**	28 (10%)	22 (8 %)
Cognition, *n*	*433*	*476*	*470*	*438*		*271*	*290*
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)
Cognitive failures (CFQ >43)	95 (22%)	114 (24%)	103 (22%)	102 (23%)	0.31	67 (25%)	74 (26%)
Sleep quality, *n*	*428*	*471*	*462*	*427*		*264*	*284*
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)
PSQI, Poor sleep quality (PSQI ≥5)	286 (67%)	311 (66%)	275 (60%)#	259 (61%)	**0.001**	179 (68%)	189 (67%)
Functioning in ADL, *n*	*448*	*499*	*491*	*449*		*271*	*302*
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)
Physical function							
Physical fitness, *n*	*452*	*492*	*487*	*447*		*276*	*297*
Physical fitness, IFIS, very poor/ poor	128 (28%)	85 (17%)*	87 (18%)#	81 (18%)	**<0.001**	70 (25%)	52 (33%)
Physical fitness, IFIS, Average/good/ very good	324 (72%)	407 (83%)	401 (82%)	366 (82%)		206 (75%)	245 (83%)
IPAQ-SF, *n*	*356*	*371*	*350*	*340*		*216*	*224*
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)
Participation, *n*	*440*	*485*	*477*	*436*		*269*	*292*
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)

after hospital discharge.

Non-ICU		ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
1 Y	**2 Y**	**3 M**	**6 M**	**1 Y**	**2 Y**	**P value**	**P value**
288	*257*	*166*	*194*	*190*	*176*		
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
162 (56%)	132 (51%)	92 (55%)	108 (56%)	103 (54%)	90 (51%)	0.64	0.86
285	*278*	*163*	*195*	*188*	*188*		
107 (38%)	113 (41%)	58 (36%)	64 (33%)	56 (30%)	74 (40%)	0.15	0.60
291	*263*	*163*	*194*	*194*	*183*		
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
28 (10%)	19 (7%)	18 (11%)	19 (10%)	25 (13%)	24 (13%)	0.49	0.01
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
28 (10%)	23 (9%)	15 (9%)	12 (6%)	22 (12%)	22 (12%)	0.99	0.004
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**
15 (5 %)	12 (5%)	23 (14%)	19 (10%)	20 (10%)	19 (11%)	0.01	0.06
282	*259*	*162*	*186*	*188*	*179*		
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
66 (23%)	58 (22%)	28 (17%)	40 (22%)	37 (20%)	44 (25%)	0.30	0.27
282	*251*	*164*	*187*	*180*	*176*		
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
164 (58%)	157 (63%)	107 (65%)	122 (65%)	111 (62%)	102 (58%)	0.81	0.21
297	*263*	*177*	*197*	*194*	*186*		
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
294	*264*	*176*	*195*	*193*	*183*		
47 (16%)	50 (19%)	58 (33%)	33 (17%)	39 (20%)	31 (17%)	0.65	0.09
247 (84%)	214 (81%)	118 (67%)	162 (83%)	154 (80%)	152 (83%)		
214	*202*	*140*	*147*	*136*	*138*		
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
287	*259*	*171*	*193*	*190*	*177*		
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 9.3 *Continued*

	Total					**Non-ICU**	
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)
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)
Employment status, n	*345*	*320*	*299*	*216*		*190*	*183*
IPCQ, not or partially returned to work	244 (71%)	158 (49%)	93 (31%)	65 (30%)	**<0.001**	107 (56%)	64 (35%)
iPCQ, fully returned to work	101 (29%)	162 (51%)	206 (69%)	151 (70%)		83 (44%)	119 (65%)
HRQoL							
EQ-5D-5L, n	*442*	*482*	*479*	*437*		*274*	*288*
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)
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)
SF-36, n	*434*	*481*	*476*	*441*		*274*	*292*
Physical component summary	41.3 (10.5)	43.4 (10.5)*	44.8 (10.4)*#	44.7 (10.6) ǂ	**<0.001**	42.1 (10.5)	44.2 (10.3)
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)

*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 9.3A-9.3B. 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.*

Non-ICU		ICU				Overall comparison, ICU vs. non-ICU	Interaction ICU * Time
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
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
176	*124*	*155*	*137*	*123*	*92*		
47 (27%)	32 (26%)	137 (88%)	94 (69%)	46 (37%)	33 (36%)	**<0.001**	**<0.001**
129 (73%)	92 (74%)	18 (12%)	43 (31%)	77 (63%)	59 (64%)		
289	*260*	*168*	*194*	*190*	*177*		
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
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
286	*262*	*161*	*190*	*191*	*179*		
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
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

** 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 ŧ between the 6-month and 2-year study visits. 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 Index; 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.*

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 9.3). Over time, as for mental health, Fig. 9.2A presents the group trajectories of PTSD and cognitive failures scores and the proportion of patients with depression and anxiety (Supplementary Table 9.4); 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 9.5). 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 9.4). 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 (Fig. 9.2B); trajectories of cognitive function and DEMMI scores were comparable (Supplementary Table 9.5). 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.

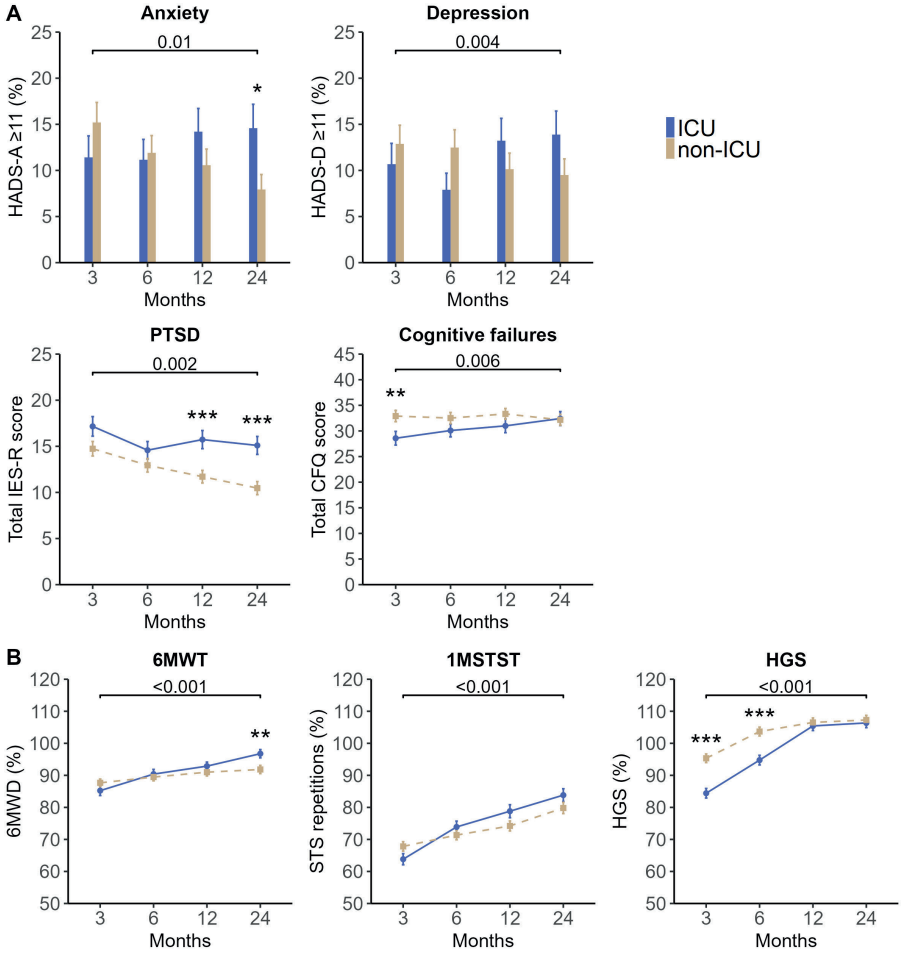


Figure 9.2 Trajectories of A: mental health and cognition and B: physical function in ICU- and non-ICU-treated patients for COVID-19 up to 2 years after hospital discharge.
*Data are presented as estimated proportions or estimated means with standard errors obtained from Generalized Estimating Equations 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 9.4. 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.*

Routine follow-up data

The PFT parameters and radiographic abnormalities for the total cohort at each visit are shown in Supplementary Table 9.6. Patients without signs of residual radiological or pulmonary function abnormalities were discharged from regular follow-up (Supplementary Fig. 9.1). 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 9.7).

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) (Fig. 9.3). 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 Fig. 9.2. 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 Fig. 9.2A). 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 Fig. 9.2B). 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 Fig. 9.2C). 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 Fig. 9.2D).

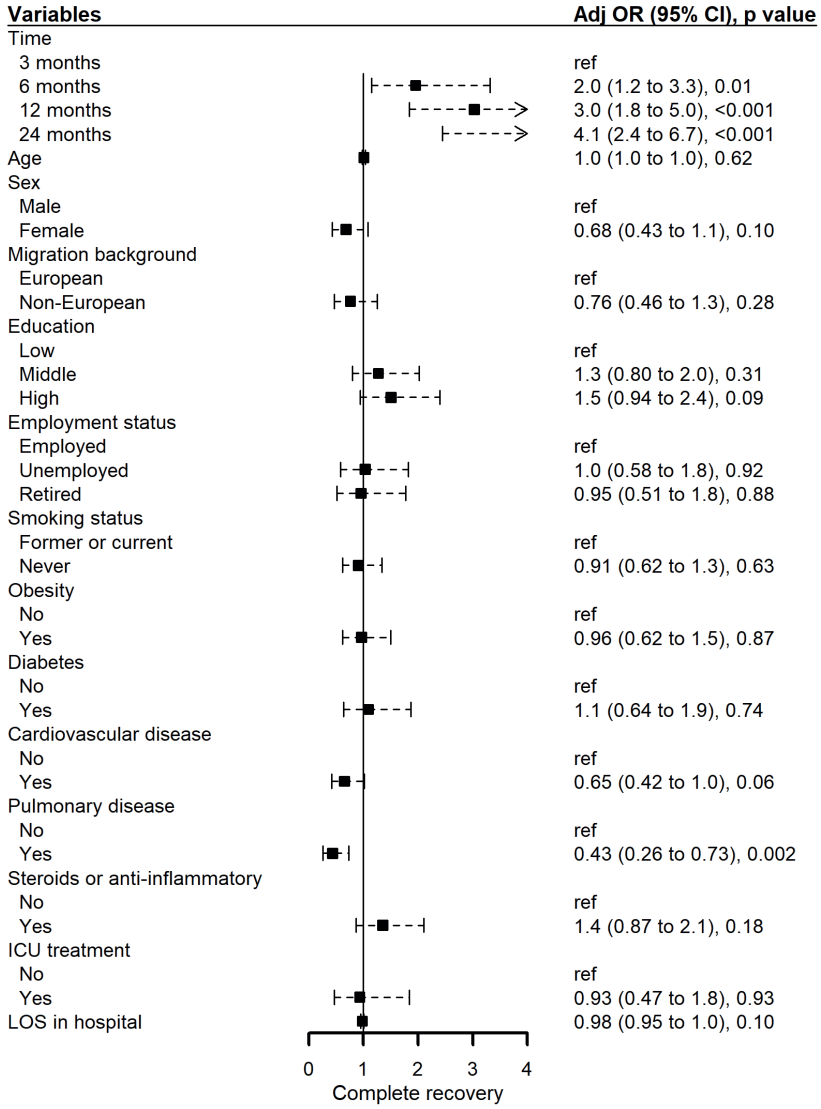


Figure 9.3 Forest plot presenting risk factors for self-reported recovery status from COVID-19.

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 the 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 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.

REFERENCES

1. WHO. WHO Coronavirus (COVID-19) Dashboard. [updated 2023 Sept 13; cited 2023 Sept 18]. Available from: https://covid19.who.int/
2. Group P-CC. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022;10(8):761-775.
3. Bek LM, Berentschot JC, Heijenbrok-Kal MH, et al. Symptoms persisting after hospitalisation for COVID-19: 12 months interim results of the CO-FLOW study. *ERJ Open Res*. 2022;8(4)
4. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863-876.
5. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol*. 2022;94(1):253-262.
6. Tene L, Bergroth T, Eisenberg A, David SSB, Chodick G. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID. *Int J Infect Dis*. 2023;128:3-10.
7. Fernández-de-Las-Peñas C, Martín-Guerrero JD, Cancela-Cilleruelo I, Moro-López-Menchero P, Rodríguez-Jiménez J, Pellicer-Valero OJ. Exploring the trajectory recovery curve of the number of post-COVID Symptoms: The LONG-COVID-EXP-CM Multicenter Study. *Int J Infect Dis*. 2022;117:201-203.
8. Seeßle J, Waterboer T, Hippchen T, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. *Clin Infect Dis*. 2021;74(7):1191-1198.
9. Yang X, Hou C, Shen Y, et al. Two-Year Health Outcomes in Hospitalized COVID-19 Survivors in China. *JAMA Netw Open*. 2022;5(9):e2231790.
10. Shen Q, Joyce EE, Ebrahimi OV, et al. COVID-19 illness severity and 2-year prevalence of physical symptoms: an observational study in Iceland, Sweden, Norway and Denmark. *Lancet Reg Health Eur*. 2023;35:100756.
11. Ballouz T, Menges D, Anagnostopoulos A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ*. 2023;381:e074425.
12. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference*. *Crit Care Med*. 2012;40(2):502-509.
13. Wahlgren C, Forsberg G, Divanoglou A, et al. Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. *Lancet Reg Health Eur*. 2023;28:100595.
14. Vlake JH, Wesselius S, van Genderen ME, van Bommel J, Boxma-de Klerk B, Wils EJ. Psychological distress and health-related quality of life in patients after hospitalization during the COVID-19 pandemic: A single-center, observational study. *PLoS One*. 2021;16(8):e0255774.
15. Dirican E, Bal T. COVID-19 disease severity to predict persistent symptoms: a systematic review and meta-analysis. *Prim Health Care Res Dev*. 2022;23:e69.
16. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2023;183(6):566-580.
17. Musheyev B, Boparai MS, Kimura R, et al. Longitudinal medical subspecialty follow-up of critically and non-critically ill hospitalized COVID-19 survivors up to 24 months after discharge. *Intern Emerg Med*. 2023;18(2):477-486.
18. NICE. COVID-19 op de Nederlandse verpleegafdelingen; Patiëntkarakteristieken en uitkomsten. [updated 2023 March 30; cited 2024 May 01]. Available from: https://stichting-nice.nl/
19. Bek LM, Berentschot JC, Hellemons ME, et al. 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 services research*. 2021;21(1):1-10.
20. Grimby G, Börjesson M, Jonsdottir IH, Schnohr P, Thelle DS, Saltin B. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports*. 2015;25 Suppl 4:119-25.

21. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med*. 2021;49(3):503-516.
22. de Kleijn WP, De Vries J, Wijnen PA, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med*. 2011;105(9):1388-95.
23. Williams N. The MRC breathlessness scale. *Occup Med (Lond)*. 2017;67(6):496-497.
24. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. Significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J*. 1959;2(5147):257.
25. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.
26. Weiss DS, Marmar CR, Wilson JP, Keane TM. Assessing psychological trauma and PTSD. The Impact of Events Scale—Revised. 1997;19:399-411.
27. Zilberg NJ, Weiss DS, Horowitz MJ. Impact of Event Scale: a cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol*. Jun 1982;50(3):407-14.
28. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16.
29. Ponds R, Boxtel M, Jolles J. De 'Cognitive Failure Questionnaire' als maat voor subjectief cognitief functioneren. *Tijdschrift voor Neuropsychologie*. 2006;1:37-45.
30. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
31. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J*. 1965;14:61-5.
32. Merellano-Navarro E, Collado-Mateo D, García-Rubio J, Gusi N, Olivares PR. Validity of the International Fitness Scale "IFIS" in older adults. *Exp Gerontol*. 2017;95:77-81.
33. Vandelanotte C, Bourdeaudhuij I, Philippaerts R, Sjostrom M, Sallis JF. Reliability and Validity of a Computerized and Dutch Version of the International Physical Activity Questionnaire (IPAQ). *J Phys Act Health*. 2005;2:63-75.
34. Post MW, van der Zee CH, Hennink J, Schafrat CG, Visser-Meily JM, van Berlekom SB. Validity of the utrecht scale for evaluation of rehabilitation-participation. *Disabil Rehabil*. 2012;34(6):478-85.
35. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.
36. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
37. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055-68.
38. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-9.
39. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.
40. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. *Clin Physiol Funct Imaging*. 2002;22(2):115-24.
41. Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip dynamometry. *Curr Opin Clin Nutr Metab Care*. 2015;18(5):465-70.
42. de Morton NA, Davidson M, Keating JL. The de Morton Mobility Index (DEMMI): an essential health index for an ageing world. *Health Qual Life Outcomes*. 2008;6:63.
43. Sommers J, Vredeveld T, Lindeboom R, Nollet F, Engelbert RHH, van der Schaaf M. de Morton Mobility Index Is Feasible, Reliable, and Valid in Patients With Critical Illness. *Physical Therapy*. 2016;96(10):1658-1666.
44. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *American journal of respiratory and critical care medicine*. 1998;158(5):1384-1387.
45. Strassmann A, Steurer-Stey C, Dalla Lana K, et al. Population-based reference values for the 1-min sit-to-stand test. *International journal of public health*. 2013;58(6):949-953.
46. Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: normative data from twelve British studies. *PloS one*. 2014;9(12):e113637.
47. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49(1)

48. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3)
49. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-43.
50. Bek LM, Hellemons ME, Berentschot JC, et al. Cognitive and psychological recovery patterns across different care pathways 12 months after hospitalization for COVID-19: A multicenter cohort study (CO-FLOW). *Ann Phys Rehabil Med*. 2023;66(5):101737.
51. Heesakkers H, van der Hoeven JG, van den Boogaard M, Zegers M, group M-Ir. Two-year physical, mental and cognitive outcomes among intensive care unit survivors treated for COVID-19. *Intensive Care Med*. 2023;49(5):597-599.
52. van Veenendaal N, van der Meulen IC, Onrust M, Paans W, Dieperink W, van der Voort PHJ. Six-Month Outcomes in COVID-19 ICU Patients and Their Family Members: A Prospective Cohort Study. *Healthcare (Basel)*. 2021;9(7)
53. Bek LM, Berentschot JC, Hellemons ME, et al. Return to work and health-related quality of life up to 1 year in patients hospitalized for COVID-19: the CO-FLOW study. *BMC Medicine*. 2023;21(1):380.
54. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-146.
55. Ely EW, Brown LM, Fineberg HV, National Academies of Sciences E, Medicine Committee on Examining the Working Definition for Long C. Long Covid Defined. *N Engl J Med*. 2024;391(18):1746-1753.
56. Global Burden of Disease Long CC, Wulf Hanson S, Abbafati C, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA*. 2022;328(16):1604-1615.
57. Norredam M, Hayward S, Deal A, Agyemang C, Hargreaves S. Understanding and addressing long-COVID among migrants and ethnic minorities in Europe. *Lancet Reg Health Eur*. 2022;19:100427.
58. Jackson C, Stewart ID, Plekhanova T, et al. Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study. *Lancet Respir Med*. 2023;11(8):673-684.
59. Li J, Zhou Y, Ma J, et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. *Signal Transduct Target Ther*. 2023;8(1):416.
60. Català M, Mercadé-Besora N, Kolde R, et al. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia. *Lancet Respir Med*. 2024;12(3):225-236.



CHAPTER 10

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

Julia C. Berentschot*
L. Martine Bek*
Manon Drost
Rita J.G. van den Berg-Emons
Gert-Jan Braunstahl
Gerard M. Ribbers
Joachim G.J.V. Aerts
Merel E. Hellemons**
Majanka H. Heijenbrok-Kal**
On behalf of the CO-FLOW Collaboration Group***

* Authors share first authorship
** Authors share senior authorship
*** Listed in Appendix

The Lancet Regional Health - Europe.2025; Ahead of publication

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.

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 (Fig. 10.1). These patients were discharged from the hospital between March 26, 2020, and May 21, 2021. Table 10.1 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≤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 10.1).

Recovery status

Overall, the proportion of patients that felt completely recovered increased over time (p<0.001) (Supplementary Table 10.2). 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.

Table 10.1 *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/m²	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%)	
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%)	

Table 10.1 *Continued*

	N[a]	Participants included in analysis	N[a]	Participants not included in analysis	P value
≥2		152 (51%)		209 (60%)	
Obesity (BMI≥30 kg/m²)		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%)	
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

	N[a]	Participants included in analysis	N[a]	Participants not included in analysis	P value
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
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]

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 (Fig. 10.2). 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 10.3). 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 10.4A and 10.4B).

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 (Fig. 10.3 and Supplementary table 10.5). 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 10.5). 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.

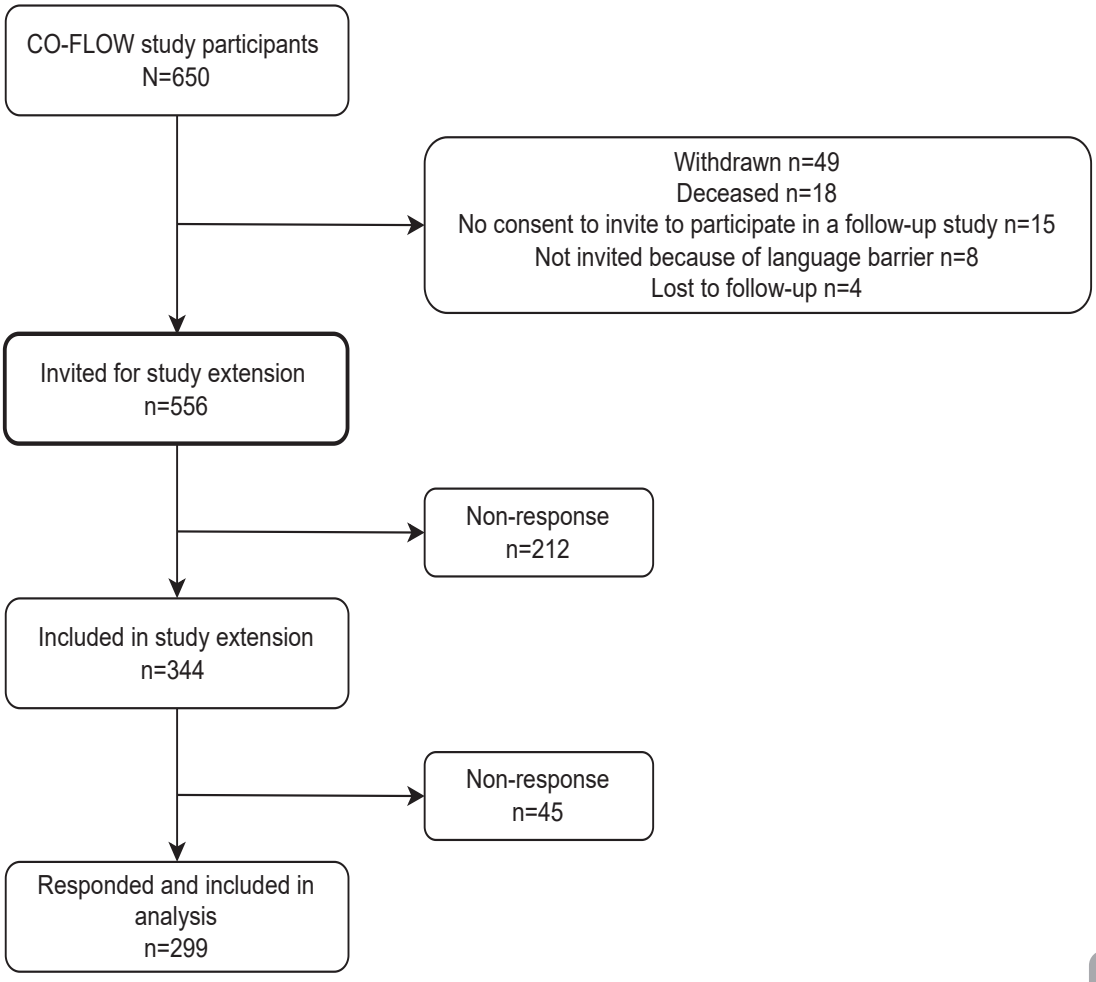


Figure 10.1 Flowchart of participants included in analysis.

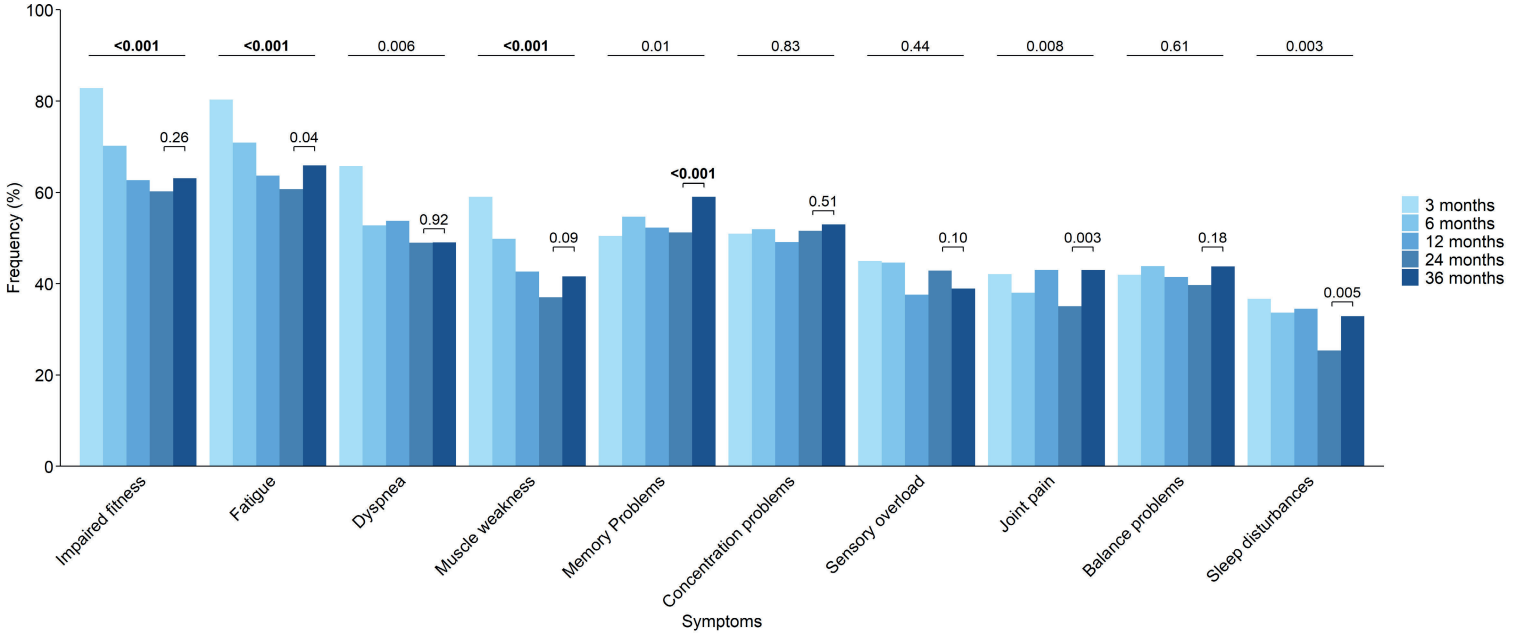


Figure 10.2 Trajectories of the ten most prevalent symptoms in patients with COVID-19 up to 3 years after hospital discharge.
P values are obtained from Generalized Estimating Equations analysis and are presented for changes over the overall follow-up period at the top and specifically from 2 to 3 years follow-up above the columns. A P value less than 0.0019 was considered statistically significant and is indicated in bold.

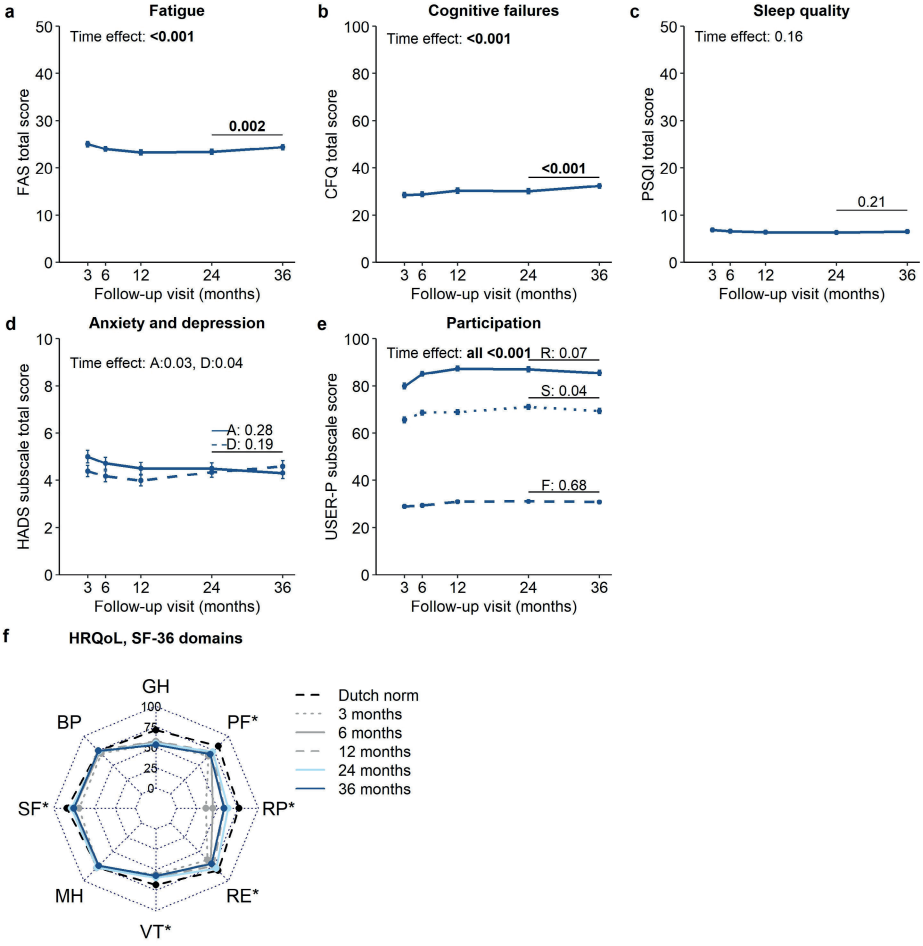


Figure 10.3 Trajectories of PROMs in patients up to 3 years after hospitalization for COVID-19. *Data are presented as estimated means with standard errors obtained from Generalized Estimating Equations analysis. The trajectories from 3 to 36 months post-discharge are presented for health outcomes of fatigue (a), cognitive failures (b), sleep quality (b), 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.*

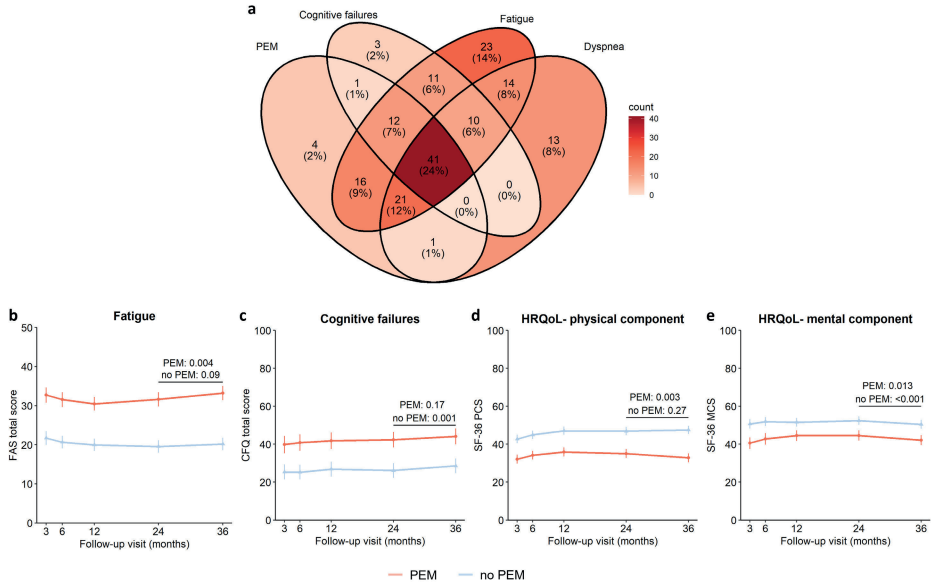


Figure 10.4 Co-occurring health problems and health outcome trajectories in patients with COVID-19 with and without PEM at 3 years.
Co-occurring health problems in patients with PEM (a) at 3 years after hospital discharge. Group comparisons were performed for the 3-year trajectories of fatigue (b), cognitive 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.

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 10.6). 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 (Fig. 10.4A). 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 10.7.

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).

Fig. 10.4B-E presents 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. Taking 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 unfavorable 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 underly mechanisms of long COVID. These include viral persistence or latent viral reactivation, immune dysregulation neuroinflammation, mitochondrial dysfunction, autoimmunity, 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 and many of whom also faced 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.

REFERENCES

1. World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed 1 Dec, 2024.
2. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863-76.
3. Berentschot JC, Bek LM, Heijenbrok-Kal MH, et al. 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). *J Intensive Care*. 2024;12(1):47.
4. National Academies of Sciences, Engineering, and Medicine. A long COVID definition: a chronic, systemic disease state with profound consequences. 2024.
5. World Health Organisation. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. 2021.
6. Ely EW, Brown LM, Fineberg HV, et al. Long Covid Defined. *N Engl J Med*. 2024.
7. Stussman B, Williams A, Snow J, et al. Characterization of Post-exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Neurol*. 2020;11:1025.
8. National Institute for Health and Care. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. https://www.nice.org.uk/guidance/ng206. Accessed 27 Oct, 2024.
9. Roma M, Marden CL, Flaherty MAK, et al. Impaired Health-Related Quality of Life in Adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Impact of Core Symptoms. *Front Pediatr*. 2019;7:26.
10. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019.
11. Twomey R, DeMars J, Franklin K, et al. Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. *Phys Ther*. 2022;102(4).
12. Cornelissen MEB, Bloemsma LD, Vaes AW, et al. Fatigue and symptom-based clusters in post COVID-19 patients: a multicentre, prospective, observational cohort study. *J Transl Med*. 2024;22(1):191.
13. An Y, Guo Z, Fan J, et al. Prevalence and measurement of post-exertional malaise in post-acute COVID-19 syndrome: A systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2024;91:130-42.
14. Buonsenso D, Yonker LM. Physical and cognitive stressors exacerbate symptoms in long COVID: more evidence triggering new research and therapeutic needs. *Lancet Reg Health Eur*. 2024;46:101109.
15. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-46.
16. Hastie CE, Lowe DJ, McAuley A, et al. True prevalence of long-COVID in a nationwide, population cohort study. *Nat Commun*. 2023;14(1):7892.
17. Fang Z, Ahrnsbrak R, Rekito A. Evidence Mounts That About 7% of US Adults Have Had Long COVID. *JAMA*. 2024;332(1):5-6.
18. Wahlgren C, Forsberg G, Divanoglou A, et al. Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. *Lancet Reg Health Eur*. 2023;28:100595.
19. Yang H, Guan L, Yang T, et al. Two- and 3-year outcomes in convalescent individuals with COVID-19: A prospective cohort study. *J Med Virol*. 2024;96(4):e29566.
20. Zhang H, Huang C, Gu X, et al. 3-year outcomes of discharged survivors of COVID-19 following the SARS-CoV-2 omicron (B.1.1.529) wave in 2022 in China: a longitudinal cohort study. *Lancet Respir Med*. 2024;12(1):55-66.
21. Cai M, Xie Y, Topol EJ, Al-Aly Z. Three-year outcomes of post-acute sequelae of COVID-19. *Nature Medicine*. 2024;30(6):1564-73.
22. Bek LM, Berentschot JC, Hellemons ME, et al. 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 services research*. 2021;21(1):1-10.
23. Grimby G, Börjesson M, Jonsdottir IH, et al. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports*. 2015;25 Suppl 4:119-25.
24. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med*. 2021;49(3):503-16.

25. Bek LM, Berentschot JC, Heijenbrok-Kal MH, et al. Symptoms persisting after hospitalisation for COVID-19: 12 months interim results of the CO-FLOW study. *ERJ Open Res*. 2022;8(4).
26. Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post-Exertional Malaise. *Diagnostics (Basel)*. 2018;8(3).
27. Kielland A, Liu J, Jason LA. Do diagnostic criteria for ME matter to patient experience with services and interventions? Key results from an online RDS survey targeting fatigue patients in Norway. *J Health Psychol*. 2023;28(13):1189-203.
28. de Kleijn WP, De Vries J, Wijnen PA, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med*. 2011;105(9):1388-95.
29. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. Significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British medical journal*. 1959;2(5147):257.
30. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.
31. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21(1):1-16.
32. Ponds R, van Boxtel, M. P. J., & Jolles, J. De Cognitive Failure Questionnaire als maat voor subjectief cognitief functioneren. *Tijdschrift voor neuropsychologie*. 2006;1(2):37-45.
33. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
34. Post MW, van der Zee CH, Hennink J, et al. Validity of the utrecht scale for evaluation of rehabilitation-participation. *Disabil Rehabil*. 2012;34(6):478-85.
35. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health*. 2015;18(6):753-8.
36. Verhoef JA, Miedema HS, Bramsen I, Roebroeck ME. Using the work limitations questionnaire in patients with a chronic condition in the Netherlands. *J Occup Environ Med*. 2012;54(10):1293-9.
37. Lerner D, Amick BC, 3rd, Rogers WH, et al. The Work Limitations Questionnaire. *Med Care*. 2001;39(1):72-85.
38. Lerner D. Scoring the Work Limitations Questionnaire (WLQ) scales and the WLQ index for estimating work productivity loss. *Technical Report*. 2003.
39. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
40. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055-68.
41. Ware J. SF-36 Physical and Mental Health Summary Scales: a User's Manual. 1993;8.
42. RIVM. Coronadashboard. Secondary Coronadashboard. 2022. https://coronadashboard.rijksoverheid.nl/. Accessed 16 Jun, 2022.
43. Pagen DME, Van Herck M, van Bilsen CJA, et al. High proportions of post-exertional malaise and orthostatic intolerance in people living with post-COVID-19 condition: the PRIME post-COVID study. *Front Med (Lausanne)*. 2023;10:1292446.
44. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2023;183(6):566-80.
45. Vélez-Santamaría R, Fernández-Solana J, Méndez-López F, et al. Functionality, physical activity, fatigue and quality of life in patients with acute COVID-19 and Long COVID infection. *Sci Rep*. 2023;13(1):19907.
46. Greenwood DC, Mansoubi M, Bakerly ND, et al. Physical, cognitive, and social triggers of symptom fluctuations in people living with long COVID: an intensive longitudinal cohort study. *Lancet Reg Health Eur*. 2024;46:101082.
47. Legler F, Meyer-Arndt L, Mödl L, et al. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort. *EClinicalMedicine*. 2023;63:102146.
48. Global Burden of Disease Long COVID Collaborators, Wulf Hanson S, Abbafati C, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA*. 2022;328(16):1604-15.
49. Möller M, Borg K, Janson C, et al. Cognitive dysfunction in post-COVID-19 condition: Mechanisms, management, and rehabilitation. *J Intern Med*. 2023;294(5):563-81.
50. Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun*. 2022;101:93-135.

51. Greene C, Connolly R, Brennan D, et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nat Neurosci*. 2024;27(3):421-32.
52. Peluso MJ, Deeks SG. Mechanisms of long COVID and the path toward therapeutics. *Cell*. 2024.
53. Català M, Mercadé-Besora N, Kolde R, et al. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia. *Lancet Respir Med*. 2024;12(3):225-36.
54. NICE. COVID-19 op de Nederlandse verpleegafdelingen; Patiëntkarakteristieken en uitkomsten 2020. https://stichting-nice.nl/. Accessed 1 May, 2024.



Chapter 11

General discussion

GENERAL DISCUSSION

When the first reports emerged of an unidentified virus in China, the full magnitude of the impact it would have on global health was unforeseeable. Breaking news reports soon revealed the culprit: a novel coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the disease now known as COVID-19. This virus spread rapidly, infecting millions and placing unprecedented strain on healthcare systems worldwide. Amidst this uncertainty of impact on patient health and healthcare systems, the CO-FLOW study was prepared during the first wave of the pandemic in the Netherlands, shortly after the first patients were hospitalized for COVID-19. Launched in June 2020, the CO-FLOW study aimed to set up a registry and to systematically and comprehensively evaluate the COVID-19 aftercare pathways and the long-term health outcomes of patients hospitalized for COVID-19 in the Rotterdam-Rijnmond-Delft region in the Netherlands. By examining patient recovery trajectories, identifying risk factors, evaluating outcomes across different COVID-19 post-hospital aftercare pathways, and assessing the perspective of both patients and healthcare professionals on the aftercare processes, the CO-FLOW study generated insights to inform and enhance the further development of COVID-19 aftercare pathways. The CO-FLOW study was conducted by two PhD students, allowing for collaborative and individual analysis of various topics, resulting in two theses, both comprising the CO-FLOW study protocol (**Chapter 2**), 1-year persisting symptoms (**Chapter 4**), and the 2-year (**Chapter 9**) and 3-year (**Chapter 10**) long-term health outcomes (Fig. 11.1). The focus of this thesis is on 6-month pulmonary, physical, and psychological outcomes (**Chapter 3**); the 1-year cognitive and psychological recovery across care pathways (**Chapter 5**); the 1-year trajectories of return to work and health-related quality of life (HRQoL) (**Chapter 6**); the association between severity of acute COVID-19 and long-term health outcomes up to 1 year (**Chapter 7**), and healthcare professionals' perspective on the organization of COVID-19 post-hospital aftercare (**Chapter 8**). In the general discussion (**Chapter 11**), the main findings of this thesis are presented and discussed, along with methodological considerations, clinical implications, and directions for future research.

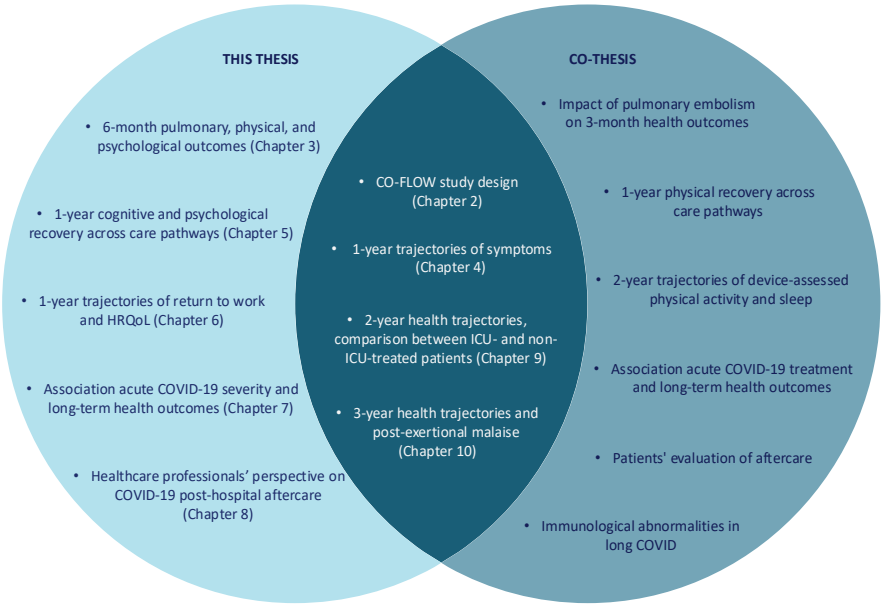


Figure 11.1 The research topics of the CO-FLOW study described in this thesis, in both theses and in the co-thesis.

MAIN FINDINGS

Trajectories and prevalence of long-term health outcomes

The trajectories of long-term health outcomes in patients who survived hospitalization for COVID-19 reveal a complex pattern of recovery. Some health domains, such as pulmonary and objectively assessed physical (cardiorespiratory fitness and muscle strength) function, showed significant improvement, especially within the first six months, with only a small proportion of patients experiencing impairments at 2 years (**Chapter 9**).[1-3] Psychological outcomes, including symptoms of anxiety, depression, and posttraumatic stress, also improved significantly within the first six months and their prevalence was low and comparable to the Dutch norm.[4,5] In most other health domains, gradual improvement was observed over time. However, a substantial proportion of patients continued to experience persistent health problems, with many reporting fatigue, impaired fitness, cognitive problems, poor sleep quality, dyspnea, and post-exertional malaise (PEM) even 3 years after discharge (Fig. 11.2) (**Chapter 10**). In fact, 76% of patients reported incomplete recovery 3 years post-discharge. These findings on persistent symptoms align with other longitudinal cohort studies in patients hospitalized

for COVID-19.[6-12] A population-based study by Ballouz et al. found that 17% of patients reported incomplete recovery 2 years post-infection[13] compared to 73% at 2 years post-hospital discharge in our study, suggesting the more severe long-term impact of COVID-19 in hospitalized compared to non-hospitalized patients.[14] The findings indicate that complete recovery may remain elusive for many. We observed that from the second to third year, outcomes such as fatigue and cognitive problems even worsened, which is consistent with findings from other studies.[9,8] These long-term health problems can profoundly impact social participation,[15] e.g., in the work setting where they could lead to limited productivity, frequent or long-term sick leave, and even job loss (**Chapter 6**),[16] causing financial instability, social isolation and reduced self-esteem.[17] In the family setting, these persistent health problems may affect an individual's ability to fulfill partner and parental roles, manage household responsibilities, and participate in social activities. This isolation distances patients from essential support networks, intensifying the personal and relational challenges they face.[18] Also, it may increase patient dependence of healthcare services and social support.[19]

PEM was a prevalent symptom in our patient population and is increasingly recognized as a defining feature in a subset of individuals with long COVID. It has recently been included in the updated Long COVID definition.[20] However, PEM has been scarcely assessed in longitudinal studies,[21] resulting in limited knowledge about its impact on patients hospitalized for COVID-19. In our study, patients with PEM reported poorer overall health outcomes and appeared more susceptible to worsening symptoms over time. These findings suggest that PEM may indicate a more severe phenotype of long COVID (**Chapter 10**),[22,23] underscoring the importance of targeted management approaches and long-term follow-up for these patients.

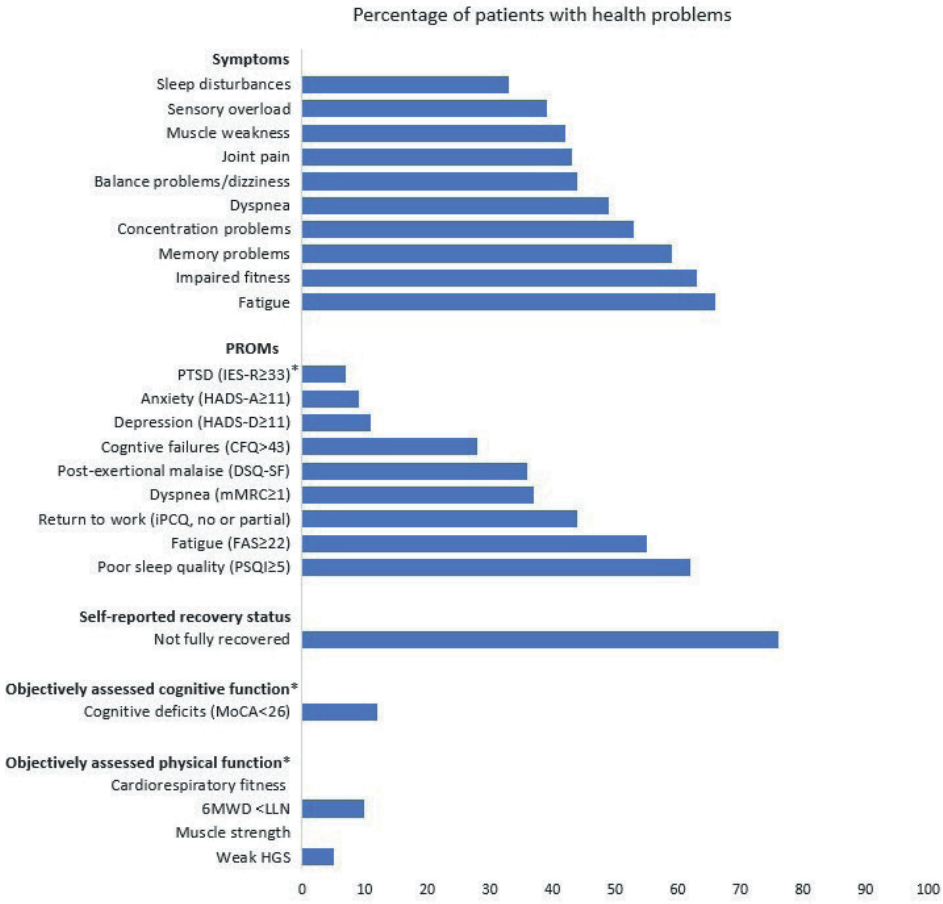


Figure 11.2 The proportion of patients with health problems up to 3 years post-hospital discharge.
*Data are presented for health outcomes 3 years after hospital discharge. Outcomes indicated by * are limited to 2 years. Symptoms were assessed on a binary scale (yes/no) and PROMs by a standardized questionnaire 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; PTSD, Posttraumatic Stress Disorder; IES-R, Impact of Event Scale-Revised; HADS-A, Hospital Anxiety and Depression Scale-subscale Anxiety; HADS-D, Hospital Anxiety and Depression Scale-subscale Depression; CFQ, Cognitive Failures Questionnaire; PEM, Post-Exertional Malaise; DSQ-SF, DePaul Symptom Questionnaire-Short Form; mMRC, Modified Medical Research Council dyspnea scale; iPCQ, iMTA Productivity Costs Questionnaire; FAS, Fatigue Assessment Scale; PSQI, Pittsburgh Sleep Quality Index; MoCA; Montreal Cognitive Assessment; 6MWD, 6-Min Walk Distance; LLN, Lower Limit of Normal; HGS, Handgrip strength.*

Predictors of long-term outcomes

We consistently found that female sex and pre-existing pulmonary and cardiovascular comorbidities were predictive of multiple adverse health

outcomes. Additionally, a longer time since discharge was associated with improved outcomes. These findings align with earlier studies.[10,14] The observation that females experienced more long-term health problems compared to males likely stems from a complex interplay of biological, hormonal, and psychosocial factors (**Chapter 3, 4, 6, 7, 9, 10**).[14] Females generally exhibit stronger immune responses compared to males; while sometimes protective, this may lead to prolonged inflammatory states that contribute to worse disease progression and persistent symptoms.[24,25] Hormonal fluctuations could further modulate immune function and recovery, potentially sustaining a hyperinflammatory state even after the acute phase of illness.[26] This heightened immune response, in combination with hormonal influences and genetic predispositions, may also contribute to the COVID-induced autoimmunity.[27] Additionally, psychosocial factors such as healthcare-seeking behaviors, pre-existing mental health conditions, societal pressures, occupational exposures, and stress levels may help explain why females are more likely to experience long-term health problems.[28,29]

Patients with chronic pulmonary and cardiovascular comorbidities were more frequently affected by long-term health problems after COVID-19 (**Chapter 3, 4, 7, and 9**).[14] Pre-existing pulmonary or cardiovascular diseases cause a reduced physiological reserve, limiting the capacity to withstand the additional stress imposed by COVID-19.[30] This is associated with a higher risk of developing severe COVID-19, which in turn is linked to a greater likelihood of long-term complications.[31] Furthermore, chronic pulmonary diseases, such as asthma, bronchiectasis, or COPD, are associated with immune system abnormalities, which may alter the immune response, potentially affecting the body's ability to effectively clear the virus and resolve inflammation.[32,33]

Although disease severity is recognized as a predictor of long-term health problems in patients with COVID-19,[3,14,12,34,35] some studies suggest that long-term health problems can occur independent of the initial disease severity.[36,11] Intensive care unit (ICU) patients are susceptible to persistent physical, cognitive, and mental health symptoms after long-term ICU treatment, collectively known as post-intensive care syndrome.[37] However, these symptoms are also reported by non-ICU or non-hospitalized patients with mild COVID-19,[38] suggesting that these symptoms may not be solely attributable to the long-term ICU treatment.[20] We found that ICU treatment was associated with a delayed return to work (**Chapter 6**) and contributed to PEM (**Chapter 10**), but it was not consistently associated with other PROMs (**Chapter 7**). Our comparative analysis of outcomes between ICU and non-ICU patients revealed that ICU patients required a longer period to

reach similar health levels as non-ICU patients. However, by 2 years post-discharge, they had made substantial progress, achieving comparable health levels in most health domains (**Chapter 9**). This suggests that disease severity might not be predictive for long-term health problems, a finding also reported by Wahlgren et al.[11] As a substantial proportion of ICU patients received multidisciplinary rehabilitation, this may have mitigated long-term health outcomes.

COVID-19 post-hospital aftercare pathways

At the onset of the COVID-19 pandemic, aftercare pathways were rapidly established without sufficient knowledge of patient's clinical and rehabilitation needs and in absence of evidence-based guidelines. After hospitalization, severely affected patients were typically referred to medical rehabilitation centers, and vulnerable patients with more comorbidities were referred to skilled nursing facilities, where they received multidisciplinary rehabilitation.[39] However, most (74%) individuals were discharged home, often receiving only monodisciplinary treatment, mostly physical therapy, through community-based rehabilitation. In the CO-FLOW cohort, 81% of patients received rehabilitation, of whom 15% in medical rehabilitation centers, 14% in skilled nursing facilities, and 52% in community-based rehabilitation centers. Patients with higher disease severity received more often rehabilitation and showed more cognitive failures and poorer psychological outcomes throughout the follow-up period compared to those who did not receive rehabilitation (**Chapter 5**). Patients who received rehabilitation showed physical recovery toward normative values, even though they were more severely affected after hospital discharge.[40] Despite these objectively assessed improvements, patients continued to report physical complaints. This disparity can be attributed to factors such as individual perceptions and memory bias, as well as the limited understanding of the underlying biological causes of persistent health problems following COVID-19. In addition, the initial underrecognition of PEM and its subsequent improper management during the early stages of the pandemic may have worsened patients' physical complaints.

While self-reported measures may depict a broader spectrum of sensations, objectively assessed tests tend to focus on specific aspects of functioning. A substantial number of patients experienced health problems beyond physical complaints, with fatigue and cognitive problems being particularly prominent, persisting up to 3 years post-discharge (**Chapter 10**). This raises questions about whether the full spectrum of post-COVID-19 sequelae was adequately addressed in aftercare. This is currently explored in a clinical trial (CO-TRAINER, a substudy of CO-FLOW) which we designed to study the effect of a computerized

cognitive rehabilitation program (RehaCom) on sustained and divided attention as well as working memory in patients experiencing cognitive complaints after hospitalization for COVID-19.

Post-exertional malaise (PEM) has been identified as a debilitating symptom in long COVID, emphasizing the importance of recognizing and addressing this condition to provide tailored aftercare. Patients with PEM experience significantly reduced load capacity,[41] making careful energy management a cornerstone of their treatment. A personalized rehabilitation approach is essential, focusing on balancing activity levels with their limited energy reserves to prevent symptom exacerbation.[42] Physical activity in these patients has been linked to worsening of symptoms and abnormal immune and metabolic responses in skeletal muscles.[43,44] To optimize recovery and minimize the risk of long-term setbacks, it is crucial to avoid overexertion and implement aftercare strategies that align with each patient's unique needs.

Our study showed that healthcare professionals generally held a favorable view of the organization of COVID-19 aftercare, especially considering the aftercare pathways were newly developed (**Chapter 8**). However, a need for a coordinated approach between primary and secondary care, with general practitioners playing a central role, as well as improved multidisciplinary collaboration among healthcare providers was considered essential for providing more comprehensive support to patients with COVID-19.

METHODOLOGICAL CONSIDERATIONS

Study design

A major strength of the study is the multicenter design, which allowed for inclusion of patients with COVID-19 with varying disease severities. Moreover, the study has a longitudinal design with multiple follow-up moments, initially set at 2 years and later extended to 3 years post-hospital discharge, allowing an evaluation of long-term recovery. The study utilized a comprehensive array of both objectively assessed physical and cognitive assessments, PROMs, and a qualitative approach to evaluate the organization of COVID-19 aftercare, enabling an in-depth examination. Additionally, the monitoring of post-hospital aftercare provided insights into its quality and highlighted potential areas for improvement.

Selection bias and generalizability

The cohort included a higher proportion of ICU patients (42%) compared to the national average (14%),[45] potentially limiting the representativeness of the cohort and overestimating poor outcomes. However, this allowed for comparison of outcomes between ICU and non-ICU patients, in which we generally did not observe significant differences in long-term outcomes, reducing the likelihood of overestimating poor outcomes. The inclusion of patients at the outpatient clinic post-discharge may introduce selection bias, as those with lingering symptoms might be overrepresented. In addition, we lack information on the total eligible recruitment population due to the surge of patients admitted to the participating centers. Nevertheless, all hospitalized patients were generally offered outpatient follow-up, and participant recruitment was independent of recovery status but mostly dependent on availability of research personnel. Furthermore, the study's requirement for Dutch or English language proficiency may have led to underrepresentation of ethnic minorities compared to the demographics of the recruitment area, potentially affecting the generalizability.[46] However, 29% of the participants were from ethnic minority groups enabling assessment of outcomes across ethnicity groups. Importantly, our participant characteristics align with those of the average Dutch patient profile hospitalized for COVID-19.[45] Further, our findings may not be generalizable to patients vaccinated prior to admission, as vaccination has consistently been shown to reduce the risk of long-term health complications.[47] Also, all assessments lacked pre-COVID information, allowing only comparisons to reference values. Moreover, data collection coincided with national lockdowns, potentially influencing outcomes, such as HRQoL, anxiety, depression, or participation, independent of COVID-19. Therefore, for some periods during follow-up comparing findings to references values may have been inaccurate, as the latter were established in non-lockdown conditions. Furthermore, we were unable to compare our findings with a control group of individuals without COVID-19 or non-hospitalized patients, which complicates the identification of symptoms specifically attributable to COVID-19.

Measurements

Patients were included up to 6 months post-discharge, although the preferred timeframe for inclusion was within 3 months post-discharge. This extended inclusion period was selected due to the time required to obtain ethical approval of the participating centers, while it was essential to include patients hospitalized during the first wave of COVID-19 in the Netherlands. However, with five follow-up assessments available for the generalized estimating equation analyses, which includes all observed outcomes despite missing data, this is unlikely to play a

major role in the validity of our results on long-term outcomes. We assessed cognitive function using the Montreal Cognitive Assessment (MoCA) at the first possible visit, with follow-up assessments only for those with an initial deviant score, potentially missing future cognitive decline. However, most patients who underwent repeated MoCA showed stable or improving scores. Next to objectively assessed measurements of physical and cognitive function, we also utilized multiple PROMs, which depend on patient reporting and can be influenced by factors such as individual perception, memory bias, or emotional state at the time of assessment.[48] Remarkably, objectively assessed physical and cognitive tests showed marked improvement, however, self-reported physical and cognitive complaints persisted. PEM was only assessed at the 3-year follow-up visit, lacking a longitudinal evaluation, and was measured using the DePaul Symptom Questionnaire rather than the gold-standard invasive two-day cardiopulmonary exercise testing.

CLINICAL IMPLICATIONS

The CO-FLOW study has provided insights into the long-term health outcomes of patients hospitalized for COVID-19, as well as into the quality and organization of COVID-19 post-hospital aftercare. Our findings highlight that many patients continue to suffer from long-term health problems, now broadly termed *long COVID*.[49,20] Here we describe specific implications for clinical practice:

Given the diverse and multifactorial nature of long COVID, its aftercare should be individualized rather than following a one-size-fits-all approach. In our study, healthcare professionals highlighted the need to integrate comprehensive screening protocols based on key risk factors to allocate resources efficiently and prioritize patients with the most complex needs. To address these needs, our findings indicated that aftercare pathways across all levels of care should incorporate multidisciplinary rehabilitation programs. These programs should offer multifaceted strategies including but not limited to respiratory and physical therapy, cognitive and psychological support, vocational rehabilitation, and symptom management, tailored to individual needs of patients. Since March 2022, such approaches have been incorporated into national guidelines[39,50,51] and in the WHO living guideline and NICE guideline,[52,53] and described in literature.[54]

Despite the establishment of these guidelines, their implementation in practice remains limited nearly 3 years after their introduction and almost 5 years after the onset of the COVID-19 pandemic. The challenge lies in the fact that establishing comprehensive programs requires substantial innovations in the structural aspects of aftercare, including overcoming policy barriers, addressing financial limitations, and handling challenges in data management. These factors might explain the gap between guideline development and real-world application.

Our findings underscore that ICU patients, females, patients with pre-existing pulmonary or cardiovascular conditions, and those with PEM are more susceptible to long-term health problems which advocate for vigilant monitoring and supporting these patient groups.

Additionally, follow-up consultations and centralized information points will also be vital in addressing ongoing patient needs and guiding them through the long-term care process.[55]

Our research also highlighted the importance of well-defined aftercare pathways, structured as an integrated, chain-based approach, fostering collaboration among healthcare professionals, insurers, and national health authorities.[56,57] Adaptability is crucial, allowing for continuous evaluation and refinement to optimize long-term outcomes for patients.

We observed that many patients continued to experience long-term health problems even years after their COVID-19 infection, highlighting critical gaps in understanding its etiology and identifying effective treatment strategies. Our findings, along with evidence from studies worldwide, emphasize the substantial burden of long COVID. Persistent advocacy by patient organizations and healthcare professionals for adequate care brought much-needed attention to this issue. In response, the government took a pivotal step in late 2024 by establishing outpatient expert clinics in three academic hospitals, representing a crucial advancement in addressing these gaps and enhancing care for long COVID patients. The integrated care model facilitates comprehensive symptom screening, routine outcome monitoring, long-term data collection, and biobanking. Our findings highlight the substantial burden of long COVID, underscoring the urgent need to deepen our understanding of its pathophysiology to alleviate symptoms and improve patients' functional performance in daily life and social participation. These clinics are uniquely positioned to explore pharmaceutical treatment options and could ideally expand

their services to include vocational support, physical and cognitive rehabilitation, and fatigue management—domains that remain problematic for many patients, even three years post-discharge. Achieving this requires collaboration between disciplines that are not typically considered partners, such as pulmonary, internal, and rehabilitation medicine, to leverage their combined expertise and provide multidisciplinary care for this complex condition. Moreover, the establishment of robust patient registries will enable the long-term tracking of disease progression, identification of predictors for outcomes, and evaluation of interventions, which is particularly critical given the significant proportion of patients still experiencing health problems three years post-discharge. Ultimately, these expert clinics hold promise for integrating pharmaceutical and rehabilitative treatments that will support personalized care strategies and deepen our understanding of long COVID, improving clinical decision-making and patient outcomes.

RECOMMENDATIONS FOR FUTURE RESEARCH

We emphasize the need for adaptable, personalized aftercare pathways that incorporate comprehensive screening protocols, evidence-based symptom management, and multidisciplinary rehabilitation programs. Ongoing evaluation of these pathways is essential to enhance patient recovery outcomes. The post-COVID expert clinics will play a central role in developing expertise on the management of long COVID patients, serving as centers for continuous data collection, establishment of patient registries, dissemination of knowledge, and provision of right care at the right time and place. To further optimize patient care and address current challenges, future research should prioritize several key areas, which are discussed below.

First, it is important to continue conducting long-term cohort studies to follow up all patients affected by COVID-19, ensuring a complete understanding of its long-term consequences. Our study demonstrates that long COVID manifests with a broad spectrum of symptoms, ranging from mild to severe, and affects multiple organ systems. The absence of diagnostic criteria and biomarkers and a clear understanding of the heterogeneity of long COVID have hindered treatment progress. Developing detailed phenotypes of long COVID will allow individualized care, which in turn, will lead to more tailored and effective therapeutic interventions.

Also, the focus should be on elucidating the underlying pathophysiological mechanisms of long COVID, required to more efficiently address its health impact. Persistent symptoms like fatigue, cognitive impairments, and PEM may stem from biological factors, such as immune dysregulation, microvascular and endothelial dysfunction, neuroinflammation, or autoimmunity.[38] Beyond pathophysiology, the biopsychosocial model highlights the importance of social and psychological factors in shaping treatment programs for long COVID.[58,59] Social determinants, such as socioeconomic status, environmental factors, workplace challenges, and family dynamics, may significantly impact patient resilience and recovery trajectories.[59] Additionally, psychological factors, such as distress, fear, coping mechanisms, and symptom attribution, are likely to influence patients' adaptation to chronic symptoms and response to treatment.[59] Research grounded in this holistic model can thus deepen our understanding of how these interconnected factors contribute to long-term recovery outcomes.

In summary, long-term health problems following COVID-19, collectively known as long COVID, persist in many patients years after their hospitalization. Symptoms such as fatigue, cognitive problems, dyspnea, impaired fitness, and PEM are among the most prevalent and have profound impacts on HRQoL, return to work, and social participation. Female patients and those with pre-existing pulmonary disease are especially vulnerable for long COVID. While rehabilitation following hospital discharge seemed beneficial for recovery, particularly in physical function, the breadth of long COVID symptoms suggests that current rehabilitation approaches may be insufficient. A patient-centered, multidisciplinary strategy is likely essential to effectively meet the diverse needs of long COVID patients. While the health problems identified in the CO-FLOW study provide an initial understanding, they represent just the tip of the iceberg. Future research should focus on defining distinct phenotypes of long COVID, unraveling its underlying pathophysiological mechanisms, and developing and evaluating the clinical efficacy of multimodal rehabilitation programs

REFERENCES

1. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *The Lancet*. 2021;398(10302):747-58.
2. Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*. 2021;9(7):747-54.
3. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863-76.
4. de Graaf R, ten Have M, van Gool C, van Dorsselaer S. Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(2):203-13.
5. de Vries GJ, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *J Trauma Stress*. 2009;22(4):259-67.
6. Yang X, Hou C, Shen Y, et al. Two-Year Health Outcomes in Hospitalized COVID-19 Survivors in China. *JAMA Network Open*. 2022;5(9):e2231790-e.
7. Cai M, Xie Y, Topol EJ, Al-Aly Z. Three-year outcomes of post-acute sequelae of COVID-19. *Nature Medicine*. 2024;30(6):1564-73.
8. Yang H, Guan L, Yang T, et al. Two- and 3-year outcomes in convalescent individuals with COVID-19: A prospective cohort study. *J Med Virol*. 2024;96(4):e29566.
9. Zhang H, Huang C, Gu X, et al. 3-year outcomes of discharged survivors of COVID-19 following the SARS-CoV-2 omicron (B.1.1.529) wave in 2022 in China: a longitudinal cohort study. *Lancet Respir Med*. 2024;12(1):55-66.
10. Greenhalgh T, Sivan M, Perlowski A, Nikolich JŽ. Long COVID: a clinical update. *The Lancet*. 2024;404(10453):707-24.
11. Wahlgren C, Forsberg G, Divanoglou A, et al. Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. *The Lancet Reg Health Eur*. 2023;28.
12. Evans RA, Leavy OC, Richardson M, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022;10(8):761-75.
13. Ballouz T, Menges D, Anagnostopoulos A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ*. 2023;381:e074425.
14. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post–COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2023;183(6):566-80.
15. Gonzalez-Aumatell A, Bovo MV, Carreras-Abad C, et al. Social, Academic, and Health Status Impact of Long COVID on Children and Young People: An Observational, Descriptive, and Longitudinal Cohort Study. *Children (Basel)*. 2022;9(11).
16. Descatha A, Evanoff BA, Fadel M. Post-COVID condition or "long COVID", return-to work, and occupational health research. *Scand J Work Environ Health*. 2023;49(3):165-9.
17. Kerksieck P, Ballouz T, Haile SR, et al. Post COVID-19 condition, work ability and occupational changes in a population-based cohort. *The Lancet Reg Health Eur*. 2023;31.
18. Aghaei A, Zhang R, Taylor S, et al. Social Life of Females with Persistent COVID-19 Symptoms: A Qualitative Study. *Int J Environ Res Public Health*. 2022;19(15):9076.
19. Schröder D, Heinemann S, Heesen G, et al. Association of long COVID with health-related Quality of Life and Social Participation in Germany: Finding from an online-based cross-sectional survey. *Heliyon*. 2024;10(4):e26130.
20. Ely EW, Brown LM, Fineberg HV, et al. Long Covid Defined. *N Engl J Med*. 2024;391(18):1746-53.
21. Buonsenso D, Yonker LM. Physical and cognitive stressors exacerbate symptoms in long COVID: more evidence triggering new research and therapeutic needs. *Lancet Reg Health Eur*. 2024;46:101109.
22. Twomey R, DeMars J, Franklin K, et al. Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. *Phys Ther*. 2022;102(4).
23. Pagen DME, Van Herck M, van Bilsen CJA, et al. High proportions of post-exertional malaise and orthostatic intolerance in people living with post-COVID-19 condition: the PRIME post-COVID study. *Front Med (Lausanne)*. 2023;10:1292446.
24. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-38.

25. Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*. 2020;588(7837):315-20.
26. Averyanova M, Vishnyakova P, Yureneva S, et al. Sex hormones and immune system: Menopausal hormone therapy in the context of COVID-19 pandemic. *Front Immunol*. 2022;13:928171.
27. Gu J, Zhang J, Liu Q, Xu S. Neurological risks of COVID-19 in women: the complex immunology underpinning sex differences. *Front Immunol*. 2023;14:1281310.
28. Maham S, Yoon M-S. Clinical Spectrum of Long COVID: Effects on Female Reproductive Health. *Viruses*. 2024;16(7):1142.
29. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, et al. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ*. 2020;11(1):29.
30. Whittaker H, Kallis C, Bolton T, et al. Risk of cardiovascular events following COVID-19 in people with and without pre-existing chronic respiratory disease. *Int J Epidemiol*. 2024;53(3).
31. Phelps M, Christensen DM, Gerds T, et al. Cardiovascular comorbidities as predictors for severe COVID-19 infection or death. *Eur Heart J Qual Care Clin Outcomes*. 2021;7(2):172-80.
32. Meng M, Wei R, Wu Y, et al. Long-term risks of respiratory diseases in patients infected with SARS-CoV-2: a longitudinal, population-based cohort study. *eClinicalMedicine*. 2024;69.
33. Nishiga M, Wang DW, Han Y, et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543-58.
34. Musheyev B, Boparai MS, Kimura R, et al. Longitudinal medical subspecialty follow-up of critically and non-critically ill hospitalized COVID-19 survivors up to 24 months after discharge. *Intern Emerg Med*. 2023;18(2):477-86.
35. Global Burden of Disease Long CC, Wulf Hanson S, Abbafati C, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA*. 2022;328(16):1604-15.
36. Darcis G, Bouquegneau A, Maes N, et al. Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: a monocentric prospective observational cohort study. *Int J Infect Dis*. 2021;109:209-16.
37. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-9.
38. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-46.
39. FMS: Langdurige klachten en revalidatie na COVID-19 Richtlijnendatabase [Internet]. The Netherlands. Federatie Medisch Specialisten; [updated 2022 March 21; cited 2025 Feb 04]. Available from:https://richtlijnendatabase.nl/richtlijn/covid-19/startpagina_-_langdurige_klachten_en_revalidatie_na_covid-19.html.
40. Berentschot JC, Heijenbrok-Kal MH, Bek LM, et al. Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW). *Lancet Reg Health Eur*. 2022;22.
41. Gloeckl R, Zwick RH, Fürlinger U, et al. Practical Recommendations for Exercise Training in Patients with Long COVID with or without Post-exertional Malaise: A Best Practice Proposal. *Sports Med Open*. 2024;10(1):47.
42. Barry PW, Kelley K, Tan T, Finlay I. NICE guideline on ME/CFS: robust advice based on a thorough review of the evidence. *J Neurol Neurosurg Psychiatry*. 2024;95(7):671-4.
43. Wright J, Astill SL, Sivan M. The Relationship between Physical Activity and Long COVID: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2022;19(9).
44. Appelman B, Charlton BT, Goulding RP, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat Commun*. 2024;15(1):17.
45. NICE. COVID-19 op de Nederlandse verpleegafdelingen; Patiëntkarakteristieken en uitkomsten. [updated 30 March 2023; cited 2024 May 01]. Available from: https://stichting-nice.nl/.
46. Norredam M, Hayward S, Deal A, et al. Understanding and addressing long-COVID among migrants and ethnic minorities in Europe. *Lancet Reg Health Eur*. 2022;19:100427.
47. Català M, Mercadé-Besora N, Kolde R, et al. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia. *Lancet Respir Med*. 2024;12(3):225-36.
48. Zini MLL, Banfi G. A Narrative Literature Review of Bias in Collecting Patient Reported Outcomes Measures (PROMs). *Int J Environ Res Public Health*. 2021;18(23).
49. National Academies of Sciences Engineering, and Medicine. A long COVID definition: a chronic, systemic disease state with profound consequences. 2024.
50. NHG-Richtlijnen: Langdurige klachten na COVID-19 [Internet]. The Netherlands. NHG-Richtlijnen: Nederlands Huisartsen Genootschap; [updated 2022 March; cited 2025 Feb 04]. Available from: https://richtlijnen.nhg.org/standaarden/langdurige-klachten-na-covid-19

51. VerenSo. COVID-19 / Coronavirus [Internet]. The Netherlands. Vereniging van specialisten ouderengeneeskunde; [updated 2022 Sep 07; cited 2024 Feb 27]. Available from: https://www.verenso.nl/kwaliteit/thema-s-en-projecten/infectieziekten/covid-19-coronavirus
52. WHO: Clinical management of COVID-19: World Health Organization [Internet]. Geneva, Switserland. World Health Organisation; [updated 2023 Aug 18; cited 2025 Feb 04]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2.
53. NICE: COVID-19 rapid guideline: managing the long-term effects of COVID-19 [Internet]. United Kingdom. National Institute for Health and Care Excellence; [updated 2024 Jan 25; cited 2025 Feb 04]. Available from: https://www.nice.org.uk/guidance/ng188
54. Owen R, Ashton REM, Ferraro FV, et al. Forming a consensus opinion to inform long COVID support mechanisms and interventions: a modified Delphi approach. *eClinicalMedicine*. 2023;62.
55. Berentschot JC, de Ridder WA, Bek LM, et al. Patients' evaluation of aftercare following hospitalization for COVID-19: satisfaction and unmet needs. *Respiratory Research*. 2024;25(1):145.
56. Wolf S, Zechmeister-Koss I, Erdös J. Possible long COVID healthcare pathways: a scoping review. *BMC Health Serv Res*. 2022;22(1):1076.
57. van der Feltz-Cornelis CM, Sweetman J, Turk F, et al. Integrated care policy recommendations for complex multisystem long term conditions and long COVID. *Sci Rep*. 2024;14(1):13634.
58. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196(4286):129-36.
59. Klinkhammer S, Duits AA, Deckers K, et al. A Biopsychosocial Approach to Persistent Post-COVID-19 Fatigue and Cognitive Complaints: Results of the Prospective Multicenter NeNeSCo Study. *Arch Phys Med Rehabil*. 2024;105(5):826-34.



APPENDIX

Summary

Samenvatting

Dankwoord

CO-FLOW Collaboration Group

About the author

Supplemental material



APPENDIX

Summary

SUMMARY

As of December 2019, the world has faced the unprecedented challenge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). The rapid global spread of the virus, facilitated by the high frequency of global travel, urbanization, and high population density, led the WHO to declare a pandemic. SARS-CoV-2 has since infected millions of people worldwide, with affected individuals exhibiting a wide spectrum of clinical manifestations. While some individuals experienced mild symptoms such as anosmia, fever, and headache, others developed moderate to severe symptoms including severe pneumonia, acute respiratory distress syndrome (ARDS), and/or multiorgan failure requiring hospitalization with or without intensive care unit (ICU) treatment. As the pandemic progressed, it became evident that many patients hospitalized for COVID-19 faced a broad spectrum of health problems post-discharge. However, the full scope of the long-term health consequences of this novel virus remained largely unknown. Aftercare pathways were rapidly established; multidisciplinary rehabilitation was offered in medical rehabilitation centers for severely affected patients and in skilled nursing facilities for vulnerable patients with more comorbidities. In community-based rehabilitation centers mostly monodisciplinary rehabilitation was offered for patients discharged home. However, whether these newly established aftercare pathways would appropriately address patient needs remained to be established. This thesis, therefore, evaluates the organization of COVID-19 aftercare pathways and long-term health outcomes of patients hospitalized for COVID-19 within the Dutch healthcare system.

Chapter 1, the general introduction of this thesis provides an overview of the emergence of COVID-19, covering the onset of the pandemic, pathophysiology of COVID-19, its variation in severity, and comparisons with previous coronavirus outbreaks. It discusses early insights into health consequences faced by patients after COVID-19 and the need for developing post-hospital aftercare pathways. Additionally, Chapter 1 presents the rationale, study design, and objectives of the CO-FLOW study, as well as the outline of the thesis.

Chapter 2 further outlines the aims and the design of the CO-FLOW study. The CO-FLOW study aimed to systematically evaluate aftercare pathways and long-term health outcomes in patients hospitalized for COVID-19 over an initial 2-year period, with an extension to a 3-year period. The study had

four key objectives: to assess 1] trajectories and identify predictors of physical, cognitive, and psychological recovery; 2] patient flows, healthcare utilization, and the perspective of healthcare professionals and patients on the COVID-19 post-hospital aftercare; 3] the effects of physical, cognitive, and psychological outcomes on social participation and health-related quality of life (HRQoL); and 4] predictors of healthcare utilization and patient satisfaction with aftercare. This multicenter prospective cohort study involved study visits at 3, 6, 12, 24, and 36 months post-discharge. Data on baseline characteristics, routine follow-up outcomes, including pulmonary, radiological, and laboratory outcomes, objectively assessed physical and cognitive outcomes, self-reported recovery status and symptoms, and patient-reported outcome measures (PROMs) were collected. Also, COVID-19 post-hospital aftercare pathways, including 1] in- and outpatient medical rehabilitation, 2] inpatient rehabilitation in skilled nursing facilities, and 3] community-based rehabilitation were evaluated.

Chapter 3 describes interim results of pulmonary function tests, radiological evaluations, and PROMs up to 6 months after hospital discharge. In general, pulmonary function, radiographic abnormalities, mental health, and HRQoL improved over time. However, several self-reported symptoms persisted, notably reduced fitness, muscle weakness, concentration and/or memory problems, and joint complaints. Also, more than half of patients experienced fatigue, and physical role functioning was the most severely impaired HRQoL domain. Predictive factors for diffusion impairments, fatigue, and limitations in physical role functioning included shorter time since discharge, female sex, and longer hospital stay. Importantly, no progressive pulmonary or radiological impairments were noted. Although patients reported improvements over time, they continued to experience health problems. The long-term trajectory of recovery remains unclear, underscoring the importance of investigating rehabilitative interventions to address ongoing patient needs.

In **Chapter 4** we investigated the persistence of symptoms, symptom clusters, and their predictors up to 1 year post-discharge. Almost all patients reported at least one lingering symptom at 1 year, with muscle weakness, exertional dyspnea, fatigue, and concentration and memory problems being the most prevalent. While symptoms in the physical and respiratory clusters improved, those in the fatigue and cognitive clusters persisted. Females were more likely to report ongoing symptoms. These findings highlight the long-term impact of COVID-19 and contribute to the growing body of evidence supporting the condition known as *long COVID*. This underscores the need for further research

into the underlying pathophysiological mechanisms and effective treatments for long COVID.

In **Chapter 5** the cognitive (objectively assessed and self-reported) and psychological recovery patterns across multiple care pathways are described up to 1 year after hospitalization for COVID-19. Cognitive deficits and psychological outcomes improved over time, while cognitive failures did not. Notably, one-fifth of patients continued to experience cognitive deficits and cognitive failures at 1 year. Patients who received medical rehabilitation showed good cognitive recovery but also experienced the most cognitive failures and psychological sequelae. In contrast, patients with community-based rehabilitation showed relatively high rates of both cognitive deficits and failures. The multifactorial and persistent impact of COVID-19 highlight the importance of integrating multidisciplinary rehabilitation, including cognitive and psychological support, into the post-COVID management plan.

As the long-term health impact of COVID-19 became more apparent, it was evident that patients faced a broad range of symptoms affecting their daily functioning to varying degrees. **Chapter 6** describes patients' ability to return to work, along with its predictors and association with HRQoL up to 1 year after hospitalization for COVID-19. Although return to work rates improved over time, one third of patients was not able to fully return to work at 1 year. ICU patients generally require more time to return to work compared to non-ICU patients, suggesting that early rehabilitation may be beneficial. Factors associated with return to work included time since discharge, ICU admission, sex, and fatigue. HRQoL also improved over time; however, patients who did not fully return to work reported lower HRQoL. Returning to work was independently associated with the physical, but not the mental HRQoL components. To promote successful work reintegration and enhance HRQoL, vocational rehabilitation programs could focus on energy management and pacing strategies, improving physical fitness, and providing cognitive and psychological support.

In **Chapter 7** we analyzed data from two multicenter prospective cohort studies — The Dutch HFNO COVID-19 study and the CO-FLOW study — to examine the association between COVID-19 disease severity and PROMs up to 1 year post-discharge, as well as to explore risk factors for long-term outcomes. Disease severity was categorized based on maximal respiratory support during hospitalization: conventional oxygen therapy (COT), high flow

nasal oxygen (HFNO), or invasive mechanical ventilation (IMV). Surprisingly, disease severity was not associated with HRQoL. However, the HFNO group reported more frequently respiratory and fatigue symptoms and poorer recovery. Interestingly, female sex, younger age, and pre-existing pulmonary disease emerged as more consistent predictors of long-term outcomes than the severity of COVID-19 itself. While the persistent respiratory symptoms observed in patients receiving prolonged HFNO remain speculative, they may be linked to the potential damaging effects of prolonged vigorous efforts during HFNO in severely hypoxemic patients.

In response to the sudden outbreak of COVID-19, structured post-hospital aftercare pathways for hospitalized patients had to be rapidly established, despite limited knowledge of patient's rehabilitation needs and without evidence-based guidelines. As the pandemic progressed, these aftercare pathways evolved, posing ongoing challenges for healthcare professionals who had to adapt rapidly to new and frequently changing protocols. In **Chapter 8** we evaluated healthcare professionals' perspective on the organization of COVID-19 post-hospital aftercare, identified barriers and facilitators they encountered, and explored strategies to overcome these barriers. Healthcare professionals emphasized the need for clear follow-up and referral procedures, and highlighted the importance of multidisciplinary treatment, an expanded healthcare workforce, and extended duration of treatment. Despite the challenges, healthcare professionals generally expressed a positive view on the aftercare provided. Key recommendations for improving the COVID-19 aftercare included implementing quality indicators to monitor follow-up care, establishing well-defined aftercare pathways, addressing resource constraints, and enhancing multidisciplinary collaboration and communication. These insights are crucial for policymakers and national healthcare authorities, offering guidance to enhance COVID-19 post-hospital aftercare and strengthen preparedness for future pandemics.

In **Chapter 9**, we examined long-term health outcomes of COVID-19 up to 2 years after hospitalization, including a comparison between ICU- and non-ICU-patients. Additionally, we identified risk factors for self-reported recovery status and prominent long-term health problems. Overall, health outcomes improved over time, however, the majority of patients felt not completely recovered at 2 years. Most outcomes were comparable between ICU- and non-ICU-patients at 2 years, though ICU-patients tended to show slower recovery in neurocognitive symptoms, mental health outcomes, and resuming work,

while showing more improvements in physical outcomes. Risk factors for persistent health problems included female sex and pre-existing pulmonary disease. These findings highlight the need for comprehensive aftercare strategies that address a wide range of long-term consequences, particularly mental health and neurocognitive problems, as physical rehabilitation alone may not be sufficient for all patients. This underscores the importance of continued research into effective interventions, including more personalized rehabilitation programs and potential pharmacological treatments.

In **Chapter 10**, we reported the 3-year follow-up results from the extended CO-FLOW study. While many health outcomes improved over time, a significant number of problems persisted up to 3 years, especially fatigue, impaired fitness, poor sleep quality, concentration and memory problems, and cognitive failures. Also, some health outcomes, particularly fatigue and cognitive problems, deteriorated in the third year post-discharge. More than one-third of patients experienced post-exertional malaise (PEM), often accompanied by other symptoms. Risk factors for PEM included female sex, pre-existing pulmonary disease, and ICU admission. Patients with PEM reported worse health outcomes and seemed more prone to worsening symptoms over time. This suggests that PEM could be indicative for a more severe phenotype of long COVID. These findings underscore the need for further research into effective management strategies for long COVID and highlight the importance of ongoing monitoring of disease trajectory to better understand the long-term impact of COVID-19.

Chapter 11 contains the general discussion. The main findings of this thesis are interpreted and discussed in the context of the current state of affairs in the field of COVID-19. Additionally, methodological considerations, clinical implications, and recommendations for future research are addressed.



APPENDIX

Samenvatting

SAMENVATTING

Sinds december 2019 heeft de wereld te maken met severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), het virus dat coronavirus disease 2019 (COVID-19) veroorzaakt. De snelle mondiale verspreiding van het virus, versterkt door internationaal reizen, verstedelijking en hoge bevolkingsdichtheid, leidde tot het uitroepen van een pandemie door de WHO. SARS-CoV-2 heeft sindsdien wereldwijd miljoenen mensen besmet, waarbij mensen een breed scala aan klinische symptomen ervaren. Terwijl sommige mensen milde symptomen vertoonden, zoals anosmie, koorts en hoofdpijn, ontwikkelden anderen ernstigere symptomen waaronder ernstige longontsteking, acute respiratory distress syndrome (ARDS) en/of multiorgaanfalen, wat ziekenhuisopname met of zonder intensive care (IC) behandeling noodzakelijk maakte. Naarmate de pandemie vorderde, werd het duidelijk dat veel patiënten die in het ziekenhuis waren opgenomen met COVID-19, na ontslag bleven kampen met verschillende gezondheidsproblemen. De volledige omvang van de langetermijngevolgen van dit nieuwe virus voor de gezondheid was echter grotendeels onbekend. Nazorgtrajecten werden snel opgezet; multidisciplinaire revalidatie werd aangeboden in medisch specialistische revalidatiecentra voor ernstig aangedane patiënten en in geriatrische revalidatiecentra voor kwetsbare patiënten met meer comorbiditeiten. In eerstelijnsrevalidatiecentra werd voornamelijk monodisciplinaire revalidatie aangeboden voor patiënten die naar huis werden ontslagen. Of deze nieuw opgezette nazorgtrajecten aan de behoeften van patiënten zouden voldoen, moest echter nog worden vastgesteld. Dit proefschrift onderzoekt daarom de organisatie van COVID-19 nazorgtrajecten en de langetermijnuitkomsten van patiënten opgenomen in het ziekenhuis voor COVID-19 binnen het Nederlandse zorgsysteem.

Hoofdstuk 1, de algemene inleiding van dit proefschrift biedt een overzicht van de opkomst van COVID-19, het begin van de pandemie, de pathofysiologie van de ziekte, de variatie in ernst en een vergelijking met eerdere coronavirus uitbraken. De eerste inzichten in de gevolgen voor de gezondheid van patiënten na COVID-19 worden besproken en de noodzaak voor het ontwikkelen van nazorgtrajecten na ziekenhuisopname. Daarnaast beschrijft hoofdstuk 1 de rationale, de studieopzet en de doelstellingen van de CO-FLOW studie, evenals de opbouw van dit proefschrift.

Hoofdstuk 2 beschrijft in meer detail de doelen en de opzet van het CO-FLOW onderzoek. Het CO-FLOW onderzoek had als doel om ten aanzien van de

patiënten die opgenomen zijn geweest in het ziekenhuis de COVID-19 nazorg en de hersteltrajecten systematisch te evalueren over een aanvankelijke periode van 2 jaar, die is verlengd naar 3 jaar. De studie had vier hoofddoelstellingen: het evalueren van 1] fysieke, cognitieve en psychische hersteltrajecten en het identificeren van voorspellers voor deze hersteltrajecten; 2] patiëntstromen, zorggebruik, en het perspectief van zorgverleners en patiënten op de COVID-19 nazorg; 3] de effecten van fysieke, cognitieve en psychische uitkomsten op sociale participatie en gezondheidsgerelateerde kwaliteit van leven (HRQoL); en 4] voorspellers voor zorggebruik en patiënttevredenheid met de nazorg. In deze multicenter prospectieve cohortstudie vonden de onderzoeksmetingen plaats op 3, 6, 12, 24 en 36 maanden na ontslag. Er werden gegevens verzameld over demografische en klinische kenmerken, routinematige follow-upuitkomsten (waaronder pulmonale, radiologische en laboratoriumuitkomsten), objectief gemeten fysieke en cognitieve uitkomsten, zelfgerapporteerde herstelstatus en symptomen en patiënt-gerapporteerde uitkomstmaten (PROMs). Ook werden COVID-19 nazorgtrajecten geëvalueerd, waaronder 1] klinische en poliklinische medisch specialistische revalidatie, 2] klinische geriatrische revalidatie en 3] eerstelijnsrevalidatie.

Hoofdstuk 3 beschrijft de tussentijdse resultaten van longfunctietesten, radiologische uitkomsten en PROMs tot 6 maanden na ziekenhuisontslag. Over het algemeen verbeterden de longfunctie, radiografische afwijkingen, mentale gezondheid en HRQoL in de loop van de tijd. Verschillende zelfgerapporteerde symptomen hielden echter aan, met name verminderde fitheid, spierzwakte, concentratie- en/of geheugenproblemen en gewrichtsklachten. Ook had meer dan de helft van de patiënten last van vermoeidheid, en rolbeperkingen door fysieke problemen was het meest aangedane HRQoL-domein. Voorspellende factoren voor diffusiebeperkingen, vermoeidheid en rolbeperkingen door fysieke problemen waren onder andere een kortere tijd sinds ontslag, het vrouwelijk geslacht en een langere ziekenhuisopname. Er werden geen progressieve long- of radiologische afwijkingen vastgesteld. Hoewel patiënten in de loop van de tijd verbeteringen rapporteerden, bleven ze gezondheidsproblemen ervaren. Hoe het herstel op de lange termijn zal verlopen is nog onduidelijk, wat het belang onderstreept van onderzoek naar revalidatie-interventies om klachten van patiënten te kunnen behandelen.

In **hoofdstuk 4** onderzochten we de persistentie van symptomen, symptoomclusters en hun voorspellers tot 1 jaar na ziekenhuisontslag. Bijna alle patiënten ervaarden minstens één aanhoudend symptoom na 1 jaar,

waarbij spierzwakte, inspanningsdyspnoe, vermoeidheid en concentratie- en geheugenproblemen het meest voorkwamen. Terwijl de symptomen in de fysieke en respiratoire clusters verbeterden, bleven die in de vermoeidheid en cognitieve clusters aanhouden. Vrouwen rapporteerden vaker aanhoudende symptomen. Deze bevindingen benadrukken de langdurige impact van COVID-19 en dragen bij aan het toenemende bewijs voor het bestaan van de aandoening die bekend staat als *long COVID*. Dit benadrukt de noodzaak voor aanvullend onderzoek naar de onderliggende pathofysiologische mechanismen en effectieve behandelingen voor long COVID.

In **hoofdstuk 5** worden de cognitieve (objectief gemeten en zelfgerapporteerde) en psychische hersteltrajecten over meerdere zorgpaden beschreven tot 1 jaar na ziekenhuisontslag. De cognitieve stoornissen en psychische uitkomsten verbeterden over de tijd, maar de cognitieve klachten niet. Opmerkelijk was dat een vijfde van de patiënten na 1 jaar nog steeds cognitieve stoornissen en cognitieve klachten ervaarde. Patiënten die medisch specialistische revalidatie volgden, vertoonden een goed cognitief herstel, maar hadden ook de meeste cognitieve en psychische klachten. Daarentegen, patiënten die eerstelijnsrevalidatie volgden, lieten een relatief hoge prevalentie zien van zowel cognitieve stoornissen als cognitieve klachten. De multifactoriële en persisterende impact van COVID-19 benadrukt het belang van het integreren van multidisciplinaire revalidatie, met cognitieve en psychische ondersteuning, in het post-COVID behandelplan.

Naarmate de langetermijngevolgen van COVID-19 duidelijker werden, bleek dat patiënten vaak kampten met een breed scala aan symptomen die hun dagelijks functioneren in meer of mindere mate beïnvloedden. In **hoofdstuk 6** wordt de terugkeer naar werk beschreven, samen met de voorspellers hiervan en de associatie met HRQoL tot 1 jaar na ziekenhuisontslag. Hoewel het percentage patiënten dat terugkeerde naar werk toenam over de tijd, was een derde van de patiënten na 1 jaar nog niet in staat om volledig aan het werk te gaan. IC-patiënten hadden over het algemeen meer tijd nodig om te re-integreren dan niet-IC-patiënten, wat suggereert dat vroegtijdige revalidatie mogelijk gunstig is. Factoren die verband hielden met terugkeer naar werk waren onder andere de tijd sinds ontslag, IC-opname, geslacht en vermoeidheid. HRQoL verbeterde ook over de tijd; echter, patiënten die niet volledig terugkeerden naar werk rapporteerden een lagere HRQoL. Terugkeer naar het werk was onafhankelijk geassocieerd met de fysieke, maar niet met de mentale HRQoL-componenten. Om succesvolle arbeidsre-integratie en een

verbetering van HRQoL te bevorderen, zouden arbeidsrevalidatieprogramma's zich kunnen richten op energiemanagement en pacingstrategieën, het verbeteren van de fysieke fitheid en het bieden van cognitieve en psychische ondersteuning.

In **hoofdstuk 7** analyseerden we gegevens van twee multicenter prospectieve cohortstudies – het Nederlandse HFNO COVID-19 onderzoek en het CO-FLOW onderzoek– om de associatie tussen de ernst van COVID-19 en PROMs tot 1 jaar na ontslag te onderzoeken, evenals risicofactoren voor langetermijnuitkomsten. De ernst van COVID-19 werd gecategoriseerd op basis van maximale zuurstoftoediening tijdens de ziekenhuisopname: conventionele zuurstoftherapie (COT), zuurstoftoediening met hoge nasale flow (HFNO) of invasieve mechanische ventilatie (IMV). Verrassend genoeg was de ernst van COVID-19 niet geassocieerd met HRQoL. De HFNO-groep rapporteerde echter wel vaker ademhalingsklachten, vermoeidheid en een slechter herstel. Het vrouwelijk geslacht, een jongere leeftijd en een voorgeschiedenis van longaandoeningen bleken consistentere voorspellers van langetermijnuitkomsten dan de ernst van COVID-19 zelf. Hoewel de aanhoudende ademhalingsklachten bij patiënten die langdurige HFNO ondergingen speculatief blijven, kunnen ze verband houden met de potentiële schadelijke effecten van langdurige krachtsinspanningen tijdens HFNO bij ernstig hypoxemische patiënten.

Na de plotselinge uitbraak van COVID-19 moesten snel gestructureerde nazorgtrajecten voor ziekenhuispatiënten worden opgezet, ondanks beperkte kennis over de revalidatiebehoeften van patiënten en zonder evidence-based richtlijnen. Naarmate de pandemie vorderde, ontwikkelden deze nazorgtrajecten zich verder, wat zorgprofessionals voor voortdurende uitdagingen stelde doordat zij zich snel moesten aanpassen aan de continue veranderende protocollen. In **hoofdstuk 8** evalueerden we het perspectief van zorgprofessionals op de organisatie van de COVID-19 nazorg, identificeerden we de barrières en faciliterende factoren die zij ervaarden in de praktijk en verkenden we strategieën om deze barrières te overwinnen. Zorgprofessionals benadrukten de noodzaak van duidelijke procedures voor follow-up en doorverwijzingen, en wezen op het belang van multidisciplinaire behandeling, meer zorgpersoneel en een langere behandelduur. Ondanks de uitdagingen waren de zorgprofessionals over het algemeen positief over de geboden

nazorg. Belangrijke aanbevelingen voor het verbeteren van de COVID-19 nazorg waren onder andere het implementeren van kwaliteitsindicatoren om de nazorg te monitoren, het opzetten van goed gedefinieerde nazorgtrajecten, het aanpakken van de capaciteitsbeperkingen en het verbeteren van de multidisciplinaire samenwerking en communicatie. Deze inzichten zijn van cruciaal belang voor beleidsmakers en nationale zorgautoriteiten en bieden aangrijpingspunten om de COVID-19 nazorg te verbeteren en de paraatheid voor toekomstige pandemieën te vergroten.

In **hoofdstuk 9** onderzochten we de langetermijnuitkomsten van COVID-19 tot 2 jaar na ziekenhuisontslag, inclusief een vergelijking tussen IC- en niet-IC-patiënten. Daarnaast identificeerden we risicofactoren voor zelfgerapporteerde herstelstatus en prominente gezondheidsproblemen op de lange termijn. Hoewel de gezondheidsuitkomsten over de tijd verbeterden, gaf de meerderheid van de patiënten aan na 2 jaar nog niet volledig hersteld te zijn. De meeste uitkomsten waren vergelijkbaar tussen IC- en niet-IC-patiënten op 2 jaar, maar IC-patiënten vertoonden een langzamer herstel in neurocognitieve symptomen, mentale gezondheidsuitkomsten en werkhervatting, terwijl ze grotere verbeteringen in fysieke uitkomsten lieten zien. Risicofactoren voor aanhoudende gezondheidsproblemen waren onder andere vrouwelijk geslacht en een voorgeschiedenis van longaandoeningen. Deze bevindingen benadrukken de noodzaak van uitgebreide nazorgstrategieën die een breed scala aan langetermijngevolgen aanpakken, met name mentale gezondheid en neurocognitieve problemen, aangezien fysieke revalidatie alleen mogelijk niet toereikend is voor alle patiënten. Dit onderstreept het belang van verder onderzoek naar effectieve interventies, waaronder gepersonaliseerde revalidatieprogramma's en mogelijke farmacologische behandelingen.

In **hoofdstuk 10** rapporteren we de resultaten van de 3-jaar follow-up van de verlengde CO-FLOW studie. Hoewel veel gezondheidsuitkomsten verbeterden over de tijd, bleef een aanzienlijk aantal problemen aanhouden tot 3 jaar na ontslag, met name vermoeidheid, verminderde conditie, slechte slaapkwaliteit, concentratie- en geheugenproblemen en cognitieve klachten. Daarnaast verslechterden sommige gezondheidsuitkomsten, met name vermoeidheid en cognitieve problemen, in het derde jaar na ontslag. Meer dan een derde van de patiënten ervaarde post-exertionele malaise (PEM), vaak in combinatie met andere symptomen. Risicofactoren voor PEM waren het vrouwelijk geslacht, een voorgeschiedenis van longaandoeningen en IC-opname. Patiënten met PEM rapporteerden slechtere gezondheidsresultaten en leken vatbaarder

voor verergering van symptomen na verloop van tijd. Het lijkt erop dat PEM wijst op een ernstiger fenotype van long COVID. Deze bevindingen onderstrepen de dringende behoefte aan verder onderzoek naar effectieve managementstrategieën voor long COVID en benadrukken het belang van gestructureerde opvolging van het ziekteverloop om de langetermijneffecten van COVID-19 beter te begrijpen.

Hoofdstuk 11 bevat de algemene discussie. De belangrijkste bevindingen van dit proefschrift worden geïnterpreteerd en bediscussieerd in de context van de huidige stand van zaken op het gebied van COVID-19. Daarnaast worden methodologische overwegingen, klinische implicaties en aanbevelingen voor toekomstig onderzoek besproken.



APPENDIX

Dankwoord

DANKWOORD

Begin 2020 was ik mijn master aan het afronden bij de afdeling Revalidatiegeneeskunde, net als velen in die tijd (#COVID) werkte ik de laatste loodjes thuis af. Wat daarna? Geen idee, promoveren stond in ieder geval niet op de agenda. Tot ik het telefoontje van Majanka kreeg: "We starten een onderzoek naar de langetermijngevolgen van COVID-19, waarschijnlijk wordt dit een promotietraject. Zou jij dat willen doen? En oh ja, over twee weken moeten we beginnen". Daar stond ik, voor de keuze wel of niet promoveren, en nu, vijf jaar later, ligt dit proefschrift er. Het was een bijzonder traject dat ik zeker niet alleen had kunnen doorstaan. Zonder de hulp van collega's, vrienden en familie waren deze mooie resultaten niet behaald.

Toen we startten met het includeren van deelnemers in juli 2020 wisten we niet hoe zij zouden reageren. Zouden ze na die heftige ziekenhuisperiode openstaan voor onderzoek, of juist met rust gelaten willen worden? Het was hartverwarmend om te zien hoe welwillend jullie waren om deel te nemen aan het onderzoek. Iedereen wilde meer weten over het nieuwe coronavirus en wat hen nog te wachten stond. In totaal bezochten jullie maar liefst vier keer het ziekenhuis voor een uur durende meting, en vulden daarnaast ook nog eens vier tot zes keer uitgebreide vragenlijsten in. Ondanks de belastende aard van sommige metingen en de noodzaak om dagen vrij te plannen om bij te komen, bleven jullie trouw verschijnen. Dankzij jullie inzet konden we een omvangrijke database opbouwen en grootschalige analyses uitvoeren om de langetermijngevolgen inzichtelijk te maken. Ik ben jullie enorm dankbaar voor jullie tijd en toewijding. Ik kijk met plezier terug aan de studiemetingen, waarbij de gesprekken met jullie zowel aangrijpend als hartverwarmend waren, en daarnaast heb ik ook veel met jullie mogen lachen. Nogmaals, mijn oprechte dank voor jullie bijdrage aan dit onderzoek.

Een project van deze omvang kan alleen worden gerealiseerd met een sterk en toegewijd team van begeleiders, collega's en studenten. Allereerst mijn dagelijkse begeleidingsteam: Rita, Majanka en Merel. In het begin van het project was er bijna dagelijks contact over de voortgang. Jullie stonden altijd klaar, zowel voor de simpele als de complexere uitdagingen. Beste Rita, dank voor de altijd kritische, scherpe en nieuwsgierige blik. Wanneer ik vastliep met schrijven, stuurde ik mijn manuscript naar jou, waarna ik een document met genoeg opmerkingen terugkreeg; lees een compleet rood document. Hoewel dat soms wat overweldigend kon zijn, zette het me altijd weer aan het denken

en vreemd genoeg verbeterde het manuscript elke keer opnieuw. Dank voor je luisterend oor, de theemomentjes en je steun wanneer ik die nodig had. Beste Majanka, al tijdens mijn masterstage hebben we uren samen achter de computer gezeten om te spelen met SPSS en resultaten uit de data te halen. Ook tijdens mijn promotie hebben we talloze analyses uitgevoerd en naar cijfers gestaard, zoekend naar betekenis. Ik kon altijd bij je aankloppen voor vragen over analyses en dan werden de SPSS-files tevoorschijn getoverd. Met jouw scherpe oog wist je altijd de laatste foutjes uit mijn manuscripten te halen. Dank voor jouw ondersteuning en precisie. Beste Merel, onze kennismaking verliep ongeveer als volgt, “hoi, ik ben Merel, wil je thee of koffie, ik heb een kat en die heb ik Castor genoemd naar het datamanagementsysteem van de CO-FLOW studie”. Ook onze meetings daarna gingen lang niet altijd over werk. Maar wanneer er tempo gemaakt moest worden, wist ik dat ik op jou kon rekenen, waarna ik weer verder kon met het onderzoek. Jouw klinische blik en werkwijze was verfrissend voor ons als onderzoekers en heeft een belangrijke bijdrage geleverd aan dit proefschrift. Ook tijdens jouw zwangerschapsverlof bleef je natuurlijk betrokken, en ik vond het geen straf om bij jou thuis updates te geven en ondertussen je baby te knuffelen. Dank dat ik altijd bij je terecht kon, of het nu ging om vragen, problemen, leuke nieuwtjes of gewoon een kop thee.

Beste Rita, Majanka en Merel, ik heb onze samenwerking als ontzettend fijn ervaren en zal onze CO-FLOW overleggen zeker missen, net als de CO-FLOW etentjes en borrels. Dank voor de leerzame momenten, de waardevolle begeleiding, het laagdrempelige contact en, vooral, de gezelligheid.

Beste Gerard, hartelijk dank voor de kans om mijn promotietraject binnen de revalidatiegeneeskunde te volgen. Jouw kritische vragen over de implementatie van de resultaten daagden me telkens weer uit en hielpen me verder. Dank voor de ruimte om me te ontwikkelen tijdens mijn promotie en voor jouw betrokkenheid bij het onderzoek.

Beste Joachim, bedankt voor de samenwerking binnen het projectteam van het CO-FLOW onderzoek. Jouw klinische en kritische blik op de projectideeën en manuscripten was van grote waarde.

Het uitvoeren van studiemetingen bij zoveel deelnemers vroeg om flink wat mankracht. Gijs, jij was een ontzettend grote steun hierin. Je hebt ontelbare deelnemers gebeld en gemeten en talloze GENEActivs uitgelezen. Hierdoor

heb jij ons veel werk uit handen genomen. Tijdens de intens lange dagen van meten, bellen en data invoeren, waren we vaak toe aan een pauze van onze beeldschermen. We speelden dan ook graag een potje tafeltennis op de 16de. Dank voor je harde werk en de leuke gesprekken!

Ook jij, Raphaela, hebt ons enorm geholpen met het bellen en meten van patiënten, het invoeren van data en het uitvoeren van de thuismetingen, waarvoor dank. Daarnaast is het altijd gezellig als jij er bent, want er is altijd wel iets om over te kletsen.

Daarnaast hadden we het onderzoek niet uit kunnen voeren zonder de hulp van alle studenten, dank voor jullie harde werk tijdens jullie stage en bovenal de gezelligheid!

Ik wil ook alle co-auteurs bedanken die een onmisbare rol hebben gespeeld bij het schrijven van de artikelen in mijn proefschrift. Daarnaast wil ik de CO-FLOW Collaboration Group hartelijk danken voor hun bijdrage aan het realiseren van een multicenterstudie en hun ondersteuning bij het includeren van patiënten.

Dan de collega's van de 16de: de eerste twee jaar was het vrij rustig op de afdeling #COVID. Lianne, Nienja, Marlissa en Julia, in het begin waren we met z'n vijven, wat ons de kans gaf om elkaar goed te leren kennen. We raakten bijna volledig op de hoogte van elkaars onderzoeken, waardoor we regelmatig konden sparren en elkaar konden helpen bij het oplossen van uitdagingen in onze projecten. Later werden we gelukkig versterkt door nieuwe PhD'ers. Lieve collega's, bedankt voor het aanhoren van mijn PhD-geklagen, het meedenken bij problemen, de lunchwandelingen door het park, de borrels, de sinterklaasavonden en vooral de gezellige gesprekken over alles behalve werk!

Celine, een maand na mijn start met mijn PhD begon jij aan die van jou. Wat was het fijn om samen het leed én de lol van het promoveren te delen. Bedankt dat ik je altijd kon appen, bellen of even langs kon komen om bij te praten, te lachen, een rondje hard te lopen, te lunchen of door Den Haag te struinen. Dankjewel dat ik altijd op je kan rekenen en dat het altijd gezellig is wanneer we samen zijn!

Lieve vriendengroep, hoewel ik jullie pas 1,5 jaar ken, hebben jullie me volledig in de groep opgenomen en laten voelen alsof ik er altijd al bij hoor. En dan zijn

er ook nog eens mensen die snappen wat ik voor werk doe, hè Suus 😉. Dank voor de gezellige avonden en het leuke vriendenweekend; ik hoop dat er nog veel meer mogen volgen!

Luuk en Ilse, als Kars en ik met jullie zijn, loopt het op de een of andere manier altijd uit de hand. Het begint met een simpele vraag over hoe het gaat en eindigt steevast met pinda's, patat en de slappe lach. Dank voor alle gezellige avonden, inclusief het plannen van jullie bruiloft, en laten we vooral nog veel spelletjesavonden houden!

Daarnaast wil ik graag mijn familie bedanken. Lieve pap en mam, bedankt voor jullie onvoorwaardelijke steun in alles wat ik doe. Ik kan altijd bij jullie terecht voor advies, een luisterend oor, gewoon om lekker mee te eten, of langs te komen omdat ik me verveel en nu ook jullie kom vervelen.
Lisanne, lieve zus, wat super leuk dat jij mijn paranimf bent. Je staat altijd voor me klaar, en ik weet dat ik met zowel de leuke als de minder leuke dingen bij je terecht kan. Als om 17 uur mijn telefoon gaat, weet ik meteen dat jij het bent. En ook al zeggen we dat we niets boeiends te vertellen hebben, zitten we toch vaak minstens een half uur aan de telefoon. Op nog meer mooie fietsweekjes samen! Een betere zus kan ik me niet wensen. Niels, mijn nummer 1—of, nou ja, sinds 2 jaar misschien toch mijn nummer 2. Het is altijd gezellig om samen een rondje te rennen, en ooit ga ik een marathon sneller rennen dan jij! Lieve Niels en Lisanne, dank dat jullie deur altijd openstaat. Lieve Nienke, ik geniet ervan om met je te knuffelen, zowel toen je nog klein was als nu je al zo groot bent. Samen naar buiten gaan, kleuren of spelletjes spelen doe ik heel graag met jou! Misschien ga jij later ook wel promoveren.

Dan mijn schoonfamilie, wat leuk dat ik jullie erbij heb gekregen zo tegen het einde van mijn promotietraject, en wat leuk dat jullie zoveel interesse tonen in het onderzoek!

Lieve Kars, dat ik iemand zoals jij tegen het lijf zou lopen had ik nooit durven dromen. Ik wil je bedanken voor je onvoorwaardelijk steun, motivatie, troost, humor, vertrouwen en bovenal jouw liefde. Jij bent er altijd voor mij als ik je nodig heb. Ik kijk uit naar onze toekomst, met mooie plannen en nieuwe avonturen.

Lieve Julia, ik mocht mede bepalen wie van de laatste drie kandidaten mijn mede-promovendus zou worden, en wat ben ik blij dat ik voor jou heb

gekozen. Dat een goede match essentieel was, bleek wel toen het project echt op gang kwam en gigantisch groot werd. Wat hebben wij intensief moeten samenwerken en ontzettend veel uren met elkaar opgescheept gezeten, en volgens mij hebben we nooit echt ruzie gehad :P.
Het is geweldig hoe we samen kunnen zitten, de taken in kaart brengen, deze verdelen en vervolgens direct aan de slag gaan. “Doe jij dit, dan doe ik dat?”, “Prima!” of “Heb jij dit al gedaan? Anders pak ik het nu even op.”—ik denk dat deze zinnen wel honderden keren over en weer zijn gegaan. Ik wist altijd precies wat ik aan jou had, en we wisten elkaar naadloos aan te vullen. Zelfs onze begeleiders konden we subtiel de richting van onze voorkeur opsturen. We hoorden soms dat onze manuscripten korter moesten (MAND!) of dat we duidelijker moesten formuleren welke boodschap we wilden overbrengen (BOODSCHAP!).
Ik waardeer enorm jouw harde werk, discipline, doorzettingsvermogen, creativiteit, steun wanneer het mij even niet lukte en vooral jouw super leuke humor! Ik had me geen betere collega kunnen wensen. Dank je wel voor deze vier bijzondere jaren!



APPENDIX

CO-FLOW Collaboration Group

CO-FLOW COLLABORATION GROUP

L. Martine Bek, Rita J.G. van den Berg-Emons. Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands.

Julia C. Berentschot, Merel E. Hellemons, Susanne M. Huijts (until October 2023), Joachim G.J.V. Aerts. Department of Respiratory Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands.

Majanka H. Heijenbrok-Kal, Rutger Osterthun, Gerard M. Ribbers. Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands; Rijndam Rehabilitation, Rotterdam, The Netherlands.

Jasper van Bommel, Michel E. van Genderen, Diederik A.M.P.J. Gommers. Department of Adult Intensive Care Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands.

Erwin Ista. Departments of Pediatrics and Pediatric Surgery, Intensive Care Unit, Erasmus MC Sophia Children's Hospital Rotterdam; Department of Internal Medicine, section Nursing Science, Erasmus MC, Erasmus University Medical Center Rotterdam, The Netherlands.

Robert van der Stoep. Department of Physical Therapy, Erasmus MC, University Medical Center Rotterdam, The Netherlands.

Chantal Luijkx (from December 2023), Jorrit Slaman (until Augustus 2022), Marieke M. Visser (until December 2023), Markus P.J.M. Wijffels. Rijndam Rehabilitation, Rotterdam, The Netherlands.

Marc van Lanen (until Augustus 2022), Stephanie van Loon-Kooij, Ronald N. van Rossem. Department of Respiratory Medicine, Reinier de Graaf Gasthuis, Delft, The Netherlands.

Janette J. Tazmi-Staal, Eva G. Willems. Laurens Intermezzo, Rotterdam, The Netherlands.

Sieshem Bindraban, Laurien Oswald. Department of Respiratory Medicine, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands.

Wouter J.B. Blox. Department of Respiratory Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands.

Shai A. Gajadin. Department of Respiratory Medicine, IJsselland Hospital, Capelle aan de IJssel, The Netherlands.

Roxane Heller. Department of Respiratory Medicine, Ikazia Hospital, Rotterdam, The Netherlands.

Rob Slingerland (until October 2023). Department of Respiratory Medicine, Maasstad Hospital, Rotterdam, The Netherlands.

Hawre Kadir (until Augustus 2022), Herbert J. van de Sande. Aafje Nursing Home, Rotterdam, The Netherlands.



APPENDIX

About the author

ABOUT THE AUTHOR

CV

Lotte Martine Bek was born in Maassluis on the 10th of March 1997. After graduating cum laude from high school at SG Spieringshoek in Schiedam in 2015, she started her study Biomedical Sciences at the Leiden University Medical Center, Leiden. She obtained her bachelor's degree in 2018, which included a minor in Genetics in Society. From 2018-2020, she completed a master's degree in Health Sciences at the Netherlands Institute for Health Sciences at the Erasmus University Medical Center in Rotterdam, from which she graduated cum laude. During her research internship at Rijndam Rehabilitation, she focused her thesis on identifying early-phase predictors for community integration and depression up to two years after moderate to severe traumatic brain injury.

In 2020, she started as a PhD candidate at the Department of Rehabilitation Medicine at the Erasmus University Medical Center, Rotterdam, working on the "CO-FLOW" study. Her research focused on the COVID-19 aftercare pathways and the long-term consequences of COVID-19. She collaborated with multiple healthcare institutions in the Rotterdam-Rijnmond-Delft region. From 2020 to 2024, she worked with Julia Berentschot to follow up a large cohort of patients with COVID-19 and analyzed various health consequences of COVID-19.

Currently, she is working as a researcher at the Department of Pulmonary Medicine at the Erasmus University Medical Center, Rotterdam on studies investigating the pathophysiological mechanisms of long COVID. The aims of the studies include to investigate immune dysregulation, viral persistence, alterations in microcirculatory oxygenation, presence of inflammation, angiogenesis and microclots in the microvasculature, and their association with long COVID symptoms.

LIST OF PUBLICATIONS

This thesis is based on the following international peer-reviewed publications:
Bek LM*, Berentschot JC*, Hellemons ME, Huijts SM, Aerts JGJV, van Bommel J, van Genderen ME, Gommers DAMPJ, 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):847.

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.

Bek LM*, Berentschot JC*, Heijenbrok-Kal MH, Huijts S, van Genderen ME, Vlake JH, van Bommel J, Aerts JGJV, Ribbers GM, van den Berg-Emons RJG** & Hellemons ME**; CO-FLOW Collaboration Group. Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *ERJ Open Res*. 2022:00355-2022.

Bek LM, Hellemons ME, Berentschot JC, Visser MM, Huijts SM, van Bommel J, van Genderen ME, Aerts JGJV, Ribbers GM, van den Berg-Emons RJG** & Heijenbrok-Kal MH**; CO-FLOW Collaboration Group. Cognitive and psychological recovery patterns across different care pathways 12 months after hospitalization for COVID-19: A multicenter cohort study (CO-FLOW). *Ann Phys Rehabil Med*. 2023;66(5):101737.

Bek LM, Berentschot JC, Hellemons ME, Remerie SC, van Bommel J, Aerts JGJV, Ribbers GM, van den Berg-Emons RJG** & Heijenbrok-Kal MH**; CO-FLOW Collaboration Group. Return to work and health-related quality of life up to 1 year in patients hospitalized for COVID-19: the CO-FLOW study. *BMC Medicine*. 2023;21(1):380.

Bek LM, Ista E, Berentschot JC, Hellemons ME, Aerts JGJV, Ribbers GM, Heijenbrok-Kal MH & van den Berg-Emons RJG; CO-FLOW Collaboration Group. Healthcare professionals' perspective on the organization of COVID-19 post-hospital aftercare: perspective, barriers and facilitators. *Int J Healthc Manag*. 2024:1-16.

Berentschot JC*, **Bek LM***, Heijenbrok-Kal MH, van Bommel J, Ribbers GM, Aerts JGJV, Hellemons ME** & van den Berg-Emons RJG**; CO-FLOW Collaboration Group. 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). *J Intensive Care*. 2024;12(1):47.

Berentschot JC*, **Bek LM***, Drost M, van den Berg-Emons RJG, Braunstahl G-J, Ribbers GM, Aerts JGJV, Hellemons ME** & Heijenbrok-Kal MH**; CO-FLOW Collaboration Group. Health outcomes up to 3 years and post-exertional malaise in patients after hospitalization for COVID-19: Results from a multicenter prospective cohort study (CO-FLOW). *Lancet Reg Health Eur*. 2025. *Ahead of publication*.

Bek LM, Türk Y, Janssen ML, Weijsters G, Berentschot JC, van den Berg-Emons RJG, Heijenbrok-Kal MH, Ribbers GM, Aerts JGJV, Hanselaar WEJJ, Endeman H, Hellemons ME & Wils EJ; CO-FLOW Collaboration Group and Dutch HFNO COVID-19 study group. Long-term multidimensional patient-centred outcomes after hospitalisation for COVID-19: do not only focus on disease severity. *BMJ Open Respir Res*. 2025 Jun 8;12(1):e002789.

Contributions to publications not included in this thesis

Berentschot JC, Heijenbrok-Kal MH, **Bek LM**, Huijts SM, van Bommel J, van Genderen ME, Aerts JGJV, Ribbers GM, Hellemons ME** & van den Berg-Emons RJG**; CO-FLOW Collaboration Group. Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW). *Lancet Reg Health Eur*. 2022;22:100485.

Lakenman PLM, Joosten KFM, van Bommel J, **Bek LM**, van den Berg-Emons RJG & Olieman JF. Nutritional status of patients with COVID-19 1-y post-ICU stay: A prospective observational study. *Nutrition*. 2023;111:112025.

Berentschot JC, Drexhage HA, Aynekulu Mersha DG, Wijkhuijs AJM, GeurtsvanKessel CH, Koopmans MPG, Voermans JJC, Hendriks RW, Nagtzaam NMA, de Bie M, Heijenbrok-Kal MH, **Bek LM**, Ribbers GM, van den Berg-Emons RJG, Aerts JGJV, Dik WA** & Hellemons ME**. Immunological profiling in long COVID: overall low grade inflammation and T-lymphocyte senescence and increased monocyte activation correlating with increasing fatigue severity. *Front Immunol*. 2023 Oct 10;14:1254899.

Berentschot JC, de Ridder WA, **Bek LM**, Heijenbrok-Kal MH, Braunstahl G-J, Remerie SC, Stuip Y, Ribbers GM, Aerts JGJV, Ista E, Hellemons ME & van den Berg-Emons RJG; CO-FLOW Collaboration Group. Patients' evaluation of aftercare following hospitalization for COVID-19: satisfaction and unmet needs. *Respir Res*. 2024;25(1):145.

Berentschot JC, **Bek LM**, Heijenbrok-Kal MH, van den Berg-Emons RJG, Ribbers GM, Aerts JGJV & Hellemons ME; CO-FLOW Collaboration Group. Acute COVID-19 treatment is not associated with health problems 2 years after hospitalization. *Int J Infect Dis*. 2024;142:106966.

Bek LM, Berentschot JC, Heijenbrok-Kal MH, Hellemons ME, Aerts JGJV, Ribbers GM & van den Berg-Emons RJG. Nazorg en langetermijngevolgen van COVID-19; interim-analyses tot 12 maanden na ziekenhuisontslag in het CO-FLOW cohort. Nederlands Tijdschrift voor Revalidatiegeneeskunde. 2023 Oct 3;4:13:20

Visser C*, Berentschot JC*, de Jong CMM, Antoni ML, **Bek LM**, van den Berg-Emons RJG, van den Borst B, ten Cate H, ten Cate-Hoek AJ, Braeken DCW, Geelhoed M, Heijenbrok-Kal MH, van Kuijk SMJ, Kroft LJM, Leentjens J, Roukens AHE, Cannegieter SC, Klok FA, Kruip MJHA** & Hellemons ME**; Dutch Covid & Thrombosis Coalition Study Group. The impact of pulmonary embolism on health outcomes of COVID-19 at 3 months after hospitalization. *Res Pract Thromb Haemost*. 2024;8(7):102573.

Berentschot JC, Broeren GWM, **Bek LM**, Hellemons ME, van Bommel J, Aerts JGJV, Ribbers GM, Bussmann JBJ, Heijenbrok-Kal MH & van den Berg-Emons RJG; CO-FLOW Collaboration Group. 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. *Submitted*.

Ghariq M, Thijs RD, **Bek LM**, van Zwet EW, Benditt DG & van Dijk JG. A higher proportion of men than of women fainted in the phase without nitroglycerin in tilt-induced vasovagal syncope. *Clin Auton Res*. 2020:1–7.

*shared first authorship, **shared senior authorship

Portfolio

Summary of PhD training and teaching	
Name PhD student:	L. Martine Bek
Erasmus MC Department:	Rehabilitation Medicine
PhD Period:	2020-2024
Research School:	Netherlands Institute for Health Sciences (NIHES)
Promotors:	Prof.dr. G.M. Ribbers and Dr. H.J.G. van den Berg-Emons
Co-promotors:	Dr. M.H. Heijenbrok-Kal and Dr. M.E. Hellemons

GENERAL COURSES	YEAR	EC
BROK ('Basiscursus regelgeving Klinisch Onderzoek'), NFU	2021	1.5
Brok Hercertificering, NFU	2024	0.2
PhD Introduction Session, Erasmus MC Graduate School	2021	0.2
Biomedical Writing and Communication, Erasmus MC Graduate School, LTC course	2021	1.5
Scientific Integrity	2021	0.3
GCP Courses, Erasmus MC, Theme Thorax	2020-2024	0.4

Specific courses		
Pulmonary Hypertension, Erasmus MC Graduate School	2021	0.5
Cardiovascular Pharmacology, Erasmus MC Graduate School	2021	0.5
Kidney & Hypertension, Erasmus MC Graduate School	2021	0.5
Logistic Regression, NIHES ESP66, Erasmus MC	2021	1.4
Joint Models for Longitudinal and Survival Data, NIHES ESP72, Erasmus MC	2021	0.7
Virology, Erasmus MC Graduate School	2021	1.4
Introduction to Global Public Health, NIHES ESP41 Erasmus MC	2022	0.7
Topics in Meta-analysis, NIHES ESP15 Erasmus MC	2022	0.7
Microbiome Data Analysis in Population-based Studies, Erasmus MC Graduate School	2022	1.4
Personal Leadership & Communication, Erasmus MC Graduate School	2022	1.0

Seminars and workshops		
PhD day, Erasmus MC Graduate School	2021	0.3
BCF Career Event, Utrecht	2022	0.3
PhD day 'Staying happy and healthy your PhD', Erasmus MC Graduate School	2022	0.3
Science Day, Department Pulmonary Medicine	2022	0.3
Clinical and Health Sciences PhD Day, Erasmus MC Graduate School	2023	0.3
PhD day 'Shaping your future', Erasmus MC Graduate School	2023	0.3
Science Day, Department Pulmonary Medicine	2023	0.3
Workshop 'Managementtraining gericht op samenwerking en ontwikkeling', Department Rehabilitation Medicine	2023	0.3
Symposium 'Onderzoek naar post-COVID', Den Bosch	2024	0.3
Symposium 'Nederlandse Long COVID dag 2024', Amersfoort	2024	0.3

Presentations		
Oral presentation: *COvid-19 Follow-Up Zorgpaden en Langetermijnuitkomsten in de Nederlandse Gezondheidszorg.* Regional symposium on post-COVID-19 syndrome, Erasmus MC, Rotterdam	2021	0.5
Poster presentation: *Fatigue, psychological, and cognitive outcomes up to 12 months after hospitalization for COVID-19.* European Respiratory Society (ERS) Congress, Barcelona, Spain, virtual congress	2021	0.4
Poster presentation: *Cognitive functioning, fatigue, and psychological outcomes up to 12 months after hospitalization for COVID-19.* Dutch Congress of Rehabilitation Medicine (DCRM), Den Bosch, The Netherlands, virtual congress	2021	0.4
Poster presentation: *Symptoms persisting after hospitalization for COVID- 19: 12 months interim results of the CO FLOW study* European Respiratory Society (ERS), Barcelona, Spain, virtual congress	2022	0.4

Oral presentation: *COvid-19 Follow-Up Zorgpaden en Langetermijnuitkomsten in de Nederlandse Gezondheidszorg*. Department of Pulmonary Medicine, Erasmus MC, Rotterdam	2022	0.5
Oral presentation: *Cognitive and Psychological 1-year Recovery Patterns Across Care Pathways in COVID-19 Survivors*. DCRM, Den Bosch, The Netherlands	2022	0.5
Oral presentation: *Predictors of depressive symptoms in COVID-19 patients up to 2 years after hospitalization*. 7th congress on Neurorehabilitation and Neural Repair, Maastricht, The Netherlands	2023	0.5
Poster presentation: *Return to Work and Health-Related Quality of Life up to 1 Year in Patients Hospitalized for COVID-19*. DCRM, Den Bosch, The Netherlands	2023	0.4
Poster Presentation: *Mental health outcomes up to 2 years in patients hospitalized for COVID-19; the CO-FLOW study*. 24th European Congress of Physical and Rehabilitation Medicine, Ljubljana, Slovenia	2024	0.4
Oral presentation: *Post-exertional malaise in patients with COVID-19 at 3 years after hospital discharge; long-term outcomes of the CO-FLOW study* DCRM, Utrecht, The Netherlands	2024	0.5
Oral presentation: Several topics of PhD trajectory. Research Meetings Department of Rehabilitation Medicine, Erasmus MC, Rotterdam	2020-2024	1

Conferences		
European Respiratory Society (ERS) Congress, Barcelona, Spain, virtual congress	2021	0.9
Dutch Congress of Rehabilitation Medicine (DCRM) 2021, Den Bosch, The Netherlands, virtual congress	2021	0.6
RehabWeek, Rotterdam, The Netherlands	2022	0.9
Dutch Congress of Rehabilitation Medicine (DCRM) 2022, Den Bosch, The Netherlands	2022	0.6
7th congress on Neurorehabilitation and Neural Repair, Maastricht, The Netherlands	2023	0.6
Dutch Congress of Rehabilitation Medicine (DCRM) 2023, Den Bosch, The Netherlands	2023	0.6

Dutch Congress of Rehabilitation Medicine (DCRM) 2024, Den Bosch, The Netherlands	2024	0.3
Other		
Participating in scientific meetings, Department of Rehabilitation Medicine, Erasmus MC, Rotterdam	2020-2024	9
Organizing scientific meetings for Department of Rehabilitation Medicine, Erasmus MC, Rotterdam	2021-2022	1
Linking-Pin PhD's in the academic staff, Department of Rehabilitation Medicine, Erasmus MC, Rotterdam	2022-2024	4.5
Member of Green Team, Department of Rehabilitation Medicine, Erasmus MC, Rotterdam	2023-2024	0.5
Presentation: SEP site-visit Theme Dijkzigt, Erasmus MC	2020	0.3
Teaching		
Lecturing		
Minor Rehabilitation Medicine for medical students. *CO-FLOW study*	2020-2022	3
Lecture for third year physical therapy students the Hague University of Applied Sciences (THUAS). *Long-term Consequences of COVID-19*.	2021	0.5
Supervising practicals		
Supervising clinical technology students in R praticals of Academische Vorming 1 (KT 1955)	2023	0.5
Supervising Master's theses		
Supervising master thesis medical students (8 students)	2020-2023	16
Supervising master thesis neuropsychology student	2021	1
Other		
Supervising high school student	2022	0.3
Supervising querido honours college student	2021	0.3
Supervising data managers CO-FLOW study	2020-2022	1
Total EC		63.8



APPENDIX

Supplementary material

SUPPLEMENTAL MATERIAL

The supplemental material of this thesis is accessible via de following QR code: